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Prophylaxis against infective endocarditis

Antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures

NICE clinical guideline 64
Developed by the Centre for Clinical Practice at NICE

NICE clinical guideline 64
Prophylaxis against infective endocarditis: antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures

Ordering information
You can download the following documents from www.nice.org.uk/CG064

- The full guideline (this document) – all the recommendations, details of how they were developed, and reviews of the evidence they were based on.
- A quick reference guide – a summary of the recommendations for healthcare professionals.
- 'Understanding NICE guidance' – information for patients and carers.

For printed copies of the quick reference guide or 'Understanding NICE guidance', phone NICE publications on 0845 003 7783 or email publications@nice.org.uk and quote:

- N1487 (quick reference guide)
- N1488 ('Understanding NICE guidance').

NICE clinical guidelines are recommendations about the treatment and care of people with specific diseases and conditions in the NHS in England and Wales

This guidance represents the view of the Institute, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. The guidance does not, however, override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer and informed by the summary of product characteristics of any drugs they are considering.

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Foreword

Infective endocarditis (IE) is a rare condition with significant morbidity and mortality. It may arise following bacteraemia in a patient with a predisposing cardiac lesion. In an attempt to prevent this disease, over the past 50 years, at-risk patients have been given antibiotic prophylaxis before dental and certain non-dental interventional procedures.

In the absence of a robust evidence base, antibiotic prophylaxis has been given empirically to patients with a wide range of cardiac conditions including a history of rheumatic fever. The efficacy of this regimen in humans has never been properly investigated and clinical practice has been dictated by clinical guidelines based on expert opinion.

Recent guidelines by the British Society for Antimicrobial Chemotherapy (Gould et al. 2006) and the American Heart Association (Wilson et al. 2007) have challenged existing dogma by highlighting the prevalence of bacteraemias that arise from everyday activities such as toothbrushing, the lack of association between episodes of IE and prior interventional procedures, and the lack of efficacy of antibiotic prophylaxis regimens.

Against this background, the Department of Health asked the National Institute for Health and Clinical Excellence (NICE) to produce a short clinical guideline which would give clear guidance on best clinical practice for prophylaxis against IE in patients undergoing dental and certain non-dental interventional procedures.

The Guideline Development Group (GDG) comprised NICE's short clinical guidelines technical team and experts from many branches of medicine and dentistry, including cardiologists and cardiac surgeons, microbiologists, pharmacists, dental practitioners, paediatric dentists and academic dentists. There were also two patient representatives. In addition, the GDG sought advice from co-opted experts in gastroenterology, obstetrics, urology, otolaryngology, respiratory medicine and anaesthetics.

The group considered the evidence available in the light of existing guidelines and attempted to generate recommendations that would be of improved benefit to the patients and would be acceptable to practising clinicians. The group were mindful that antibiotic administration is not without risk to the individual patient, notwithstanding the implications of unnecessary antibiotic use on antimicrobial resistance. A new piece of health economic analysis was also undertaken to inform the GDG on the cost effectiveness of prophylaxis for patients undergoing dental procedures.

The GDG were unanimous in their conclusions about which patients with preexisting cardiac lesions are at risk of developing IE. They also agreed that the body of clinical and cost-effectiveness evidence reviewed in this guideline supported a recommendation that at-risk patients undergoing interventional procedures should no longer be given antibiotic prophylaxis against IE. In particular, the GDG were convinced by the evidence suggesting that current antibiotic prophylaxis regimens might result in a net loss of life. It should be emphasised that antibiotic therapy is still thought necessary to treat active or potential infections.

The GDG recognised that these recommendations, which are detailed and justified in this document, are a paradigm shift from current accepted practice. Dissemination of the new recommendations and the rationale underpinning them is a pre-requisite to their acceptance by patients and their healthcare professional carers. The GDG hope that the following sections provide sufficient clarity for this short clinical guideline to be accepted and implemented.

Professor David Wray
Guideline Development Group Chair

Patient-centred care

This guideline offers best practice advice on antimicrobial prophylaxis against infective endocarditis (IE) before an interventional procedure for adults and children in primary dental care, primary medical care, secondary care and care in community settings.

Treatment and care should take into account patients' needs and preferences. Patients should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If patients do not have the capacity to make decisions, healthcare professionals should follow the Department of Health (2001) guidelines – 'Reference guide to consent for examination or treatment' (available from www.dh.gov.uk). Healthcare professionals should also follow a code of practice accompanying the Mental Capacity Act (summary available from www.publicguardian.gov.uk).

If the patient is under 16, healthcare professionals should follow guidelines in 'Seeking consent: working with children' (available from www.dh.gov.uk).

Good communication between healthcare professionals and patients is essential. It should be supported by evidence-based written information tailored to the patient's needs. Treatment and care, and the information patients are given about it, should be culturally appropriate. It should also be accessible to people with additional needs such as physical, sensory or learning disabilities, and to people who do not speak or read English.

If the patient agrees, families and carers should have the opportunity to be involved in decisions about treatment and care.

Families and carers should also be given the information and support they need.

Care of young people in transition between paediatric and adult services should be planned and managed according to the best practice guidance described in 'Transition: getting it right for young people' (available from www.dh.gov.uk).

Adult and paediatric healthcare teams should work jointly to provide assessment and services to young people with IE. Diagnosis and management should be reviewed throughout the transition process, and there should be clarity about who is the lead clinician to ensure continuity of care.

1 Summary

1.1 List of all recommendations

Adults and children with structural cardiac defects at risk of developing infective endocarditis

1.1.1 Healthcare professionals should regard people with the following cardiac conditions as being at risk of developing infective endocarditis:

- acquired valvular heart disease with stenosis or regurgitation
- valve replacement
- structural congenital heart disease, including surgically corrected or palliated structural conditions, but excluding isolated atrial septal defect, fully repaired ventricular septal defect or fully repaired patent ductus arteriosus, and closure devices that are judged to be endothelialised
- previous infective endocarditis
- hypertrophic cardiomyopathy.

Patient advice

1.1.2 Healthcare professionals should offer people at risk of infective endocarditis clear and consistent information about prevention, including:

- the benefits and risks of antibiotic prophylaxis, and an explanation of why antibiotic prophylaxis is no longer routinely recommended
- the importance of maintaining good oral health
- symptoms that may indicate infective endocarditis and when to seek expert advice
- the risks of undergoing invasive procedures, including non-medical procedures such as body piercing or tattooing.

Prophylaxis against infective endocarditis

1.1.3 Antibiotic prophylaxis against infective endocarditis is not recommended:

- for people undergoing dental procedures
- for people undergoing non-dental procedures at the following sites[1]:
  - upper and lower gastrointestinal tract
  - genitourinary tract; this includes urological, gynaecological and obstetric procedures, and childbirth
  - upper and lower respiratory tract; this includes ear, nose and throat procedures and bronchoscopy.

1.1.4 Chlorhexidine mouthwash should not be offered as prophylaxis against infective endocarditis to people at risk of infective endocarditis undergoing dental procedures.

Infection

1.1.5 Any episodes of infection in people at risk of infective endocarditis should be investigated and treated promptly to reduce the risk of endocarditis developing.

1.1.6 If a person at risk of infective endocarditis is receiving antimicrobial therapy because they are undergoing a gastrointestinal or genitourinary procedure at a site where there is a suspected infection, the person should receive an antibiotic that covers organisms that cause infective endocarditis.

[1] The evidence reviews for this guideline covered only procedures at the sites listed in this recommendation. Procedures at other sites are outside the scope of the guideline (see appendix 1 for details).

1.2 Overview

1.2.1 Antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures

Infective endocarditis (IE) is an inflammation of the endocardium, particularly affecting the heart valves, caused mainly by bacteria but occasionally by other infectious agents. It is a rare condition, with an annual incidence of fewer than 10 per 100,000 cases in the normal population. Despite advances in diagnosis and treatment, IE remains a life-threatening disease with significant mortality (approximately 20%) and morbidity.

The predisposing factors for the development of IE have changed in the past 50 years, mainly with the decreasing incidence of rheumatic heart disease and the increasing impact of prosthetic heart valves, nosocomial infection and intravenous drug misuse. However, the potentially serious impact of IE on the individual has not changed (Prendergast 2006).

Published medical literature contains many case reports of IE being preceded by an interventional procedure, most frequently dentistry. IE can be caused by several different organisms, many of which could be transferred into the blood during an interventional procedure. Streptococci, *Staphylococcus aureus* and enterococci are important causative organisms.

It is accepted that many cases of IE are not caused by interventional procedures (Brincat et al. 2006), but with such a serious condition it is reasonable to consider that any cases of IE that can be prevented should be prevented. Consequently, since 1955, antibiotic prophylaxis that aims to prevent endocarditis has been used in at-risk patients. However, the evidence base for the use of antibiotic prophylaxis has relied heavily on extrapolation from animal models of the disease (Pallasch 2003) and the applicability of these models to people has been questioned. With a rare but serious condition such as IE it is difficult to plan and execute research using experimental study designs. Consequently, the evidence available in this area is limited, being drawn chiefly from observational (case–control) studies.

The rationale for prophylaxis against IE is: endocarditis usually follows bacteraemia, certain interventional procedures cause bacteraemia with organisms that can cause endocarditis, these bacteria are usually sensitive to antibiotics; therefore, antibiotics should be given to patients with predisposing heart disease before procedures that may cause bacteraemia (Durack 1995).

For prophylaxis to be effective, certain requirements must be fulfilled: identification of patients at risk, identification of the procedures that are liable to provoke bacteraemia, and choice of a suitable regimen. There should also be a favourable balance between the risks of side-effects from prophylaxis and development of the disease (Moreillon et al. 2004). Underlying these principles is the assumption that antibiotic prophylaxis is effective for the prevention of IE in dental and non-dental procedures. However, many researchers consider this assumption to be not proven (Prendergast 2006), which has led to calls to significantly reduce the use of antibiotic prophylaxis in this setting. This shift in opinion is reflected in national and international clinical guidelines for prophylaxis against IE. Guidelines used to recommend antibiotic prophylaxis for IE for patients with a wide range of cardiac conditions be given for a range of interventional procedures, both dental and non-dental. They now tend to recommend that only those with one of a small number of high-risk cardiac conditions should receive antibiotic prophylaxis when they undergo a limited number of specified dental procedures.

Throughout the history of prophylaxis being offered against IE, professional organisations have sought to clarify the groups of patients that are considered to be at risk of IE and the procedures (dental and non-dental) for which prophylaxis may be considered. The Guideline Development Group (GDG) used the decision making and conclusions of relevant national and international guidelines to help inform its own decision making. This decision-making process has been important because, for many of the key clinical questions covered in this guideline, there is no evidence base that would meet rigorous quality criteria. Four clinical guidelines on the prevention of IE are discussed in subsequent sections: American Heart Association (AHA) 2007 (Wilson et al. 2007), British Society for Antimicrobial Chemotherapy (BSAC)

2006 (Gould et al. 2006), European Society of Cardiology (ESC) 2004 (Horstkotte et al. 2004) and British Cardiac Society (BCS)/Royal College of Physicians (RCP) 2004 (Advisory Group of the British Cardiac Society Clinical Practice Committee 2004).

The recommendations of these four guidelines, and where reported the rationale for their recommendations, have been considered by the GDG in the development of this guideline. However, it should be emphasised that the GDG has based its recommendations on an independent consideration of the available clinical and cost-effectiveness evidence and, where appropriate, expert opinion. The guideline developers have also sought to make the rationale for their recommendations as transparent as possible, set out in the relevant 'Evidence to recommendations' sections.

This clinical guideline aims to provide clear guidance to the NHS in England, Wales and Northern Ireland regarding which dental and non-dental interventional procedures require, or do not require, antimicrobial prophylaxis against IE. In contrast to other recently published national and international guidelines, it explicitly considers the likely cost effectiveness as well as the clinical effectiveness of antibiotic prophylaxis.

In summary, this guideline recommends that antibiotic prophylaxis solely to prevent IE should not be given to people at risk of IE undergoing dental and non-dental procedures. The basis to support this recommendation is:

- there is no consistent association between having an interventional procedure, dental or non-dental, and the development of IE
- regular toothbrushing almost certainly presents a greater risk of IE than a single dental procedure because of repetitive exposure to bacteraemia with oral flora
- the clinical effectiveness of antibiotic prophylaxis is not proven
- antibiotic prophylaxis against IE for dental procedures may lead to a greater number of deaths through fatal anaphylaxis than a strategy of no antibiotic prophylaxis, and is not cost effective.

Given the difficulties in relative risk definition, a simple classification of conditions into either groups at risk and not at risk was undertaken.

1.2.2 The NICE short clinical guideline programme

'Prophylaxis against infective endocarditis: antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures' (NICE clinical guideline 64) is a NICE short clinical guideline.

For a full explanation of the process, see www.nice.org.uk/guidelinesmanual.

1.2.3 Using this guideline

This document is intended to be relevant to healthcare professionals who have direct contact with patients within primary medical and dental care, secondary care and community settings. The target population is adults and children with known underlying structural cardiac defects, including those who have previously had IE.

This is the full version of the guideline. It is available from www.nice.org.uk/CG064. Printed summary versions of this guideline are available: 'Understanding NICE guidance' (a version for patients and carers) and a quick reference guide (for healthcare professionals). These are also available from www.nice.org.uk/CG064

1.2.4 Using recommendations and supporting evidence

The Guideline Development Group took into consideration the overall benefits, harms and costs of the reviewed interventions. It also considered equity and the practicality of implementation when drafting the recommendations set out within this guideline. To enable patients to participate in the process of decision making to the extent that they are able and willing, clinicians need to be able to communicate information provided in this guideline. To this end, recommendations are often supported by evidence statements that provide summary information to help clinicians and patients to discuss options.

2 Evidence review and recommendations

2.1 People with cardiac conditions and their risk of developing infective endocarditis

2.1.1 Introduction

Patients with certain cardiac conditions are known to be at risk of developing infective endocarditis (IE)[2]. Guidelines and discussion on prophylaxis against IE start from the premise that it is possible to classify those with underlying cardiac conditions into those who are at increased risk and those whose risk is considered to be the same as, or little greater than, the general population. However, the stratification of patients into high-risk or low-risk groups has proved to be difficult. Steckelberg and Wilson (Steckelberg and Wilson 1993) highlighted that the degree of risk associated with specific valvular lesions cannot be directly inferred from their frequency among endocarditis patients, because the prevalence of these lesions varies widely. The arbitrary nature of some of the decisions concerning risk identification has also been discussed (Durack 1995). Nonetheless, consideration of which underlying conditions affect a person's risk of developing IE is important because it will influence decisions made about offering prophylaxis.

Even with advanced diagnostic imaging, improved antimicrobial chemotherapy and potentially curative surgery, IE continues to have high rates of mortality and morbidity (Prendergast 2006). Therefore, when considering prophylaxis for IE, in tandem with detailing which underlying cardiac conditions affect a person's risk of developing IE, it is logical to consider whether the underlying cardiac condition also affects the outcome of IE.

Guidelines in the area

Stratification of people with cardiac conditions into risk groups has proved difficult and has been tackled in different ways in different guidelines. The

[2] The abbreviation IE for infective endocarditis will be used throughout this guideline. However, where research papers have used the term bacterial endocarditis (BE) the term used within the paper will be used when discussing it.

American Heart Association (AHA) (Wilson et al. 2007) guidelines considered the underlying conditions that over a lifetime cause the highest predisposition to IE, and the conditions that are associated with the highest risk of adverse outcomes when IE develops. The British Society for Antimicrobial Chemotherapy (BSAC) (Gould et al. 2006) guideline defined a category of high-risk cardiac conditions requiring antibiotic prophylaxis. The British Cardiac Society (BCS)/Royal College of Physicians (RCP) (Advisory Group of the British Cardiac Society Clinical Practice Committee 2004) guideline defined those with preexisting cardiac conditions as being at high, moderate or low risk of developing IE in the event of significant bacteraemia occurring following an interventional procedure. Finally, the European Society of Cardiology (ESC) guideline (Horstkotte et al. 2004) considered that it was impossible to determine the relative risk of specific cardiac conditions and sought to identify those conditions associated with an IE risk that is higher than that in the general population; this group included conditions that are associated with a worse prognosis if endocarditis occurs.

2.1.2 Overview

Few studies are of sufficient quality to allow conclusions to be drawn on the relative risk of different cardiac conditions for the development of IE and to allow this risk to be directly compared between different cardiac conditions. Initially seven were included; three cohort studies (Gersony et al. 1993; Li and Somerville 1998; Morris et al. 1998) and four case–control studies (Clemens et al. 1982; Danchin et al. 1989; Hickey et al. 1985; Strom et al. 1998). There was limited evidence relating to the range of possible predisposing cardiac conditions, so 11 case series studies of patients with IE that considered possible predisposing cardiac conditions and that included 50 or more participants were also reviewed and the relevant results presented[3].

The impact of underlying cardiac conditions on the outcomes of IE was considered. Outcome data were identified from five cohort studies (Li and Somerville 1998; Gersony et al. 1993; Anderson et al. 2005; Wang et al. 2005,

[3] It should also be noted that where incidence has been reported in patient–years there is not consistency between the studies in the time period used for these.

2007) and 12 case series papers. Three studies used data from the International Collaboration on Endocarditis Database.

2.1.3 Preexisting cardiac conditions in adults and children and their effect on the risk of developing infective endocarditis

Recommendation number 1.1.1

Healthcare professionals should regard people with the following cardiac conditions as being at increased risk of developing infective endocarditis:

- acquired valvular heart disease with stenosis or regurgitation
- valve replacement
- structural congenital heart disease, including surgically corrected or palliated structural conditions, but excluding isolated atrial septal defect, fully repaired ventricular septal defect or fully repaired patent ductus arteriosus, and closure devices that are judged to be endothelialised
- previous infective endocarditis
- hypertrophic cardiomyopathy.

Evidence review

Congenital heart disease

a) Aortic stenosis, pulmonary stenosis, ventricular septal defect

The Second Natural History Study (1983–9) (Level 2+) followed up a cohort of 2401 people with aortic stenosis, pulmonary stenosis and ventricular septal defect (VSD) who had initially been entered into the First Natural History Study of Congenital Heart Defects (1958–65) in the UK (Gersony et al. 1993). The incidence of bacterial endocarditis (BE) was: aortic stenosis 27.1 per 10,000 person–years (n = 22/462, confidence interval [CI] 17.0 to 41.0);

pulmonary stenosis 0.9 (n = 1/592, CI 0.02 to 5.2) and VSD 14.5 (n = 32/1347, CI 9.9 to 20.5).

The ratio of postoperated aortic stenosis compared with non-operated was 2.6 (CI 1.1 to 6.6, p = 0.0150), with BE more than twice as likely to develop in people whose aortic stenosis was managed surgically than in those whose aortic stenosis was medically managed. There was no significant difference in the incidence of BE in those with and without regurgitation.

For VSD the ratio of non-operated to postoperated BE was 2.6 (CI 1.1 to 6.7, p = 0.0122), with BE more than twice as likely to occur before surgical closure. There was no significant difference in the incidence rates of BE between the categories of severity of VSD. The rates of IE in VSD patients with associated aortic regurgitation were significantly higher than in those without aortic regurgitation (p = 0.0002).

The overall rate of developing IE based on the 2401 patients with aortic stenosis, pulmonary stenosis or VSD was found to be nearly 35 times the population-based rate.

b) Congenital heart population cohort, un-operated and definitive repair groups

A retrospective (up to 1993) and prospective (1993–6) study (Level 2+) reported on the UK-based cohort from the grown-up congenital heart (GUCH) population (Li and Somerville 1998). This included 185 patients (n = 214 episodes of IE), who were divided into Group I (un-operated or palliative procedures; n = 128) and Group II (definitive repair including aortic, pulmonary, mitral and/or tricuspid valvotomy, repair or valve replacement; n = 57).

IE developed most frequently in those with left ventricular outflow tract lesions (42 patients, 45 episodes); the incidence was similar in both Group I and Group II. In patients with VSD there was a higher incidence in Group I (31 patients, 37 episodes) than in Group II (six patients, six episodes).

The other cardiac lesions in patients with IE were: tetralogy of Fallot (Group I = 12, Group II = 11); corrected transposition (Group I = 11, Group II = 2); mitral valve prolapse (Group I = 17, Group II = 1[4]); pulmonary atresia (Group I = 10, Group II = 2); single ventricle (Group I = 12, Group II = 0); classical transposition (Group I = 5, Group II = 3); atrioventricular defect (Group I = 2, Group II = 8); coarctation (Group I = 1, Group II = 3); common trunk (Group I = 2, Group II = 1); infundibular pulmonary stenosis (Group I = 2, Group II = 0); duct (Group I = 1, Group II = 0) and Ebstein's anomaly (Group I = 0, Group II = 1).

c) Repair of major congenital heart defects

A cohort study (Level 2+) completed in the USA reported on 3860 people who had had surgical repair of major congenital heart defects (follow-up data available for 88%); this was further expanded to include 12 major heart defects (Morris et al. 1998).

For the major heart defects the annualised risk was categorised into high, moderate-to-low and no documented risk.

[4] Same patient in Group I who had recurrent IE after radical repair.

Table 1 IE risk following repair of major congenital heart defects

Risk for endocarditis		No. of cases per 1000 patient–years
High	Pulmonary atresia with VSD	11.5
	Tetralogy of Fallot with palliative systemic-to-pulmonary shunt	8.2
	Aortic valve stenosis[a]	7.2
	Pulmonary atresia [a]	6.4
	Un-operated VSD	3.8
Moderate-to-low	Primum ASD with cleft mitral valve [a]	1.8
	Coarctation of the aorta [a]	1.2
	Complete atrioventricular septal defect [a]	1.0
	Tetralogy of Fallot [a]	0.7
	Dextrotransposition of the great arteries [a]	0.7
	VSD [a] (no cases occurred with closed VSD in the absence of other abnormalities)	0.6
No documented risk	ASD*	0
	Patent ductus arteriosus [a]	0
	Pulmonic stenosis [a]	0

[a] After definitive surgical repair.

The highest incidence of IE following surgical repair of congenital heart disease was in the cohort with aortic valve stenosis, at 7.2 cases per 1000 patient–years[5]. The incidence appeared to increase more rapidly after 5 years, and by 25 years the cumulative incidence was 13.3% (standard error [SE] 3.8%). Of those with aortic stenosis, 28 (16%) had aortic valve replacement; for prosthetic valves there were three cases of IE (10-year incidence 26%), for native valves there were 10 cases of IE (10-year incidence 5%). IE in other underlying conditions following surgery: coarctation

[5] This excludes those with isolated supravalvular or subvalvular aortic stenosis in whom there were no cases of IE.

of the aorta n = 8; tetralogy of Fallot n = 5, all of which occurred within 10 years of surgery; pulmonary atresia with VSD n = 3; VSD n = 4.

Endocarditis in the immediate postoperative period explained 22% of the cases occurring in children with tetralogy of Fallot, primum atrial septal defect (ASD), coarctation, pulmonary atresia, and pulmonary atresia with intact septum.

Case–control studies [6]

a) Valvular disease

A population-based case–control study (Level 2+) was undertaken in the USA (Strom 1998). There was one control for each case, matched for age, sex, ethnicity, education, occupation and dental insurance status; 273 cases were identified from surveillance of 54 hospitals in eight counties and controls were selected from the community for each case patient using a modified random-digit method.

Patient-reported history of any cardiac valvular abnormality was highly associated with IE (adjusted[7] odds ratio 16.7; CI 7.4 to 37.4)

[6] It should be noted that the control groups in these studies include those with cardiac conditions that have not been excluded in the criteria specific to the study.

[7] Adjusted for socioeconomic status variables (ethnic group, education, occupation, health insurance status, and dental insurance status).

Table 2 Risk of IE with valvular disease

Risk factor	Cases (n = 273)	Controls (n = 273)	Adjusted OR[8] (95% CI)
Other valvular heart disease	12 (4.4%)	1 (0.4%)	131 (6.9 to 2489)
Cardiac valvular surgery	37 (13.6%)	2 (0.7%)	74.6 (12.5 to 447)
Previous episode of endocarditis	17 (6.2%)	1 (0.4%)	37.2 (4.4 to 317)
Mitral valve prolapse	52 (19.0%)	6 (2.2%)	19.4 (6.4 to 58.4)
Any cardiac valvular abnormality [a]	104 (38.1%)	17 (6.2%)	16.7 (7.4 to 37.4)
Rheumatic fever	32 (11.7%)	10 (3.7%)	13.4 (4.5 to 39.5)
Congenital heart disease	26 (9.5%)	7 (2.6%)	6.7 (2.3 to 19.4)
Heart murmur (no other known cardiac abnormality)	37 (13.6%)	14 (5.1%)	4.2 (2.0 to 8.9)

[a] Includes any of: mitral valve prolapse, congenital heart disease, rheumatic fever with heart involvement, cardiac valvular surgery, previous episode of endocarditis and other valvular heart disease. Those reporting more than one of these factors were only reported once.

b) Mitral valve prolapse

Three studies (Level 2+) used a case–control methodology to consider the risk of endocarditis in those with mitral valve prolapse (MVP).

[8] Adjusted for socioeconomic status variables (ethnic group, education, occupation, health insurance status, and dental insurance status), diabetes mellitus and severe kidney disease.

Table 3 Risk of IE with mitral valve prolapse

	Clemens et al. 1982	Danchin et al. 1989	Hickey et al. 1985
MVP in cases	n = 13 (25%)	n = 9 (19%)	n = 11 (20%)
MVP in controls	n = 10 (7%)	n = 6 (6%)	n = 7 (4%)
Matched sets	16 sets, cases and controls discordant in the presence or absence of MVP; matched OR 8.2 (2.4 to 28.4), p < 0.001	Risk of developing BE cases to controls: OR 3.5 (1.1 to 10.5)	11 sets had BE and MVP, in one of these MVP was also present in a control; 39 sets BE without MVP, in six of these MVP was present in a control; OR for the association of MVP and BE 5.3 (2.0 to 14.4)
Systolic murmur	NA	BE in MVP with systolic murmur, cases (n = 7), controls (n = 1) OR 14.5 (1.7 to 125) Without systolic murmur, cases (n = 2), controls (n = 5) OR 1.0 (0.2 to 5.5)	n = 9/11 had MVP and BE and preexisting systolic murmurs: OR for the association between BE and MVP with systolic murmur 6.8 (2.1 to 22.0)

A case-controlled evaluation (Level 2+) in the USA considered MVP and BE (Clemens et al. 1982). There were three age- and sex-matched controls for each case; 51 cases were identified from records that fulfilled the criteria for BE, the 153 controls were selected from those who had undergone

echocardiography during the period covered in the study[9]. This study undertook further analyses, which included adjustment for risk factors for endocarditis that were unequally distributed between the cases and controls; the association initially identified remained.

A French case–control study (Level 2+) reported on MVP as a risk factor for IE (Danchin et al. 1989). This study used two age- and sex-matched controls for each case; 48 cases were identified from records of those with BE admitted to cardiology and cardiovascular surgery, and 96 controls were identified from a random sample of people who had echocardiography during routine screening and randomly from patients admitted for surgery of the limbs.

A further case–control study (Level 2+), in Australia, considered MVP and BE (Hickey et al. 1985). There were three age-, sex- and date of echocardiography-matched controls for each case; 56 cases were selected from those admitted with BE, and 168 controls were selected from inpatients who did not have BE and underwent an echocardiography during the study period[10]. This study also calculated a probability of developing endocarditis based on the incidence in the adult population of New South Wales and an assumption that 15% of those with BE had known high-risk lesions other than MVP and mitral regurgitation. This found a probability of BE occurring in a person with MVP in a 1-year period of 0.00014, which is 4.7 times greater than that in the general population.

Case series

Eleven case series (Level 3) were identified with 50 or more participants that considered those with IE and the possible predisposing cardiac conditions.

[9] Controls with antecedent heart disease were excluded.

[10] Controls with antecedent high-risk cardiovascular lesions for BE were excluded, except those with mitral regurgitation and/or MVP.

Table 4 Case series papers with results that are relevant to possible risk factors

Reference	Study/dates/ location	Relevant results			
Benn et al. 1997	Retrospective review	Predisposing factors in 62 episodes of IE (59 patients)			
	January 1984 to December 1993 Denmark	Congenital heart disease – total	7	Acquired heart disease – total	34
		Aortic stenosis	2	Aortic valve prosthesis	6
		Aortic, mitral and triscuspid regurgitation	1	Mitral valve prosthesis	2
		Floppy mitral valve	1	Pacemaker and mitral valve prosthesis	1
		Fistula in septum	1	Aortic regurgitation	5
		Ebstein's anomaly	1	Aortic stenosis	6
		Transposition of great arteries and VSD	1	Mitral stenosis	8
				Mitral stenosis, rheumatic	3
				Aortic stenosis, rheumatic	3
Bouza et al. 2001	Prospective study	109 episodes of IE (n = 39 intravenous drug users [IVDU]), underlying conditions			
	March 1994 to October 1996 Spain	Native valve endocarditis	52	Prosthetic valve endocarditis	18
		Cardiac diseases	18 (34.6%)	Cardiac diseases	18 (100%)
		Rheumatic valves	6 (11.4%)	Valvular prosthesis	18 (100%)
		Arteriosclerotic valves	4 (7.7%)	Previous endocarditis	3 (16.6%)
		Mitral prolapse	1 (2%)		
		Other	7 (13.4%)		

Cecchi et al. 2004	Prospective multicentre survey	147 cases of IE, 104 considered to be related to predisposing heart disease			
	January 2000 to December 2001	Prosthetic valves	37 (25%)	Aortic insufficiency	6
		Native valves	67 (45%)	Mitral insufficiency	3
	Italy	Mitral valve prolapse	25	Mitral and aortic insufficiency	5
		Aortic stenosis	5	Bicuspid aortic valve	8
		Aortic stenosis and insufficiency	6	Interventricular septal defect	1
		Mitral stenosis	2	Previous mitral valvuloplasty	2
		Mitral stenosis and insufficiency	3	Aortic valve sclerosis	2
Choudhury et al. 1992	Retrospective review	190 episodes of IE (186 patients), underlying heart disease (rheumatic heart disease) n = 79 (42%), normal n = 17 (9%)			
	January 1981 to July 1991	Congenital heart disease – total	62 (33%)	Uncertain aetiology	24 (13%)
		Bicuspid aortic valve	25	Aortic regurgitation	15
	India	VSD	15	Mitral regurgitation	9
		Patent ductus arteriosus	7		
		Tetralogy of Fallot	3	Prosthetic valves	2 (1%)
		Ruptured sinus of Valsalva	3	Mitral valve prolapse	2 (1%)
		Double-outlet right ventricle	2		
		Aortic stenosis	2		
		Pulmonary stenosis	2		

		Atrial septal defect	2		
		Coronary AV fistula	1		
Chu et al. 2004	Case review	65 episodes of IE (62 patients), predisposing heart conditions, normal valves 25 (40.3%)			
	1997 to 2002				
	New Zealand	Congenital heart disease – total	8	Acquired heart disease – total	29
		Bicuspid aortic valve	5 (8.1%)	RHD with mitral stenosis	1 (1.6%)
		Tetralogy of Fallot[a]	1 (1.6%)	Aortic stenosis	8 (12.9%)
		Transposition of the great arteries[a]	1 (1.6%)	Mitral valve prolapse	4 (6.5%)
		Abnormal pulmonary valve	1 (1.6%)	Prosthetic valves	15 (24.2%)
				Implantable cardioverter defibrillator	1 (1.6%)
		[a] post repair			
Dyson et al. 1999	Epidemiol-ogical review	128 episodes of IE (125 patients), predisposing cardiac risk factors for native valve endocarditis (NVE) episodes (no identifiable risk factor n = 29 (37.7%)			
	March 1987 to March 1996				
	Wales	Congenital heart lesion	21 (26.9%)	Mitral valve prolapse	9 (11.5%)
		Biscuspid aortic valve	13 (16.7%)	Rheumatic heart disease	8 (11.1%)
		Ventricular septal defect	3 (3.8%)	Marfan syndrome	2 (2.6%)
		Congenital aortic stenosis	2 (2.6%)		
		Complex structural malformation	2 (2.6%)		

		Hypertrophic obstructive cardiomyopathy	1 (1.3%)
Griffin et al. 1985	Population-based study	78 residents with IE identified	
	1950 to 1981	Rheumatic heart disease	20 (26%)
		Mitral valve prolapse	13 (17%)
	Minnesota, USA	Congenital heart disease	11 (14%)
		Degenerative heart disease[b]	7 (9%)
		Aortic arch prosthesis	1 (1%)
		Prior systolic murmur	15 (19%)
		[b] calcific aortic stenosis, calcified mitral valve, papillary muscle dysfunction	
Mansur et al. 2001	Case series	420 adult and paediatric, underlying cardiac conditions	
	Mean follow-up 6.1 years for survivors, 3.7 for those who died	Valvular heart disease	177 (42.1%)
		Congenital heart disease	49 (11.7%)
		Hypertrophic cardiomyopathy	3 (0.7%)
	Brazil	Chagas' cardiomyopathy	1 (0.2%)
		Endocardial fibroelastosis	1 (0.2%)
		Prosthetic heart valve	91 (21.7%)
Salman et al. 1993	Case review in children	62 cases of paediatric IE, 70% had structural heart disease	
		Complex cyanotic heart disease	22
	January 1977	VSD	9

	to February 1992	Other acyanotic lesions	5
		Mitral valve prolapse	4
		Rheumatic heart disease	3
	USA		
Tleyjeh et al. 2005	Population-based survey	107 episodes of IE, underlying cardiac disease	
		Prosthetic valve	23 (21%)
	1970 to 2000	Rheumatic heart disease	14 (13%)
	USA	Mitral valve prolapse	18 (17%)
		Congenital heart disease	8 (7%)
		Bicuspid aortic valve	7 (7%)
		Acquired valvular disease	12 (11%)
		Previous IE	8 (7%)
van der Meer 1992	Consecutive case series	The crude incidence of BE was 15 per million person–years, adjusted for age and sex was 19 per million person–years	
		Native valve	
	November 1986 to November 1988	NVE – total n = 349 (79.7% of the total), crude incidence of NVE was 12 per million person–years, adjusted for age and sex was 15 per million person–years	
		197 (56.4%) had a previously known cardiac lesion predisposing to BE	
	Netherlands	145 (41.6%) had heart disease at admission that had not been recognised previously	
		7 (2%) had no heart disease	
		Underlying heart disease in n = 349 NVE	
		Aorta	110 (31.5%)
		Bicuspid valve	2
		Bicuspid valve and aortic insufficiency/	3
		Mitral	125 (35.8%)
		Prolapse	1
		Prolapse and regurgitation	27

aortic stenosis			
Sclerotic valve	7	Prolapse and stenosis	1
Regurgitation	64	Regurgitation	89
Regurgitation and stenosis	17	Regurgitation and stenosis	4
Stenosis	9	Stenosis	3
Hypertrophic obstructive cardiomyopathy	8	Right-sided	21 (6.0%)
Mitral and aortic	36 (10.9%)	Tricuspid regurgitation	19
Regurgitation and stenosis	36	Pulmonary regurgitation	1
Congenital heart disease	38 (10.9%)	Pulmonary and tricuspid regurgitation	1
ASD	1	Other	19 (5.4%)
VSD	13		
VSD and right sided valvular disease	6		
Patent arterial duct	5		
Tetralogy of Fallot	5		
Other	8		

Prosthetic valve

Prosthetic valve endocarditis (PVE) – total n = 89 (20.3% of the total), crude incidence of PVE was 3 per million person–years, adjusted for age and sex was 6 per million person–years

11 (12.4%) had early PVE (≤ 60 days after implantation) and 78 (87.6%) had late PVE (> 60 days)

n = 39 (43.8%) aortic prosthesis, n = 22 (24.7%) mitral prosthesis, n = 28 (31.5%) multiple prostheses

Evidence statements

The following cardiac conditions are associated with a risk of developing IE: acquired valvular heart disease with stenosis or regurgitation, valve replacement, structural congenital heart disease (including surgically corrected or palliated structural conditions) and hypertrophic cardiomyopathy.

The following cardiac conditions are not associated with a risk of IE:

- *isolated atrial septal defect*
- *repaired ventricular septal defect*
- *repaired patent ductus arteriosus*
- *closure devices that are judged to be endothelialised.*

2.1.4 Preexisting cardiac conditions associated with relatively poorer outcomes from infective endocarditis

Evidence review

A retrospective (up to 1993) and prospective (1993–6), UK based study (Level 2+) reported on a cohort from the grown-up congenital heart (GUCH) population (Li and Somerville 1998). This included 185 patients (214 episodes of IE), who were divided into Group I (un-operated or palliative procedures; n = 128) and Group II (definitive repair including aortic, pulmonary, mitral and/or tricuspid valvotomy, repair or valve replacement; n = 57).

Recurrent attacks of IE occurred in 21 people, 11% (19 of these were from Group I); of these 19 cases, six were VSD, three were congenital corrected transposition of the great arteries with VSD and pulmonary stenosis, two were pulmonary atresia with VSD, two were single ventricle, two were MVP, one was tetralogy of Fallot with aortic regurgitation, one was transposition of the great arteries with VSD, and two were congenital abnormal valves.

The cardiac lesions of the eight patients who died during endocarditis (n = 3 Group I and n = 5 Group II) were: VSD; aortic stenosis/aortic regurgitation; pulmonary atresia/VSD (n = 2); aortic stenosis/aortic regurgitation/mitral regurgitation (n = 2); aortic stenosis/coarctation; and transposition of the great arteries/VSD/pulmonary stenosis.

The Second Natural History Study (Level 2+) (1983–9) followed up a cohort of 2401 patients with aortic stenosis, pulmonary stenosis and ventricular septal defect (Gersony et al. 1993). Of the 22 patients with aortic stenosis, 13 had complications; of the 32 with VSD, 15 had complications.

A prospective observational cohort study (Level 2+) included patients with prosthetic valve endocarditis (PVE) enrolled in the International Collaboration on Endocarditis – Prospective Cohort Study from 61 medical centres in 28 countries, from June 2000 to August 2005; 2670 had IE (Wang et al. 2007). Those with PVE compared with those with native valve endocarditis (NVE) had significantly higher rates of in-hospital death (22.8% versus 16.4%, $p < 0.001$) and other systemic embolisation (not stroke) (24.7% versus 14.9%, $p < 0.001$). Complications that were not significant between those with NVE and those with PVE were; heart failure, stroke, surgery during admission, and persistent bacteraemia. Comparison across geographical regions[11] identified no significant difference in in-hospital mortality for those with PVE.

A study (Level 2+) in the USA considered data on 159 cases collected by the International Collaboration on Endocarditis – Merged Endocarditis Database (Anderson et al. 2005). A prosthetic valve was involved in 45 cases, and native valves in 114. With enterococcal endocarditis, those with PVE were significantly more likely to have intracardiac abscesses than those with NVE ($p = 0.009$), whereas those with enterococcal NVE were significantly more likely to have detectable vegetations than those with PVE ($p < 0.001$). Complication rates were not significantly different between the PVE and NVE for heart failure, all embolism, central nervous system (CNS) complications, stroke, valvular surgery during this episode, and death during hospitalisation (14% versus 12%).

The International Collaboration on Endocarditis – Merged Database (Level 2+) was used to consider a cohort of 355 cases who had surgical therapy for PVE (Wang et al. 2005). In-hospital complications were; congestive heart failure (CHF) 38.6%, systemic embolisation 27.3%, brain embolisation 18.9%,

[11] Regions: United States, South America, Australia/New Zealand, North/Central Europe, Southern Europe/Middle East/South Africa.

intracardiac abscess 19.4% and in-hospital death 24.1%. Analysis of variables associated with in-hospital mortality and a matched propensity for surgical treatment showed *S. aureus* infection and brain embolisation to be independently associated with in-hospital mortality.

Case series

Twelve case series papers (Level 3) provided data related to outcomes of IE and cardiac conditions.

Table 5 case series papers on outcomes of IE and cardiac conditions

Reference	Study/dates/location	Relevant results
Bouza et al. 2001	Prospective study March 1994 to October 1996 Spain n = 109 patients	Mortality: IE related mortality was 25.7% (total 109 patients): • 25% (n = 13) with NVE • 100% (n = 6) with early PVE • 25% (n = 3) with late PVE. Early PVE was significantly related to mortality (with multivariate analysis) Valve replacement: Required in a total of n = 25: • 16 (30.7%) of those with NVE • 2 (33%) of those with early PVE • 6 (50%) of those with late PVE
Chu et al. 2004	Case review 1997 to 2002 New Zealand n = 62 patients	Mortality: Overall n = 20: • 11 (55%) with NVE • 6 (30.0%) with PVE
Dyson et al. 1999	Epidemiological review March 1987 to March 1996 Wales n = 125 patients	Mortality: Overall n = 21: • 9 (12.3%) with NVE • 12 (24.5%) with PVE

Gentry and Khoshdel 1989	Consecutive case review 1983 to 1989 USA n = 94 patients	Therapeutic failure[12]: Overall failure 24% (14% death; 11% relapse): • NVE failure was 28% (17% death; 11% relapse) • PVE failure was 20% (10% death; 10% relapse)
Mansur et al. 2001	Case series Mean follow-up 6.1 years for survivors, 3.7 for those who died Brazil n = 420 adult and paediatric patients	Relapse[13]: Overall n = 14: • Prosthetic valve n = 7 (50%) • Valvular heart disease n = 2 • Congenital heart disease n = 1 • Cardiac pacemaker n = 1 • No known cardiac disease n = 3 Valve replacement: PVE was a risk factor for having valve replacement (risk ratio 1.61, p = 0.0099)
Calderwood et al. 1986	Case series/review 1975 to 1982 USA n = 116 with PVE	n = 76/116 (64%) complicated PVE[14] Mortality n = 27 (23%) during initial hospitalisation Significantly lower with coagulase-negative staphylococci (OR < 1) Complications: • 89 discharged

[12] Defined as relapse caused by the same organism or as in-hospital death.
[13] Resumption of clinical picture of endocarditis in the first 6 months after treatment, an infecting organism of the same genus and species, no change in underlying cardiac condition.
[14] Complicated PVE was defined as infection associated with any of the following; a new or increasing murmur of prosthetic valve dysfunction; new or worsening CHF related to dysfunction of the prosthesis; fever for 10 or more days during antibiotic therapy; new or progressive abnormalities of cardiac condition.

		• 71 had mild or no CHF • 13 moderate CHF • n = 5 severe CHF Relapse: n = 11 (12%) (not significantly affected by valve site or infecting organism)
Habib et al. 2005	Consecutive case series January 1991 to March 2003 France n = 104 with PVE	Mortality: n = 22 (21%) died in-hospital 32 month mean follow-up; n = 61 (58%) survival Significantly associated with in-hospital mortality; severe comorbidity (p = 0.05), renal failure (p = 0.05), moderate-to-severe regurgitation (p = 0.006), staphylococcal infection (p = 0.001), occurrence of any complication (p = 0.05) Predictors of in-hospital death; severe heart failure (OR 5.5, 95% CI 1.9 to 16.1), *S. aureus* infection (OR 6.1, 95% CI 1.9 to 19.2) Complications: Similar between early and late endocarditis
Sett et al. 1993	Retrospective review 1975 to 1988 Canada n = 3200 with porcine bioprosthesis	PVE incidence: n = 56/3200 (1.8%) Mortality overall n = 18 (32%): • early PVE 75% • late PVE 25%[15] Predictors of death; renal status, presence of ongoing sepsis, mode of treatment, presence of

[15] Early endocarditis was within 60 days of surgery, late was after 60 days.

		fever, previous dental procedure, lack of dental prophylaxis, time to diagnosis, age > 65 years ($p < 0.05$)
		Predictors of early death; renal status ($p < 0.05$), mode of treatment ($p < 0.05$), time to diagnosis ($p < 0.04$), age ($p < 0.05$)
Hricak et al. 1998	National survey 1992 to 1996 Slovakia n = 180 NVE	Mortality: n = 40 (22.2%), n = 140 survival at day 60 Risk factors for death; age > 60 years ($p = 0.05$), vascular phenomenon (emboli, infarct, bleeding), infection with viridans streptococci ($p < 0.03$) or staphylococci ($p < 0.002$), three or more positive blood cultures ($p < 0.05$)
Verheul et al. 1993	Consecutive case series 1966 to 1991 The Netherlands n = 130	Mortality: 91 (90%) survived the hospital phase Mean follow-up 8.7 years, 64 (63%) survived, of these 45 did not have recurrent endocarditis or valve replacement Complications: Heart failure (RR 47.6, 95% CI 9.1 to 249.0) and aortic valve endocarditis (RR 3.0, 95% CI 1.7 to 14.3) were associated with a high risk for urgent surgery or death or both
Ishiwada et al. 2005	Case series/ (registered by professional body) 1997 to 2001 Japan	Mortality: n = 20 (10.6%), highest mortality < 1 year old (n = 5/16, 31.3%) Complications: Occurred in 67%; no significant difference in complications between causative organisms

	n = 188 paediatric and adults with CHD	
Martin et al. 1997	Retrospective review 1958 to 1992 USA n = 73 paediatric patients	Mortality: 13 (18%) died during initial hospitalisation Complications: • 30 (41%) recovered with no complications • 30 (41%) had complications

Evidence statements

Prosthetic valve endocarditis and native valve endocarditis are associated with high rates of in-hospital mortality.

Patients with prosthetic valve endocarditis have higher rates of in-hospital mortality compared with those with native valve endocarditis.

Evidence to recommendations

The Guideline Development Group (GDG) discussed the evidence presented and considered that the numbers involved for specific types of congenital heart disease, acquired valvular disease and those previously having IE in the included studies were small and therefore drawing conclusions about the relative risk of developing IE was not possible.

The GDG debated the potential for confusion that can arise from stratification of risk groups, with uncertainty having been identified in knowing how to treat those who are identified as being in groups of intermediate risk. Given the difficulties in relative risk definition, the GDG decided that a simple classification of conditions into either at risk or not at risk groups would assist with clarity. However, the GDG also considered it important to acknowledge that patients with different cardiac conditions may not be at the same risk of developing IE. This was identified with particular relevance to patients with prosthetic valves who are known to be at a higher risk.

At risk groups were agreed using the evidence presented and the expertise within the GDG to achieve consensus.

The GDG considered that where cardiac conditions were not associated with a risk of developing IE it was appropriate not to offer prophylaxis against IE for interventional procedures.

The impact of the underlying cardiac conditions on the outcomes of IE was discussed by the GDG. The focus of the discussion was on the difference in mortality rates identified between prosthetic and native valve endocarditis. The GDG noted that those with prosthetic valves have increased rates of mortality and morbidity when compared to those with other underlying cardiac conditions. However, irrespective of underlying cardiac condition, the GDG noted the overall high levels of morbidity and mortality associated with IE. The GDG further discussed, irrespective of underlying cardiac condition, the impact of the causative organism with specific reference to those with enterococcal and staphylococcal endocarditis. Following analysis of the evidence and further discussion, the GDG did not consider that a separate recommendation on the need for prophylaxis against IE could be made on the basis of different outcomes between cardiac conditions.

2.2 Bacteraemia: interventional procedures and infective endocarditis

2.2.1 Introduction

Infective endocarditis (IE) is a rare condition and as such it is difficult to determine which interventional procedures (dental and other) are associated with an increased incidence of IE in those with defined preexisting cardiac conditions (see section 2.1 ‘People with cardiac conditions and their risk of developing infective endocarditis’). Consideration in this area has therefore become dependent on the premise that certain interventional procedures cause a bacteraemia. These transient bacteraemias are usually eradicated naturally in healthy people; however those with certain conditions may be at risk of this bacteraemia leading to the development of IE. Consideration also has to be given to the fact that transient bacteraemias arise spontaneously

with normal daily activities such as chewing or toothbrushing (Moreillon et al. 2004). These transient bacteraemias are likely to contribute to the large proportion of cases of IE that occur without a history of specific dental or non-dental interventional procedures (as many as 60–75% of cases) (Steckelberg and Wilson 1993).

Experimental animal models have shown that bacteraemia can cause IE. However, the intensity of bacteraemia used has been very high when compared with that detected in both adults and children following interventional dental procedures (Roberts 1999). Therefore it is important to determine whether there is any evidence of a level of postprocedure bacteraemia that can be considered to be significant in terms of the pathogenesis of IE – that is, a threshold level that is considered to result in risk of developing IE.

It is also important to consider the organisms that cause bacteraemia following interventional procedures and that, in certain cases, lead to the development of IE. A population-based study that collected data in the Netherlands during a 2-year period identified the following groups of organisms in cases of BE: viridans streptococci (n = 200/419, 48%), staphylococci (n = 124/419, 30% – *S. aureus* n = 91, other staphylococci n = 33), enterococci (n = 40/419, 10%), haemolytic streptococci (n = 17/419, 4%), pneumococci (n = 5/419, 1%), other (n = 33/419, 8%). Thus the three most common organisms reported as causing IE are viridans streptococci, staphylococci and enterococci.

The groups of interventional procedures considered in this guideline are those set out in the guideline scope (appendix 1): dental, upper and lower gastrointestinal (GI) tract, genitourinary (GU) tract and upper and lower respiratory tract procedures.

2.2.2 Existing guidelines

Interventional procedures

Dental procedures: the AHA guideline (Wilson et al. 2007) discussed case reports/reviews that identified a dental procedure having been undertaken

prior to the diagnosis of IE (often 3 to 6 months). This guideline also noted that it cannot be assumed that manipulation of a healthy-appearing mouth or a minimally invasive dental procedure reduces the likelihood of a bacteraemia. Many existing guidelines have discussed the importance of good oral health in reducing the risk of endocarditis (Gould et al. 2006; Horstkotte et al. 2004; Advisory Group of the British Cardiac Society Clinical Practice Committee 2004). The ESC (Horstkotte et al. 2004) and BCS/RCP (Advisory Group of the British Cardiac Society Clinical Practice Committee 2004) guidelines included this alongside discussion noting the assumption that dental procedures are associated with a risk of developing IE.

Non-dental procedures: the AHA guideline (Wilson et al. 2007) noted that conclusive links have not been demonstrated between respiratory tract procedures and IE and that for GI and GU tract procedures the possible association with IE has not been studied extensively. The BSAC guideline (Gould et al. 2006) noted that there are no good epidemiological data on the impact of bacteraemia from non-dental procedures on the risk of developing endocarditis. The ESC guideline (Horstkotte et al. 2004) identified bacteraemia associated with respiratory, GI and GU procedures. The BCS/RCP guideline (Advisory Group of the British Cardiac Society Clinical Practice Committee 2004) considered that evidence for significant bacteraemia after many GI, GU, respiratory or cardiac procedures had not been proven, though it noted that cases of IE have been reported to follow these procedures.

Bacteraemia

There are conflicting views as to the significance of bacteraemia caused by interventional procedures in existing clinical guidelines. The AHA, ESC and BSAC guidelines noted that transient bacteraemia does not just follow dental (and other) procedures but also occurs after routine oral activities such as toothbrushing, flossing and chewing gum (Wilson et al. 2007; Gould et al. 2006; Horstkotte et al. 2004). The AHA guideline (Wilson et al. 2007) also noted that few published studies exist on the magnitude of bacteraemia after a dental procedure or from routine daily activities, and most of the published

data used older, often unreliable microbiological methodology. Furthermore, the BSAC guideline (Gould et al. 2006) highlighted that the significance of both the magnitude and duration of bacteraemia is unknown. In contrast, the BCS/RCP guideline (Advisory Group of the British Cardiac Society Clinical Practice Committee 2004) considered that the risk of developing IE is probably directly related to the frequency and severity of bacteraemia that occurs with each individual procedure.

2.3 Interventional procedures associated with risk of developing infective endocarditis

2.3.1 Overview

A nationwide prospective study of the epidemiology of bacterial endocarditis (BE) was completed in the Netherlands; this study considered antecedent procedures and use of prophylaxis (van der Meer et al. 1992b). There were two case–control studies identified that considered preceding events and procedures in the cases that had developed IE and compared these with control groups. In one of the studies, cases and controls were distributed into three groups of underlying cardiac conditions; native valve disease, prosthetic valve or no known cardiac disease (Lacassin et al.1995). In the other study the cardiac status of the control group was unknown (Strom et al. 2000; Strom et al. 1998[16]). One case series considered a 28-year trend of IE associated with congenital heart disease (Takeda et al. 2005). A further paper used a survey of 2805 adults, applied the results to the adult population and estimated the risk of endocarditis with predisposing cardiac conditions undergoing dental procedures with or without antibiotic prophylaxis (Duval et al. 2006).

[16] One study reported in two papers, one for dental procedures and one for oral hygiene and non-dental procedures.

2.3.2 Dental and other interventional procedures associated with risk of infective endocarditis in people with defined preexisting cardiac conditions

Evidence review

The study (Level 2+) completed in the Netherlands (population 14.5 million) considered the epidemiology of bacterial endocarditis (BE), using all suspected cases of bacterial endocarditis (based on blood cultures) over a 2-year period (van der Meer et al. 1992b). Of the 427 suspected cases, 149 (34.9%) had undergone a procedure[17] within 180 days of the onset of symptoms, with 89 (20.8%) having undergone a procedure for which prophylaxis was indicated. Endocarditis due to α-haemolytic streptococci in those with NVE appeared to be associated with known heart disease, natural dentition and recent dental procedures, with endocarditis occurring 4.9 times more often in those with all three factors compared with those without any (RR 4.9, 95% CI 2.8 to 8.7).

A French case–control study (Level 2+) interviewed 171 people following diagnosis of IE[18] and the same number of matched controls (matched for age, sex and group of underlying cardiac conditions) (Lacassin et al. 1995). Eighty eight (51.5%) of the cases and 70 (41%) of the controls had undergone at least one procedure[19]. Adjusted OR for the risk of IE related to a procedure was 1.6 (95% CI 1.01 to 2.53, $p < 0.05$). For all procedures, the mean number of procedures was significantly higher in cases than controls (4.5 versus 2.0, $p < 0.05$). The risk of IE increased with the number of procedures per case, RR 1.2 for one procedure, 1.7 for two procedures, 3.6 for three or more procedures ($p = 0.005$).

Any dental procedure (including dental extraction) showed no increased risk with cases compared with controls. Any urological procedure and any GI procedure also showed no increased risk with cases compared with controls. Multivariate analysis showed that only infectious episodes (OR 3.9; 95% CI

[17] The questionnaire listed procedures for which antibiotic prophylaxis is needed, according to the recommendations of the Netherlands Heart Foundation.
[18] Information reported in the interviews was verified with the cited practitioner.
[19] Interviewees were asked regarding all procedures involving cutaneous and mucosal surfaces within the previous 3 months.

2.1 to 7.3, $p < 0.05$) and skin wounds (OR 3.9; 95% CI 1.6 to 9.6, $p < 0.05$) contributed significantly and independently to the risk of IE (variables included extraction, scaling, root canal treatment, urological, GI and surgical procedures, skin wounds and infectious episodes).

A population based case–control study (Level 2+) that considered dental risk factors (Strom et al. 1998) and the risk factors of oral hygiene and non-dental procedures (Strom et al. 2000) was undertaken in the USA. There was one control for each case (273 of each) matched for age, sex, ethnicity, education, occupation and dental insurance status; controls were selected from the community for each case patient using a modified random-digit method.

Dental procedures: 16.8% of cases and 14.3% of controls had dental treatment in the 2 months before the study date and 23% of both groups had dental treatment in the 3 months before the study date. Tooth extraction, in the 2 months before hospital admission, was the only dental procedure significantly associated with IE ($p = 0.03$, although numbers were small – 6 cases and 0 controls). Compared with their controls, the 56 cases who were infected with dental flora showed no significant increased risk with dental treatment.

Oral hygiene: no association was found between IE and the frequency of routine dental care within the previous year, toothbrushing or use of toothpicks.

Other conditions and procedures: urinary tract infections and skin infections were not significantly related to endocarditis, although when restricted to cases (and matched controls) who were infected with skin flora the OR for skin infections increased to 6.0 (95% CI 1.3 to 27, $p = 0.019$). Following multivariate analysis, only barium enema remained significant, OR 11.9 (95% CI 1.34 to 106, $p = 0.026$), (not significantly different were pulmonary procedures, lower GI endoscopy, upper GI endoscopy, gynaecological surgery, urinary catheterisation, other genitourinary, cardiac procedure, other surgery, intravenous therapy and nasal-oxygen therapy).

A Japanese case series (Level 3) considered a 28-year trend of IE associated with congenital heart disease (Takeda et al. 2005). Preceding events were documented in 61 out of 183 patients. These events were dental procedures in 38 cases (21%), atopic dermatitis in 3 (2%) and 'other' in 10 (5%).

A French study (Level 3) considered the estimated risk of endocarditis in adults with predisposing cardiac conditions (PCC) undergoing dental procedures with or without antibiotic prophylaxis (Duval et al. 2006). The authors discussed the difficulties of identifying a clear relationship between the onset of IE and preceding dental procedures and, to contribute to the debate, offered an estimate of the risk. The risk was estimated using the formula: risk = annual number of IE cases after at-risk dental procedures in adults with known PCC /annual number of at-risk dental procedures in adults with known PCC The prevalence of PCC was 104 native valve and 24 prosthetic valve conditions. Twelve of the 15 dental procedures were unprotected (that, is the patient did not receive antibiotic prophylaxis); two of the four dental procedures on patients with prosthetic valves were unprotected). Applying these to the French population of 1999 showed an estimate of a known PCC in 3.3% (n = 1,287,296; 95% CI 2.6 to 4%) of the 39 million adults, with a rate of 2.1 procedures per subject per year (with 62% performed without antibiotic prophylaxis). Of 182 cases of IE, 12 occurred in adults with known PCC after dental procedures and were considered to be caused by an oral microorganism (n = 10 unprotected). The estimated risk of IE after dental procedure in adults with known PCC was 1 case per 46,000 (95% CI 36,236 to 63,103) for unprotected dental procedures; 1 case per 54,300 (95% CI 41,717 to 77,725) for unprotected dental procedures in those with native valve PCC; 1 case per 10,700 (95% CI 6000 to 25,149) for unprotected dental procedures in those with prosthetic valve PCC; 1 case per 149,000 (95% CI 88,988 to 347,509) for protected dental procedures.

Evidence statement

For dental and non-dental procedures the studies showed an inconsistent association between recent interventional procedures and the development of infective endocarditis.

2.4 Levels of bacteraemia associated with interventional procedures and everyday activities

2.4.1 Overview

The basis for many of the decisions that have been made regarding which procedures merit antibiotic prophylaxis is the assumption that the bacteraemia that arises following interventional procedures is a key part of the causative process in the development of infective endocarditis (IE). Therefore searches were completed to identify studies that considered the levels of bacteraemia associated with interventional procedures; this included dental procedures and non-dental interventional procedures. Randomised controlled trials (RCTs) were identified for bacteraemia related to dental procedures; however, for bacteraemia related to other procedures the majority of the studies used an uncontrolled case series study design.

Nine of the studies identified considered bacteraemia related to dental procedures. These included six RCTs, all of which involved children attending hospitals in London for a variety of dental procedures (Lucas et al. 2000; Lucas et al. 2002; Roberts et al. 2000; Roberts et al. 2006; Roberts et al. 1997; Roberts et al. 1998). The majority of studies included considered bacteraemia levels at one or two time points following the procedure; one study considered the duration of bacteraemia following dental extraction (Roberts et al. 2006). There was also a controlled study in children requiring dental extractions (Peterson et al. 1976), a case series that considered bacteraemia following dental extraction in adults and children (Tomas et al. 2007) and a retrospective theoretical analysis that considered the records of children with congenital disease having dentogingival procedures (Al Karaawi et al. 2001). A brief description of an abstract relating to tooth extraction, use of antibiotics and toothbrushing has also been included (Lockhart et al. 2007).

Seventeen studies considered bacteraemia related to GI procedures. There were also two controlled studies that considered bacteraemia related to upper endoscopic procedures (Sontheimer et al.1991; Zuccaro et al.1998). The remaining studies were predominantly case series studies (Barawi et al. 2001;

Barragan Casas et al. 1999; el Baba et al.1996; Ho et al. 1991; Kullman et al. 1992; Lo et al. 1994; London et al. 1986; Low et al. 1987; Melendez et al. 1991; Mellow and Lewis 1976; Roudaut et al. 1993; Shull et al. 1975; Shyu et al. 1992; Weickert et al. 2006).

There was little evidence from which to draw conclusions relating to bacteraemia caused by urological, gynaecological and respiratory tract procedures. Six studies were included: an RCT that considered preoperative enema effects on prostatic ultrasound (Lindert et al. 2000), a case series that considered bacteraemia during caesarean delivery (Boggess et al. 1996), a case series on extracorporeal shock wave lithotripsy (Kullman et al. 1995), a case series on bacteraemia during nasal septoplasty (Silk et al. 1991), a case series on bacteraemia related to fibreoptic bronchoscopy (Yigla et al. 1999) and a case series on bacteraemia during tonsillectomy (Lucas et al. 2002).

Evidence review

Dental

Six RCTs (Level 1+) considered paediatric patients referred for dental treatment at hospitals in London. One considered 155 people referred for cleaning procedures under general anaesthetic (52 in a toothbrushing group, 53 in a professional cleaning group, 50 in a scaling group) and a control group of 50, using data taken from a previous study (Lucas et al. 2000). There was no significant difference in the number of positive blood samples, or the intensity of bacteraemia between the study groups. The bacteria isolated from the blood cultures were similar.

A second study (Level 1+) considered 142 patients undergoing general anaesthesia receiving treatment in four groups: upper alginate impression, separator, fit/placement of band and archwire adjustment (Lucas et al. 2002). There was no significant difference in the number of positive blood cultures between baseline and the dentogingival manipulations (taken 30 seconds after the procedure). The mean total number of aerobic and anaerobic bacteria isolated from the blood samples was significantly greater following the placement of a separator ($p < 0.02$); there was no significant difference

between baseline and an upper alginate impression or placement of a band or archwire adjustment.

The largest RCT (Level 1+) considered 735 children (non-manipulation group, cleaning procedures, minimal manipulation group, conservative dentistry procedures, oral surgery group and the group having antibiotic prophylaxis) (Roberts et al. 1997). All procedures were associated with a bacteraemia: the highest association was found with intraligamental injection, the lowest was with a fast drill. A comparison of proportions of bacteraemia compared with baseline showed the following significant differences: toothbrushing 12.8 compared with 45.4%, polishing teeth 0.7 compared with 29.4%, scaling teeth 14.0 compared with 47.2%, intraligamental injection 76.9 compared with 97.3%, rubber dam placement 4.8 compared with 35.1%, matrix band placement 7.4 compared with 38.0%, single extraction 12.5 compared with 45.9%, multiple extractions 24.2 compared with 58.6% and mucoperiosteal flap 13.4 compared with 46.2%. No significant differences were identified with dental examination, nasotracheal tube, slow drill and fast drill.

One RCT (Level 1+) considered bacteraemia associated with conservative dentistry in 257 children in five groups; rubber dam placement, slow drill, fast drill, matrix band and wedge, and a baseline group having no procedure (Roberts et al. 2000). Positive blood cultures were identified at baseline in (9.3%), rubber dam placement (31.4%), slow drill (12.2%), fast drill (4.3%) and matrix band and wedge (32.1%). There were significant differences in the number of positive cultures between the following groups: baseline versus rubber dam placement ($p < 0.005$), baseline versus matrix band ($p < 0.003$), rubber dam placement versus slow drill ($p < 0.02$), rubber dam placement versus fast drill ($p < 0.001$), slow drill versus matrix band ($p < 0.02$), fast drill versus matrix band ($p < 0.0001$). There were no significant differences between: baseline versus slow drill; baseline versus fast drill; rubber dam placement versus matrix band; slow drill versus fast drill. There was no significant difference between any of the groups in the intensity of bacteraemia.

A further RCT (Level 1+) considered bacteraemia following local anaesthetic injections in 143 children (Roberts et al. 1998). Positive blood cultures were identified in baseline (8.0%), buccal infiltration (15.6%), modified intraligimental (50.0%) and conventional intraligamental (96.6%). There were significant differences between baseline versus modified intraligamental ($p < 0.0001$), baseline versus conventional intraligamental ($p < 0.0001$), buccal infiltration versus modified intraligamental ($p < 0.003$), buccal infiltration versus conventional intraligamental ($p < 0.0001$) and modified intraligamental versus conventional intraligamental ($p < 0.0001$). There was no significant difference between baseline versus buccal injection.

The final RCT (Level 1+) considered the duration of bacteraemia in 500 children after dental extraction (Roberts et al. 2006). The children were allocated to time groups, which ranged from 10 seconds to 1 hour. The intensity of bacteraemia (colony-forming units [CFU]/6 ml sample) showed significant differences in the median measures before extraction and after extraction at 10 seconds ($p = 0.001$), 30 seconds ($p = 0.001$), 1 minute ($p = 0.003$), 2 minutes ($p = 0.009$), 4 minutes ($p = 0.002$) and 7.5 minutes ($p = 0.002$). The differences were not significant for the median before extraction and after extraction at 15-minute, 45-minute and 1-hour time points[20]. The odds of having a positive culture were significantly greater in the postextraction time than the preextraction time (OR > 1) at each time point up to and including a postprocedure time of 7.5 minutes, but not after this.

A controlled trial (Level 2+) in the USA considered the incidence of bacteraemia in 107 paediatric patients following tooth extraction (Peterson et al. 1976). This study had four groups: group I, extraction of healthy teeth for reasons other than disease; group II, removal of teeth that had diseased or necrotic pulps and associated abscesses; group III, removal of permanent teeth for orthodontic reasons; and group IV, restorative dental treatment, which served as a negative control. Positive cultures were identified in 35.7% of people in group I, 52.9% in group II, 61.1% in group III and there were no positive cultures identified in the control group, group IV. There was no

[20] The 30-minute difference was not determined due to a lack of difference between before and after procedure values.

significant correlation found between the number of teeth extracted and the postprocedural blood culture.

One case series (Level 3) considered bacteraemia in adults and children at three time points following dental extractions in 53 patients in Spain (Tomas et al. 2007). At baseline 9.4% had positive blood cultures, at 30 seconds it was 96.2%, at 15 minutes it was 64.2% and at 1 hour it was 20%. At 15 minutes the following were not significantly related to bacteraemia: age, levels of plaque and calculus, presence of periodontal pockets, dental mobility, number of decayed teeth, presence of submucosal abscesses and/or periapical lesions and number of teeth extracted. None of the variables showed significant association with bacteraemia at the 1-hour time point.

A retrospective theoretical analysis (Level 3) considered children with severe congenital heart disease and dentogingival manipulative procedure. This study considered theoretical calculated cumulative exposure derived from the following equation: intensity[21] x tally[22] x prevalence[23] x duration[24] = cumulative exposure in CFU/ml/procedure/year (Al Karaawi et al. 2001). The greatest cumulative exposure was for the placement of a rubber dam with clamps, followed by multiple extractions (primary and permanent), mucoperiosteal surgery, polishing teeth, local anaesthetic infiltration, matrix band placement, dental examination, fast drill, scaling, slow drill, single extraction of a permanent tooth, and single extraction of a primary tooth.

An abstract has been presented of a double-masked RCT with 290 participants that considered the production of bacteraemia with endocarditis-related pathogens in three groups: tooth extraction with antibiotic (amoxicillin), tooth extraction with placebo, and toothbrushing (Lockhart et al. 2007). The incidence of bacteraemia was: toothbrushing group (32%), antibiotic group (56%) and placebo group (80%), $p < 0.0001$. However, the toothbrushing and amoxicillin groups and the amoxicillin and placebo groups were similar to each other in the incidence of some bacterial pathogens reported to cause IE.

[21] Number of colony forming units (CFU)/ml blood.
[22] Average number of a given dentogingival manipulative procedure performed annually.
[23] The number of positive cultures expressed as a proportion.
[24] Length of bacteraemia, which is 15 minutes.

The placebo group had a significantly greater number of positive cultures at 20 minutes (18%) compared with the amoxicillin (4%) and toothbrushing (10%) groups. The authors of this abstract concluded that, given the nature, incidence, duration and daily occurrence of bacteraemia, toothbrushing may represent a greater risk for IE than invasive dental procedures.

Gastrointestinal

Two controlled studies (Level 2+) were identified: the first considered bacteraemia in 120 patients following operative upper GI endoscopy, with a control group of 40 who had diagnostic endoscopy with or without sample biopsies (Sontheimer et al. 1991). This study identified that bacteraemia occurred significantly more frequently in operative endoscopies compared with diagnostic endoscopies ($p < 0.05$). A second controlled study considered bacteraemia in 103 of those with dysphagia having upper GI endoscopy and stricture dilation with a control group of 50 patients without dysphagia undergoing upper GI endoscopy for reasons unrelated to swallowing disorders (Zuccaro et al. 1998). Streptococcal bacteraemia occurred in 21.4% ($n = 22/103$) after stricture dilation compared with 2% ($n = 1/50$) in the control group, $p = 0.001$. Bacteraemia decreased over time; 23% had positive blood cultures after stricture dilation at 1 minute, compared with 17% at 5 minutes and 5% at 20 to 30 minutes. There was no significant difference in the rate of streptococcal bacteraemia among those with the presence or absence of periodontal disease.

Case series (Level 3): there were 14 case series studies identified related to GI procedures. These case studies considered bacteraemia following interventional gastrointestinal procedures. However, the majority analysed only one or two postprocedure blood culture time points. Therefore assessment of the duration of intervention related bacteraemia is difficult.

Table 6 Bacteraemia associated with interventional procedures

Reference	No. of patients	Procedure	Outcomes
Barawi et al. 2001	100	Endoscopic ultrasound guided fine needle aspiration	No significant bacterial growth not considered related to contaminants Follow-up 1 week no infectious complications
Barragan Casas et al. 1999	102	n = 44 gastroscopy n = 30 colonoscopy n = 28 endoscopic retrograde cholangiopancreatography (ERCP)	Gastroscopy – positive cultures, n = 8 at 5 minutes, n = 6 at 30 minutes Colonoscopy – positive cultures, n = 3 at 5 minutes, n = 1 at 30 minutes ERCP – positive cultures, n = 4 at 5 minutes, n = 9 at 30 minutes
el Baba et al. 1996	95 children	n = 68 oesophagastroduodenoscopy n = 29 colonoscopy n = 11 flexible sigmoidoscopy	n = 4 post endoscopy blood cultures were positive, none were indigenous oropharyngeal or GI flora Follow-up 72 hours after procedure those with positive culture were afebrile and without any evidence of sepsis
Ho et al. 1991	72	n = 36 emergency endoscopy n = 36 sclerotherapy groups	Emergency endoscopy n = 5 postprocedure positive blood cultures Sclerotherapy – elective endoscopic variceal sclerotherapy (EVS) n = 5, emergency EVS n = 10 postprocedure positive blood cultures No significant differences between the postendoscopy positive blood cultures, no significant difference within groups for the sclerotherapy groups, there was a difference

			within the emergency endoscopy group for the pre and postcultures, p = 0.03
Kullman et al. 1992	180	n = 115 diagnostic ERCP n = 65 therapeutic ERCP	15% of diagnostic and 27% of therapeutic procedures had bacteraemia within 15 minutes, no significant difference between the groups Follow-up 4 to 26 months no bacteraemic patients developed clinically overt endocarditis
Lo et al. 1994	105	n = 50 endoscopic injection sclerotherapy (EIS) n = 55 endoscopic variceal ligation (EVL)	17.2% of the EIS group had positive blood cultures compared with 3.3% in the EVL group, p < 0.03 Infectious complications were bacterial peritonitis, empyema and pneumonia
London et al. 1986	50	Colonoscopy	In two cases the positive culture was considered to be directly related to the colonoscopy
Low et al. 1987	270	n = 165 colonoscopy only n = 105 colonoscopy plus polypectomy	Colonoscopy only 4.1% blood cultures were positive at 10 or 15 minutes, polypectomy group 3.6% positive at 30 seconds, 5 or 10 minutes, there was no significant difference between the groups Follow-up, no patients developed clinical evidence of sepsis during the 24 hours following the procedure
Melendez et al. 1991	140	Transoesophageal echocardiography (TOE)	Positive blood cultures in n = 2 within 5 minutes and n = 2 at 1 hour, the relative risk of bacteraemia immediately after and 1 hour after TOE were not

			significantly different from baseline, no correlation between positive blood cultures and difficulty in intubation or presence of an indwelling intravenous line Follow-up 12 weeks no patients had developed BE or other infections requiring the administration of therapy
Mellow and Lewis 1976	100	Upper GI endoscopy	Positive blood cultures in n = 3 after endoscopy, no correlation between associated medical conditions, GI lesions, or endoscopic manipulation and postendoscopy bacteraemia Follow-up, none of those with bacteraemia had any detectable symptoms of subsequent sepsis
Roudaut et al. 1993	82	TOE	2.4% had a single positive blood culture Follow-up, average 4 months, no signs of endocarditis detected
Shull et al. 1975	50	Upper GI endoscopy	Bacteraemia detected in 8% at 5 or 30 minutes, no blood samples taken during the procedures were positive Follow-up of those with positive cultures showed no clinical manifestations of bacteraemia
Shyu et al. 1992	132	TOE	None of the blood samples taken immediately after the procedure were positive, n = 1 patient had positive cultures 4 hours after the procedure Follow-up, no evidence of endocarditis in these patients

Weickert et al. 2006	100	n = 50 conventional laparoscopy n = 50 mini laparoscopy	n = 4 cultures taken immediately after laparoscopy were positive, there was no difference identified between those with and without positive cultures Follow-up, none of the patients developed fever or other signs of infection in the follow-up

Other procedures

There were six studies identified that considered bacteraemia related to other interventional procedures, one RCT (Level 1+) and five case series (Level 3). The RCT considered bacteraemia after transrectal ultrasound guided prostate biopsy; one group had a preoperative enema (n = 25) and the other did not (n = 25) (Lindert 2000). Eight people (16%) had positive blood cultures after biopsy, enteric flora were identified in five people (seven who did not have the enema and one who did, p = 0.0003 for the difference). There was no correlation between positive blood cultures with patient age, history of dysuria and/or urinary tract infection (UTI), prostate-specific antigen (PSA), number of biopsies, obstructive voiding symptoms, prostate volume, cancer, or postbiopsy haematuria or voiding symptoms.

Case series (Level 3) (see table 7)

Table 7 Bacteraemia associated with interventional procedures

Reference	Number of patients	Procedure	Blood cultures
Boggess et al. 1996	93	Caesarean delivery	14% bacteraemia after labour or rupture of membranes Positive blood cultures were associated with earlier median gestational age at delivery (< 32 weeks, OR 13.9; 3.5 to 54.8), lower median birth weight (< 2500 g, OR 10.5; 2.8 to 39) and positive chorioamnionic membrane culture (OR 6.4; 1.7 to 24.7)
Kullman et al. 1995	76	Extra corporeal shock wave lithotripsy (ESWL)	Positive blood cultures during ESWL n = 16, after 5 minutes n = 12, after 20 minutes n = 6, after 18 hours n = 3 During follow-up no patients developed sepsis or clinically overt endocarditis
Silk et al. 1991	50	Nasal septoplasty	None of the blood cultures showed bacterial growth
Yigla et al. 1999	200	Fibreoptic bronchoscopy	13% (n = 26) positive blood cultures, n = 13 at 0 and 20 minutes, n = 13 at 20+ minutes. Defining true bacteraemia as those cases in which two postprocedure cultures yielded the same organism decreased the bacteraemia to 6.5%

			Indications for bronchoscopy, macroscopic findings, size of bronchoscope, and rate of invasive procedures did not differ between those with positive cultures and those without
Yildirim et al. 2003	64	Tonsillectomy	27.3% of blood cultures taken within 2 minutes of tonsillectomy were positive, 6.5% of those taken at 15 minutes, difference p = 0.027 Follow-up, the patients with bacteraemia did not have any clinical signs/symptoms of a serious infection

Significant bacteraemia

A number of the papers addressed the intensity of bacteraemia and differences between levels of intensity in the procedures studied, notably in the studies by Roberts et al. on dental procedures. However, consideration of what would be considered significant bacteraemia associated with dental or other interventional procedures was not defined in the studies. The two studies that did classify the bacteraemia did not use similar categories. One controlled study (Ho et al. 1991) did categorise positive blood cultures based on previous studies; into significant and non-significant – these categories were dependent on the microorganisms isolated and related numbers of positive cultures. A second controlled study (Sontheimer et al. 1991) used their evaluation criteria to classify the results into certain or questionable bacteraemia and contamination.

Levels of bacteraemia associated with everyday activities

There were studies identified that considered bacteraemia associated with toothbrushing. Toothbrushing was found to have no significant difference in

the prevalence and intensity of bacteraemia when compared with other cleaning methods, professional cleaning and scaling (Lucas et al. 2000). Similarly toothbrushing was identified as having significant increases in the percentage of positive blood cultures alongside other non-everyday activities such as, polishing teeth, scaling teeth, intraligamental injection, rubber dam placement, matrix band placement, single extraction, multiple extractions and mucoperiosteal flap (Roberts et al. 1997). One further study considered a comparison of transient bacteraemia between brushing with a conventional toothbrush and with an electric toothbrush (Bhanji et al. 2002). Toothbrushing was associated with positive blood cultures in 46% of manual toothbrush users and in 78% of those using the electric toothbrush ($p = 0.022$). No studies were identified that considered levels of bacteraemia associated with other everyday dental activities.

It is important to note that no studies were identified that looked at whether non-dental everyday activities (for example urination or defaecation) were associated with bacteraemia.

Evidence statements

Bacteraemia occurs spontaneously and is also caused by toothbrushing and the following interventional procedures:

- *dental*
- *GI*
- *urological*
- *obstetric*
- *respiratory*
- *ear, nose and throat (ENT).*

There is no evidence to link level, frequency and duration of bacteraemia with the development of infective endocarditis.

Evidence to recommendations

The GDG noted that the evidence presented shows an inconsistent association between having a dental or non-dental interventional procedure and the development of IE. Accordingly, the evidence does not show a causal

relationship between having an interventional procedure and the development of IE.

In consideration of the overall applicability of the evidence presented, the GDG noted that it is difficult to directly compare the level of bacteraemia that has been identified as associated with dental and non-dental procedures owing to the use of different methodologies across the bacteraemia studies. Nonetheless, the GDG concluded that bacteraemia is associated with interventional procedures, toothbrushing and also occurs spontaneously with physiological activity (many included studies reported bacteraemia in preprocedural blood samples).

The GDG also considered that there are difficulties with the concept of significant bacteraemia as there is no evidence to link level, frequency and duration of bacteraemia to the development of IE in those undergoing interventional procedures.

The GDG discussed the evidence related to bacteraemia associated with everyday oral activity, with specific relation to toothbrushing, alongside the bacteraemia associated with dental procedures. The GDG agreed with the concept that an everyday oral activity – regular toothbrushing – must represent a much greater risk of IE than a single dental procedure because of the repetitive exposure to bacteraemia with oral flora during the process of daily dental care. The GDG therefore considered that it was biologically implausible that a dental procedure would lead to a greater risk of IE than regular toothbrushing.

Further discussion within GDG dealt with the organisms that have been implicated in the pathogenesis of IE and the most likely source of their origin, with particular reference to oral streptococci, staphylococci and enterococci. The GDG's consensus was that it was important to consider the impact of enterococcal causation of IE because the outcomes for those who develop IE from this organism may be poor (enterococci are inherently more resistant to antibiotics, with an increase having been identified in the frequency of

antimicrobial resistant strains of enterococci to penicillins, vancomycin and aminoglycosides [Wilson et al. 2007]).

The GDG agreed that the evidence presented did identify bacteraemia arising from a range of non-dental interventional procedures (though as was identified for dental procedures, studies also reported bacteraemia in preprocedural blood samples). The GDG concluded that as cases of IE occur with blood cultures positive to organisms that occur in the GU and GI tracts, then it logically follows that IE may occur following bacteraemias that arise from non-dental interventions. The GDG also discussed the possibility of bacteraemias arising from non-oral everyday activities and the lack of an available evidence base relating to this. Their view was that there is no current proof to support or refute the hypothesis that activities such as defaecation or urination or other everyday activities cause a background level that might account for bacteraemias and may therefore be significant in the development of IE.

Recommendation statement

The GDG considered that recommendations on prophylaxis against IE could not be made solely based on the evidence relating to whether interventional procedures were associated with IE and the presence of postinterventional procedure bacteraemia. The evidence concerning antibiotic effectiveness, the health economic evidence and the health economic model needed to be incorporated into the decision making. Thus the recommendations are presented following a review of this evidence in section 2.5.

2.5 Antibiotic prophylaxis to prevent infective endocarditis

2.5.1 Introduction

Criteria for antibiotic prophylaxis against infection[25] have been developed and these include the following: the health benefits must outweigh the antibiotic

[25] Antibiotic prophylaxis may be defined as the use of an antimicrobial agent before any infection has occurred for the purpose of preventing a subsequent infection (Brincat et al. 2006).

risks, the choice of antibiotic should be made on the single microorganism most likely to cause an infection, and the cost–benefit ratio must be acceptable (Pallasch 2003).

Whether antibiotic prophylaxis is effective in reducing the incidence of infective endocarditis (IE) when given before an interventional procedure is a question for which there is limited available evidence. Thus the efficacy of antibiotic prophylaxis in the prevention of IE remains controversial (Prendergast 2006). The difficulty in determining whether antibiotics can reduce the incidence of a rare event (IE) has led to the use of postprocedure bacteraemia as a surrogate outcome measure in some studies of antibiotic effectiveness. A further problem is that the efficacy of prophylactic antibiotics is based on experimental studies done using animal models (Moreillon et al. 2004) and there are significant concerns that such models are not comparable with the pathophysiology of IE in humans. In addition, it is important to consider the risks of causing serious adverse events, in particular anaphylaxis, when antibiotics are given for prophylaxis.

Other methods of antimicrobial prophylaxis have also been proposed for dental procedures, notably the use of topical oral antimicrobials, although there has also been concern that their routine use may provoke the selection of resistant microorganisms (Brincat et al. 2006).

Existing guidelines

Existing guidelines identified the gaps and inconclusive nature of the evidence available relating to antibiotic prophylaxis, although there is more evidence available for dental than for non-dental procedures. They also identified a lack of prospective, randomised RCTs on the efficacy of antibiotic prophylaxis to prevent IE. The AHA guideline (Wilson et al. 2007) noted that some studies reported that antibiotics administered prior to a dental procedure reduced the frequency, nature and/or duration of bacteraemia whereas others did not. The BSAC guideline (Gould et al. 2006) commented on the need for a prospective double-blind study to evaluate the risk/benefit of prophylactic antibiotics, but also noted that this is unlikely to be undertaken due to the numbers of patients

that would be required and while guidelines continue to recommend prophylaxis. The ESC guideline (Horstkotte et al. 2004) discussed that antibiotic prophylaxis may not be effective in preventing bacterial endocarditis if the amount of bacteraemia in terms of colony forming units (CFU) is very large. These guidelines assessed and discussed the available evidence and reached conclusions that ranged in emphasis with the AHA taking an approach that would involve fewer patients than previously getting antibiotic prophylaxis, while the BCS/RCP (Advisory Group of the British Cardiac Society Clinical Practice Committee 2004) continued to recommend antibiotic prophylaxis for many dental and non-dental procedures.

Contradictory evidence and conclusions were identified regarding topical antiseptics. The AHA guideline considered that the body of evidence showed no clear benefit (Wilson et al. 2007); the BCS/RCP guideline (Advisory Group of the British Cardiac Society Clinical Practice Committee 2004) advised the use of chlorhexidine as an oral rinse, although it did note that recent work has questioned its effectiveness.

2.5.2 Overview

There are only a small number of studies that provide any evidence on the effect of antibiotic prophylaxis in those at risk of developing IE. There were seven studies identified; these included a Cochrane review that considered penicillins for prophylaxis against bacterial endocarditis in dentistry (Oliver et al. 2004). A study that considered the epidemiology of bacterial endocarditis identified those who had developed endocarditis who had and had not had antibiotic prophylaxis (van der Meer et al. 1992b). There were two case–control studies that considered procedures associated with IE (Lacassin et al. 1995) and risk factors for endocarditis (Strom et al. 2000); these studies also identified and discussed antibiotic prophylaxis. The third case–control paper reviewed was the one included in the Cochrane review (van der Meer et al. 1992a). An observational study considered two groups: those who had and those who had not received prophylaxis (Horstkotte et al.1987). A study that estimated the risk of IE considered the potential impact with 100% prophylaxis (Duval et al. 2006).

Recommendation number 1.1.2

Healthcare professionals should offer people at risk of infective endocarditis clear and consistent information about prevention, including:

- the benefits and risks of antibiotic prophylaxis, and an explanation of why antibiotic prophylaxis is no longer routinely recommended
- the importance of maintaining good oral health
- symptoms that may indicate infective endocarditis and when to seek expert advice
- the risks of undergoing invasive procedures, including non-medical procedures such as body piercing or tattooing.

Recommendation number 1.1.3

Antibiotic prophylaxis against infective endocarditis is not recommended:

- for people undergoing dental procedures
- for people undergoing non-dental procedures at the following sites[26]:

– upper and lower gastrointestinal tract

– genitourinary tract; this includes urological, gynaecological and obstetric procedures, and childbirth

– upper and lower respiratory tract; this includes ear, nose and throat procedures and bronchoscopy

[26] The evidence reviews for this guideline covered only procedures at the sites listed in this recommendation. Procedures at other sites are outside the scope of the guideline (see appendix 1 for details).

Recommendation number 1.1.4

Chlorhexidine mouthwash should not be offered as prophylaxis against infective endocarditis to people at risk of infective endocarditis undergoing dental procedures.

Recommendation number 1.1.5

Any episodes of infection in people at risk of infective endocarditis should be investigated and treated promptly to reduce the risk of endocarditis developing.

Recommendation number 1.1.6

If a person at risk of infective endocarditis is receiving antimicrobial therapy because they are undergoing a gastrointestinal or genitourinary procedure at a site where there is a suspected infection, the person should receive an antibiotic that covers organisms that cause infective endocarditis.

2.5.3 Antibiotic prophylaxis given to those at risk before a defined interventional procedure

Evidence review

Procedures

There was a Cochrane review (Level 1++) completed on penicillins for the prophylaxis of bacterial endocarditis (BE) in dentistry (Oliver et al. 2004). This review aimed to determine whether prophylactic penicillin administration compared with no such administration or placebo before invasive dental procedures in people at risk of BE influences mortality, serious illness or endocarditis incidence. This review did not search specifically for papers on harms from the doses of amoxicillin. This review included one case–control study (van der Meer et al. 1992a – reviewed separately below). This review

assessed the odds of developing endocarditis in those receiving prophylaxis compared with those not receiving prophylaxis and identified an odds ratio that was not significant for any of the groupings. This review concluded that it is unclear whether antibiotic prophylaxis is effective or ineffective against bacterial endocarditis in people at risk who are about to undergo an invasive dental procedure.

A case–control study (Level 2+) completed in the Netherlands considered the efficacy of antibiotic prophylaxis for the prevention of NVE (van der Meer et al. 1992a). Cases were 48 patients with known cardiac disease in whom endocarditis developed within 180 days of a medical or dental procedure. Two hundred randomly selected controls were age matched and had undergone a medical or dental procedure with an indication for prophylaxis within 180 days of the interview. The use of prophylaxis was similar between cases (17%) and controls (13%). For procedures within 180 days and within 30 days of onset of symptoms the OR was not significantly different between the two groups[27].

A case–control study (Level 2+) of cases and matched controls for procedures associated with IE in adults (Lacassin et al. 1995) considered the protective efficacy of antibiotics. Eight cases of IE had occurred in those who had received an appropriate antibiotic prophylaxis: four with prosthetic valves and four with native valves. Procedures included multiple extractions (n = 3), scaling (n = 3), ENT procedure (n = 1) and urthrocystoscopy (n = 1). Among those with known heart disease who had a dental procedure (n = 48), six (23%) of the cases and six (27%) of the controls had received appropriate antibiotics (the authors considered protective efficacy to be 20%).

Bacteraemia

The epidemiology of bacterial endocarditis study (Level 2+) considered the use of antibiotic prophylaxis (van der Meer et al. 1992b). Antibiotic prophylaxis was administered to 16.7% (n = 8/48) of those with a native valve condition who were known to have heart disease (six of these people received

[27] The authors consider that the stratified OR of 0.51 for cases with first-time endocarditis and a procedure within 30 days of onset seems to provide the best estimate of the risk reduction obtained with prophylaxis, on the assumption that the incubation period is 30 days. The protective effect of prophylaxis is 49%, this is not significant.

antibiotics in accordance with the Netherlands Heart Foundation guidelines). In the cases where endocarditis developed despite prophylaxis, the bacteria were not resistant to the administered antibiotics. Prophylaxis was given to 56.3% (n = 9/16) of those with prosthetic valves (one person received antibiotics in accordance with the Netherlands Heart Foundation guidelines; the antibiotics administered to the other patients could be considered to offer equivalent protection).

A population-based case–control study (Level 2+) that considered risk factors for IE (Strom et al. 1998) identified that 2.2% of cases and 0.7% of controls received antibiotic prophylaxis within 1 month of the study date; 5.1% and 8.8% within 2 months; and 1.1% and 1.1% within 3 months. Adjustment for this in the multivariate analysis (restricting analysis of dental procedures to those who did not have prophylaxis) did not substantively change the results. For participants with cardiac valvular abnormalities who had dental treatment, the risk of IE remained the same regardless of the use of prophylaxis.

An observational study (Level 2+) compared patients in whom diagnostic and therapeutic procedures were performed using antibiotic prophylaxis (n = 229) with those who had undergone a procedure requiring endocarditis prophylaxis without having received any antibiotics (n = 304) (Horstkotte et al. 1987). In those who received prophylaxis no cases of PVE were observed, whereas in those who had not received prophylaxis there were six cases, an incidence of 1.5 cases per 100 procedures (urological procedures 5.1%, oropharyngeal surgery 2.6%, gynaecological interventions 2.2%). Two cases of PVE occurred in 117 dental procedures done without prophylaxis.

One study (Level 3) estimated that if antibiotics had been administered in 100% of dental procedures in patients with a known PCC in France in 1999 (that is, 2.7 million administered antibiotic courses – 2,228,545 for those with native valve conditions and 517,829 for those with prosthetic valve conditions) 41 cases (95% CI 29 to 53) of IE would have been prevented in those with native valve conditions and 39 cases (95% CI 11 to 72) would have been prevented in those with prosthetic valve predisposing cardiac conditions (Duval et al. 2006).

Evidence statement

There is insufficient evidence to determine whether or not antibiotic prophylaxis in those at risk of developing infective endocarditis reduces the incidence of IE when given before a defined interventional procedure (both dental and non-dental).

2.5.4 Oral chlorhexidine prophylaxis given to those at risk before a defined interventional procedure

Evidence review

There were no studies identified in the searches that considered the impact of oral chlorhexidine in those at risk of developing IE when used before a defined interventional (dental) procedure.

Evidence statement

There is no evidence to determine whether or not oral chlorhexidine prophylaxis in those at risk of developing infective endocarditis reduces the incidence of infective endocarditis when given before a dental interventional procedure.

2.5.5 Effect of antibiotic prophylaxis on the level and duration of bacteraemia

Evidence review

Dental procedures

There were nine studies that addressed antibiotic prophylaxis and dental procedures (Diz et al. 2006; Lockhart et al.2004; Hall et al. 1993, 1996a, 1996b; Roberts et al. 1987, 2002; Wahlman et al. 1999; Shanson 1985).

A Spanish RCT (Level 1+) with 221 participants compared groups who were given amoxicillin (2 g), clindamycin (600 mg) or moxifloxacin (400 mg) taken orally 1 to 2 hours before anaesthesia induction with a control group, for adult patients undergoing dental extractions under general anaesthetic (Diz et al. 2006). There was a significant difference in the proportion of polymicrobial blood cultures in the control group (29%) versus amoxicillin (0%) and versus moxifloxacin (14.8%).

Table 8 Effect of antibiotic prophylaxis on the level and duration of bacteraemia

Bacteraemia	Amoxicillin	Clindamycin	Moxifloxacin	Control	Differences
Baseline	5%	12.5%	7.5%	9.4%	Significant differences all postprocedure time points: • control versus amoxicillin • control versus moxifloxacin • amoxicillin versus clindamycin • moxifloxacin versus clindamycin
30 seconds	46.4%	85.1%	56.9%	96.2%	
15 minutes	10.7%	70.4%	24.1%	64.2%	
1 hour	3.7%	22.2%	7.1%	20%	

A US RCT (Level 1+) with 100 participants compared amoxicillin elixir (50 mg/kg) with a placebo taken 1 hour before intubation in children having dental treatment in the operating room (Lockhart et al. 2004). Eight blood draws were taken: D1, after intubation prior to treatment; D2, after restorative treatment and cleaning; D3, 10 minutes later as a baseline before dental extraction; D4, 90 seconds after initiation of the first extraction; D5, following the extraction of the remaining teeth; D6, 15 minutes after the end of extraction; D7, 30 minutes after the end of extraction; D8, 45 minutes after the end of extraction. The overall incidence of bacteraemia from all eight blood draws was greater in the placebo group than the amoxicillin group (84% versus 33%, $p < 0.0001$). There was a significant decrease in the incidence of bacteraemia with amoxicillin at all but one draw. D5 had the greatest decrease: 15% amoxicillin versus 76% placebo, $p < 0.0001$. Logistic regression analysis suggested that the incidence of bacteraemia associated with extraction blood draws increases with the age of the participant ($p = 0.025$) and the number of teeth extracted ($p = 0.002$) and also that the use of amoxicillin significantly reduced the incidence of bacteraemia ($p = 0.03$). Analysis for the intubation blood draw also showed that amoxicillin significantly reduced bacteraemia ($p = 0.03$).

Details of the remaining six studies are given in table 9.

Table 9 Effect of antibiotic prophylaxis on the level and duration of bacteraemia

Reference	Study type	Antibiotics	Bacteraemia	Differences
Hall et al. 1993	Contr-olled trial n = 60	Penicillin (2 g) Amoxicillin (3 g) Placebo Orally 1 hour before dental extraction Level 1+	Preprocedure: no growth During extraction: • 90% penicillin • 85% amoxicillin • 90% placebo 10 minutes after surgery: • 70% penicillin • 60% amoxicillin • 80% placebo	No significant difference in the incidence or magnitude of bacteraemia, viridans streptococci, or anaerobic bacteria among the three groups at any time point
Hall et al. 1996a	RCT n = 38	Erythromycin stearate (0.5 g) clindamycin (0.3 g) Orally 1 hour prior to dental extraction Level 1+	Preprocedure: no growth During extraction: • 79% erythromycin • 84% clindamycin 10 minutes extraction: • 58% erythromycin • 53% clindamycin	No significant difference in total bacteraemia, bacteraemia with viridans streptococci or anaerobic bacteraemia between the two groups at any time point
Hall et al. 1996b	RCT n = 39	Cefaclor (0.5 g x 2) placebo (x2) Orally 1 hour before dental extraction Level 1+	Preprocedure: no growth During extraction: • 79% cefaclor (streptococci 79%) • 85% placebo • (streptococci 50%)	

			10 minutes after extraction: • 53% cefaclor (streptococci 26%) • 47% placebo (streptococci 30%)	
Roberts et al. 1987	RCT n = 108	Amoxicillin (50 mg/kg) control group Orally 2 hours before surgery Level 1+	Preprocedure: samples negative 2 minutes after intubation: • n = 0/47 amoxicllin • n = 3/47 control Postextraction; • n = 1/47 amoxicllin • n = 18/47 control	Postextraction; control versus amoxicillin, $p < 0.001$
Wahlmann et al. 1999	RCT n = 59	Cefuroxime (1.5 g) placebo (0.9% NaCl) IV 10 minutes before multiple tooth extractions Level 1+	10 minutes: • 23% cefuroxime • 79% control 30 minutes: • 20% cefuroxime • 69% control 10 or 30 minutes: • 33% cefuroxime • 86% control	Cefuroxime versus placebo significant at 10 minutes, 30 minutes and 10 or 30 minutes Duration of surgical procedure was not significant
Shanson 1985	RCT	Erythromycin (1.5 g) matched placebo	Streptococcal bacteraemia;	Erythromycin versus control,

n = 109 side effects study	Orally 1 hour before dental extraction	- 15% erythromycin - 43% control	p = 0.01
n = 82 bacte-raemia study	Level 1+	Side effects - 52% erythromycin versus - 19% placebo	

A retrospective analysis (Level 2+) was undertaken to consider the efficacy of prophylactic intravenous antibiotic regimens in the prevention of odontogenic bacteraemia in 92 children with severe congenital heart defects receiving dental treatment under general anaesthetic (Roberts and Holzel 2002). All of the children received intravenous antibiotic drugs immediately upon attainment of anaesthesia. Ampicillin (n = 42/92) and teicoplanin and amikacin (n = 35/92) were the major antibiotics used. There was no significant difference in the positive blood cultures between these two groups.

Evidence statements

Antibiotic prophylaxis does not eliminate bacteraemia following dental procedures but some studies show that it does reduce the frequency of detection of bacteraemia post procedure.

It is not possible to determine the effect of antibiotic prophylaxis on the duration of bacteraemia.

Non-dental procedures

Nine studies were identified relating to non-dental procedures and antibiotic prophylaxis. These included seven RCTs related to transurethral prostatectomy (Allan and Kumar 1985), transrectal prostatic biopsy (Brewster 1995) endoscopic retrograde cholangiopancreatography (ERCP) (Niederau 1994 et al.; Sauter et al. 1990) transcervical resection or laser ablation of the endometrium (Bhattacharya et al.1995) and sclerotherapy (Rolando et al.

1993; Selby et al. 1994). Also identified were a meta-analysis that considered antibiotic prophylaxis with ERCP (Harris et al. 1999) and a systematic review that considered antibiotic prophylaxis with transurethral resection of the prostate (TURP) (Qiang et al. 2005).

Table 10 non-dental procedures and antibiotic prophylaxis

Reference	Study type	Antibiotics	Bacteraemia	Differences
Allan and Kumar 1985	RCT n = 100	Mezlocillin (2 g) Control group IV at about the time of induction of anaesthesia Level 1+	Bacteraemia postoperation: • 4% mezlocillin • 36% control	Postoperation: mezlocillin versus control, $p < 0.001$ First day postoperation and after catheter removal no significant difference between the groups
Brewster 1995	RCT n = 111	Cefuroxime (1.5 g) Piperacillin/tazobactam IV 20 minutes before procedure Level 1+	Bacteraemia 48 hours: • n = 1 cefuroxime • n = 0 piperacillin/tazobactam	
Bhattacharya et al. 1995	RCT	Augmentin 1.2 g Control group IV at the induction of anaesthesia Level 1+	Bacteraemia immediately following procedure: • 2% augmentin • 16% control	$p < 0.02$
Rolando et al. 1993	RCT n = 97 (n = 115	Imipenem/cilastatin Dextrose-saline control IV Level 1+	Early bacteraemia: • 1.8% imipenem/cilastatin • 8.6% control	No significant difference between the groups

	proce-dures)			
Sauter et al. 1990	RCT n = 96 (n = 100 proce-dures)	Cefotaxime 2 g Control group IV 15 minutes before procedure Level 1+	Bacteraemia during and 5 minutes after: • 2% cefotaxime • 16% control	p < 0.02
Selby et al. 1994	RCT n = 31 (n = 39 proce-dures)	Cefotaxime 1 g Control group IV immediately before procedure Level 1+	Bacteraemia 5 minutes: • n = 1 cefotaxime • n = 5 control 4 hours: • n = 2 control 24 hours: • n = 0 either group	
Niederau et al. 1994	RCT n = 100	Cefotaxime (2 g) Control group IV 15 minutes before endoscopy Level 1+	Bacteraemia, 15 and 30 minutes: • n = 0 cefotaxime • n = 4 controls	

A meta-analysis was completed (Level 2+), which included seven RCTs that were placebo controlled and considered antibiotic prophylaxis in ERCP (Harris et al. 1999). Of these seven studies, four reported bacteraemia, the relative risk (RR) for those receiving antibiotics compared with those receiving placebo was not significant.

The systematic review (Level 2+) considered antibiotic prophylaxis for TURP in men with preoperative urine containing less than 100,000 bacteria per ml;

this included 28 studies (10 placebo controlled, 18 with no treatment control group) (Qiang et al. 2005). This review found that antibiotic prophylaxis significantly decreased the frequency of postoperative bacteraemia (4.0% versus 1.0%) in 10 placebo or no treatment control trials, risk difference −0.20 (95% CI −0.28 to −0.11).

Evidence statements

Antibiotic prophylaxis does not eliminate bacteraemia following non-dental procedures but some studies show that it does reduce the frequency of detection of bacteraemia post procedure.

It is not possible to determine the effect of antibiotic prophylaxis on the duration of bacteraemia.

2.5.6 Oral chlorhexidine prophylaxis to reduce the level and duration of bacteraemia

Evidence review

Six studies were identified that considered the use of oral chlorhexidine with dental procedures and the effect on bacteraemia. There were three RCTs that considered chlorhexidine with control/placebo (Brown et al. 1998; Lockhart 1996; Tomas et al. 2007), two RCTs that considered chlorhexidine and other oral topical rinses (Rahn et al. 1994; Jokinen 1978) and one case–control study (MacFarlane et al. 1984).

The first RCT (Level 1+) considered intraoral suture removal in 71 patients who needed the removal of a third molar, which would require at least eight sutures (Brown et al. 1998). Chlorhexidine 0.12% was used as a preprocedural rinse with a no-treatment control group. Pretreatment blood samples were negative. Samples taken 90 seconds following suture removal had positive cultures in 4 out of 31 in the chlorhexidine group and 2 out of 24 in the control group; there was no significant difference between the groups.

The second RCT (Level 1+) considered the use of chlorhexidine hydrochloride 0.2% rinse for 30 seconds, repeated 1 minute later compared with a placebo rinse in adults having single tooth extractions (Lockhart 1996). There was no

significant difference between the 1 minute or 3 minute samples either in incidence of blood cultures or between the chlorhexidine and the placebo groups.

The third RCT (Level 1+) included 106 adults and children undergoing dental extractions under general anaesthetic and a comparative control group. Following intubation, the treatment group had their mouths filled with 0.2% chlorhexidine digluconate for 30 seconds (Tomas et al. 2007). At baseline 9% in the chlorhexidine and 8% in the control group had positive blood cultures. There were significant differences between the bacteraemia rates in the chlorhexidine and the control groups at all time points; 30 seconds 79% versus 96% ($p = 0.008$); 15 minutes 30% versus 64% ($p < 0.01$); 1 hour 2% versus 20% ($p = 0.005$). The risk of bacteraemia after dental extraction at 30 seconds was a factor of 1.21 (95% CI 1.04 to 1.40) higher in the control group; at 15 minutes this was 2.12 (95% CI 1.34 to 3.35); and at 1 hour it was 10 (95% CI 1.32 to 75.22).

The fourth RCT (Level 1+) compared 0.2% chlorhexidine with 10% povidone-iodine and with a sterile water control, injected into the sulcus of the affected tooth with an endodontic syringe in 120 people having treatment involving either intraligamental injection or elective extraction of a molar (Rahn et al. 1994). Preprocedure blood samples were negative. Postprocedure bacteraemia was identified in 18 cases (45.0%) with chlorhexidine, 11 (27.5%) with povidone-iodine and 21 (52.5%) in the control group. The difference between the povidone-iodine and the control groups was significant ($p < 0.05$).

A fifth study (Level 1+) of 152 people used four prophylactic regimens: rinsing with 1% iodine solution, operative field isolation, operative field isolation and disinfection with 10% iodine, and operative field isolation with 0.5% chlorhexidine solution. Participants were included for cleaning of the mouth or because of acute symptoms in the mouth or periodontal tissues that indicated a need for dental extraction (Jokinen 1978). Positive cultures were found in 21 cases (55%), with iodine mouth rinses, 13 (34%), with operative field isolation, 12 (32%) with operative field isolation and iodine, and five (13%)

with operative field isolation and chlorhexidine. A significant difference ($p = 0.05$) was found between operative field isolation and iodine and operative field isolation and chlorhexidine.

The case–control paper (Level 2+) considered the effect on the incidence of postextraction bacteraemia of irrigating the gingival crevice with three groups of participants: 1% chlorhexidine, 1% povidone-iodine and normal saline (20 participants in each group) (MacFarlane et al. 1984). Preextraction blood cultures were negative. Postextraction positive cultures were found in five of the chlorhexidine group, eight of the povidone-iodine group and 16 of the saline control group. This difference was significant for both chlorhexidine compared with control ($p < 0.001$) and for povidone-iodine compared with control ($p < 0.01$). Differences between chlorhexidine and povidone-iodine were not significant.

Evidence statements

Oral chlorhexidine used as an oral rinse does not significantly reduce the level of bacteraemia following dental procedures.

2.5.7 Rates of adverse events (in particular, anaphylaxis) in those taking antibiotic prophylaxis

The studies included in this review that considered antibiotic prophylaxis against IE did not adequately report rates of adverse events or identify any episodes of anaphylaxis. Published rates of serious adverse events following antibiotic use are considered in the following section.

Health economics

Published health economics literature

A literature review was conducted to identify cost-effectiveness evidence on antimicrobial prophylaxis against IE in individuals with a predisposing cardiac condition undergoing interventional procedures. To identify economic evaluations, the NHS Economic Evaluation Database (NHS EED) and the Health Economic Evaluations Database (HEED) were searched. Search filters to identify economic evaluations and quality of life studies were used to

interrogate bibliographic databases (MEDLINE). There were no date restrictions imposed on the searches.

A total of five relevant studies were identified that considered both costs and outcomes. All studies, aside from that by Caviness and coworkers (Caviness et al. 2004), considered only dental procedures. In addition, only Caviness and coworkers modelled a paediatric population. Only one UK based study was identified (Gould and Buckingham 1993). Two US based analyses (Agha et al. 2005 and Caviness et al. 2004) provided outcomes in terms of quality-adjusted life years and took a societal perspective in the estimation of costs. All studies were quality assessed and data abstracted into evidence tables (see appendix 6.7 for full details).

Gould and Buckingham (1993) examined the cost effectiveness of penicillin prophylaxis in UK dental practice to prevent IE. The authors estimated that out of a total of 482 deaths due to IE (the mean figures from population data for the years 1985 and 1986), 15% (72.3) of deaths were after dental procedures. Of these, it was assumed that 60% were the result of 'high-risk' procedures. The authors further assumed that penicillin was entirely effective in reducing the risk of developing IE following a dental procedure, although in sensitivity analyses the effectiveness of antibiotic prophylaxis was reduced to 50%. Costs were calculated from an inspection of the notes of 63 patients who had had IE in Grampian over the decade 1980–90. Costs of a stay in hospital, valve replacement operations and outpatient visits were supplied by the health authority. The authors also aimed to take account of the lifetime costs for survivors. The cost-effectiveness of penicillin prophylaxis for high-risk patients undergoing procedures other than extractions was £1 million per life saved. It was found that prophylaxis for dental extractions saved lives and reduced overall costs versus no prophylaxis.

Agha and coworkers (Agha et al. 2005) developed a decision model that included a Markov subtree (for the estimation of long-term outcomes) to evaluate the cost effectiveness of antibiotic prophylaxis in US adults aged 40 undergoing a dental procedure. In their hypothetical population, all patients had native heart valves and met the then latest AHA (American Heart

Association) criteria for endocarditis prophylaxis, based on the presence of underlying cardiac conditions associated with moderate or high risk of endocarditis, and were to undergo an invasive dental procedure as defined by the AHA criteria. The model considered eight antibiotic prophylaxis strategies, including no antibiotics.

Patients entering the Markov subtree of the Agha model could exist in one of four states: 1) patients who did not develop endocarditis and those that recovered without any complications; 2) patients with valve replacement; 3) patients with congestive heart failure and valve replacement; and 4) dead. The cycle length was 1 year. Utility estimates for these long-term health states were derived from the Beaver Dam Health Outcomes study. (Fryback et al. 1993). This study assessed health related quality of life through the use of the Short-form 36 and Quality of Well-being index in US cohort.

The authors assumed that all the considered antibiotics were equally effective and, from four case–control studies, estimated a pooled odds ratio for the risk of developing endocarditis following prophylaxis of 0.46 (95% CI 0.2 to 1.1). For the base case analyses, Agha and coworkers used this pooled odds ratio as a measure of the RR. During sensitivity analyses, the RR was varied between 0.09 and 1.0. The base case probability of developing IE following an unprotected ‘high-risk’ dental procedure (preventive procedures, oral surgery, and endodontic procedures) was estimated to be 22 per million procedures.

Under base case assumptions the authors found that for a hypothetical cohort of 10 million patients, 119 cases of BE would be prevented using antibiotic prophylaxis. Each prophylactic strategy was compared with no antibiotics only. In the base case, oral clarithromycin and oral cephalexin were associated with incremental cost effectiveness ratios (ICERs) of US$88,000 and US$99,000 per QALY respectively. Oral and parenteral clindamycin, and parenteral cefaxolin were dominated strategies. Oral amoxicillin and parenteral ampicillin resulted in a net loss of lives secondary to fatal anaphylaxis which was estimated to occur in 20 per million patients receiving a dose of these antibiotics. Oral amoxicillin and parenteral ampicillin were consequently dominated by a strategy of giving no antibiotics.

A number of sensitivity analyses were undertaken and these included varying the baseline risk of developing IE following an unprotected dental procedure. When the probability of developing IE following an unprotected dental procedure was doubled (it was assumed that this represented the risk status of patients with prior endocarditis), ICERs ranged from US$38,000 to US$200,000 per QALY gained. Again oral amoxicillin and parenteral ampicillin were dominated by a strategy of giving no antibiotics. It was assumed that patients with prosthetic valves had a four-fold greater risk of developing IE. When this assumption was included in the model, ICERs ranged from US$14,000 (oral cephalexin) to US$498,000 (parenteral ampicillin) per QALY gained. Agha and coworkers conclude that predental antibiotic prophylaxis is cost-effective only for people with a moderate or high risk of developing endocarditis. Clarithromycin should be considered the drug of choice and cefalexin (a cephalosporin) as an alternative drug of choice.

The studies by Devereux and coworkers (Devereux et al. 1994) and Clemens and Ransohoff (Clemens and Ransohoff 1984) considered the impact of antibiotic prophylaxis in patients with mitral valve prolapse undergoing dental procedures.

Clemens and Ransohoff compared oral and parenteral penicillin regimens with no prophylaxis. Their analysis estimated a risk of postdental endocarditis in MVP of only 4.1 cases per million procedures, which was outweighed by a greater risk of fatal anaphylaxis following parenteral penicillin (15 deaths per million courses). For oral penicillin, the risk of fatal anaphylaxis was estimated to be 0.9 deaths per million courses. However, it was only found to spare life in older adults with MVP (50 years and older) at a cost of greater that US$1.3 million per spared year of life.

Devereux and coworkers (Devereux et al. 1994) assessed three prophylactic options for patients with MVP with or without a mitral regurgitant murmur: oral amoxicillin, oral erythromycin and intravenous or intramuscular ampicillin. Their analysis estimated that amoxicillin and ampicillin would have an efficacy of 80% and erythromycin of 60%. Severe allergic reactions to oral amoxicillin were estimated to occur with a frequency of 0.9 per million patients. For

intravenous ampicillin, this was assumed to be higher: 15 per million. As per the study by Clemens and Ransohoff, Devereux and coworkers estimated a cost per year of life saved and took into account of the costs of chronic sequelae of IE. It was found that the cost effectiveness of antibiotic prophylaxis for all MVP patients ranged from US$20,000 per year of life saved for the oral regimens to a net loss of life using intravenous ampicillin secondary to fatal anaphylaxis. In a sensitivity analysis that restricted the population to MVP patients with systolic murmur, average cost effectiveness ratios for the oral regimens were around US$3000; the cost per life year saved for IV ampicillin versus no prophylaxis was around US$800,000.

Caviness and coworkers (Caviness et al. 2004) examined a paediatric population of children aged 0 to 24 months who had moderate-risk cardiac lesions requiring bacterial endocarditis prophylaxis, and who presented to an emergency department with fever. The analysis considered the risk of developing bacterial endocarditis following urinary catheterisation. According to AHA guidelines at that time, moderate-risk cardiac lesions include most congenital cardiac malformations, acquired valvular dysfunction, hypertrophic cardiomyopathy, and mitral valve prolapse with valvular regurgitation and/or thickened leaflets. Only two antibiotics were considered in this study – amoxicillin and vancomycin – and these were assumed to be equally effective in preventing bacteraemia. The model relied on adult data to a large extent due to an apparent paucity of evidence from paediatric populations. The prophylactic efficacy of antibiotics (assumed to be 89% in both cases) was determined from one trial (Allan and Kumar 1985) and the analyses of Bor and Himmelstein (Bor and Himmelstein 1984) and Clemens and Ransohoff (Clemens and Ransohoff 1984). On the basis of the data presented in the text, unprotected antibiotic prophylaxis leads to approximately seven to eight cases of IE per million children. Quality of life weights were based on the “Years of Healthy Life” Measure (Gold et al. 1998).

The results produced by the Caviness and coworkers model suggests that antibiotic prophylaxis is extremely cost ineffective, and potentially leads to a net loss of life. Excluding antibiotic related deaths, it was found that the cost

effectiveness of amoxicillin was US$10 million per QALY gained (US$70 million per BE case prevented). In the case of vancomycin, the average cost effectiveness of prophylaxis versus no prophylaxis was US$13 million per QALY gained (US$95 million per BE case averted). When the analysis included antibiotic related deaths, the antibiotic strategy was dominated by a policy of no prophylaxis.

In summary, there is contradictory evidence on the cost effectiveness of antibiotic prophylaxis for at-risk patients undergoing interventional procedures. However, it has been commonly observed that penicillin could result in many more deaths (at least in the short term) secondary to anaphylaxis compared with a strategy of no prophylaxis. In addition, the cost effectiveness of antibiotic prophylaxis appears to also critically depend on the baseline risk of developing IE. This might explain why some studies found antibiotic prophylaxis to be cost effective while others (for example Clemens and Ransohoff and Caviness et al.) estimated that prophylaxis would be very cost-ineffective. It is not apparent if any of the economic evaluations took into account the recurring risk of IE and the additional future costs of antibiotic prophylaxis.

De novo economic evaluation

Given the lack of up-to-date, UK relevant analyses, it was considered useful to undertake a de novo analysis. A very simple model was developed to explore the cost-effectiveness of antibiotic prophylaxis for IE in adults with predisposing cardiac conditions undergoing dental procedures. There is a much greater paucity of data in relation to the use of antimicrobial prophylaxis for individuals undergoing other interventional procedures and consequently no separate model was developed in that instance.

In the model, nine antibiotic prophylaxis options were compared against a strategy of no antibiotic prophylaxis. The prophylactic options explored were those set out in the ‘British National Formulary’ 54th edition (Mehta 2007) because they represent current UK practice at the time the guideline was developed. All antibiotic strategies were assumed to be of equal effectiveness. Full details of the modelling are presented in appendix 6.6.

The model suggests that prophylactic antibiotic strategies are not cost effective under all scenarios explored in the present analysis unless optimistic assumptions are made with regard to a number of parameters, chiefly the risk of developing IE following a dental procedure. Sensitivity analysis indicated that the risk of developing IE had to be at least 16 cases per million procedures for the incremental cost per QALY of the lowest cost strategy to lie around £20,000 (50-year time horizon). (All other parameters in the analysis were kept at their base case values.) When the estimated costs and potential benefits of future prophylaxis are included in the analysis, this threshold rises to 48 per million. Even when optimistic assumptions are made with regard to antibiotic efficacy and the risk of developing IE following a dental procedure, the risk of antibiotic side effects (particularly with respect to amoxicillin-containing strategies) can potentially increase the ICERs markedly and even lead to greater deaths through fatal anaphylaxis than a strategy of no antibiotic prophylaxis.

Evidence to recommendations

Dental

The GDG considered that there is insufficient evidence to determine whether or not antibiotic prophylaxis in those at risk of developing IE is effective in reducing the incidence of IE when given before dental procedures. It also noted that cases of IE have been documented in which antibiotic prophylaxis for dental procedures had been given. The GDG discussed that this would be consistent with the findings of the bacteraemia studies that show that prophylactic antibiotics given before a dental procedure reduce, but do not eliminate, post procedural bacteraemia.

The GDG discussed the possible adverse effects of taking antibiotic prophylaxis. They concluded that although antibiotic-related anaphylaxis is a rare event, it is potentially fatal and therefore the possibility of anaphylaxis needs consideration. The occurrence of other adverse effects of antibiotic usage, notably the risk of increasing antibiotic resistance, was also acknowledged.

The GDG felt that regular tooth-brushing almost certainly presents a greater risk of IE than a single dental procedure because of repetitive exposure to bacteraemia with oral flora (see section 2.2). The Group considered that it was biologically implausible that a single dental procedure would lead to a greater risk of IE than regular toothbrushing.

The GDG discussed instances where there is concern about the undertaking of a dental procedure at the site of an oral (or tissue) infection. It was considered that a person will be having repetitive bacteraemias from the infected site with regular toothbrushing. Furthermore, if an antibiotic is being prescribed for the infection this will cover the oral flora involved and therefore will cover any potential IE-causing organisms from this site. Therefore with a recommendation to emphasise the need to promptly treat any infection in those who are at risk of developing IE, further recommendations in this area were not considered necessary.

The GDG considered that the presented cost effectiveness analyses demonstrated that the adverse consequences of penicillin use in patients at risk of IE undergoing dental procedures may be greater than any benefits that might accrue from prophylaxis. In addition the GDG felt that the risk of developing IE following a dental procedure is very much lower than the base case estimates used in a number of the published cost effectiveness studies and possibly also than used in the present de novo analysis. The GDG therefore concluded that offering antibiotic prophylaxis before dental procedures is not clinically beneficial and was associated with a risk of harm (anaphylactic reaction to antibiotics, notably penicillins).

The GDG considered that oral chlorhexidine mouthwash should not be used for prophylaxis against IE because the evidence shows that it does not reduce the frequency of bacteraemia following dental procedures.

The GDG highlighted the importance of oral health in those at risk of IE. The basis for this is the consensus view that maintaining good oral health will lead to a lower magnitude of bacteraemia caused by both everyday activities and

dental procedures. The GDG noted that the maintenance of good oral health would be assisted with an emphasis on preventive dentistry.

Non-dental

The GDG considered that insufficient evidence exists to determine whether or not antibiotic prophylaxis in those at risk of developing IE is effective in reducing the incidence of IE when given before non-dental interventional procedures. The GDG also noted that although the evidence base is limited, those studies that considered non-dental interventional procedures and the development of IE identified no association with GI and GU procedures. The GDG also noted that the findings of the bacteraemia studies show that prophylactic antibiotics given before non-dental procedures reduce, but do not eliminate, post procedural bacteraemia.

The GDG discussed the possible adverse effects of taking antibiotic prophylaxis and the fact that although antibiotic related anaphylaxis is a rare event it is nonetheless potentially fatal when it occurs and therefore the possibility of anaphylaxis needs consideration. The occurrence of other adverse effects of antibiotic usage, notably the risk of increasing antibiotic resistance, was also acknowledged.

The GDG considered that both the lack of available evidence and the heterogeneity of the non-dental interventional procedures listed in the guideline scope precluded a health economic analysis of the use of antibiotic prophylaxis for non-dental procedures.

The GDG considered the rationale for prophylaxis to prevent IE for procedures likely to result in a bacteraemia from organisms usually identified within the oropharyngeal tract, specifically ENT, upper GI tract, and upper respiratory tract procedures and bronchoscopy. The Guideline Development Group considered that the repetitive bacteraemias resulting from regular tooth-brushing will logically present a greater risk of IE than a single ENT, upper GI tract, upper respiratory tract or bronchoscopy procedure because of repetitive exposure to bacteraemia with oral flora.

The GDG considered that there is important evidence present in the dental literature that is absent from the non-dental interventional procedure literature. Specifically, there is a lack of published evidence to support the hypothesis that non-oral daily activities (for example, urination, defaecation and physical exercise) lead to a repetitive exposure to non-oral flora. It is therefore not possible to conclusively argue (as it can be argued for dental procedures) that it is biologically implausible that a single lower GI or urological procedure would lead to a greater risk of IE than regular urination or defaecation.

The GDG noted that increasing numbers of lower GI and GU interventional procedures are being undertaken and a sizeable number of such procedures are carried out annually in the NHS. The GDG considered that if it was likely that these commonly undertaken procedures are consistently associated with the development of IE, then logically there should exist a stronger evidence base than the small number of case reports that offer anecdotal evidence of an association between a prior GI or GU procedure and the development of IE. The GDG also noted that there has been no reported rise in incidence of IE in spite of a considerable increase in GI and GU procedures being undertaken over recent years.

The sizeable number of GI and GU procedures being carried out was also considered to have implications for possible antibiotic adverse effects (notably anaphylaxis), and the possibility that the risk of this would be higher than the risk of developing IE.

The GDG therefore considered that prophylaxis solely against IE is not recommended for lower GI and GU interventional procedures.

The GDG also discussed antibiotic therapy for sites of infection through which a GI or GU procedures may be being undertaken, and agreed that good practice should be for any antibiotic therapy that is being prescribed to cover organisms that have been known to cause IE.

Furthermore, in recognition of the high levels of mortality and serious morbidity associated with IE, the GDG did consider that it was important to

promptly identify and treat of any infections in those who are at risk of IE to reduce any potential for the development of IE.

2.6 Patient perspectives on prophylaxis against infective endocarditis

2.6.1 Introduction

Until publication of the recent AHA (Wilson et al. 2007) and BSAC (Gould et al. 2006) guidelines, antibiotic prophylaxis was universally prescribed to cover dental and other interventional procedures in patients at risk of infective endocarditis (IE). There are, accordingly, a large number of patients with a long history of taking antibiotic prophylaxis against IE for dental procedures for whom it is no longer considered appropriate. The information and support needs for such patients are likely to be significant because they will need to be fully informed about the risks and benefits of antibiotic prophylaxis in order to make an informed decision not to continue to take it. It is, therefore, important to determine if there is any evidence of a detailed understanding of patient (and family/carer) perspectives relating to antibiotics taken specifically for prophylaxis against IE.

2.6.2 Issues that at-risk individuals report as important in relation to prophylaxis against infective endocarditis

Evidence review

The literature search in this area identified 17 studies that considered the current knowledge of patients (or their families) about their cardiac conditions, knowledge about IE and the procedures for which antibiotics are used or attitudes towards dental treatment (Balmer and Bulock 2003; Barreira et al. 2002; Bulat and Kantoch 2003; Cetta and Warne 1995; Cetta 1993a; Cetta 1993b; Chessa et al. 2005; Cheuk et al.2004; da Silva et al. 2002; De Geest et al. 1990; Kantoch et al. 1997; Leviner et al. 1991; Moons et al. 2001; Saunders 1997; Seto et al. 2000; Sholler and Celermajer 1984; Stucki et al. 2003). However, these studies did not consider the specific issues around prophylaxis against IE that patients (and their families/carers) may have. Consequently these papers have not been included.

Evidence to recommendations

The Guideline Development Group (GDG) discussed issues relating to patient perspectives on prophylaxis against IE. The issue of conflicting information being provided by cardiologists, general dental practitioners and general medical practitioners was raised as a potential significant problem. Therefore, the importance of clear and consistent information for patients and families was emphasised by the GDG. The GDG also re-emphasised the need for information and support to help achieve and maintain good oral health.

The GDG further discussed the need for those with defined preexisting cardiac conditions to be made aware that some cases of IE have been associated with interventional procedures and that, accordingly, unnecessary interventions (both medical and non-medical) should not be undertaken.

2.7 Research recommendations

It is noted that infective endocarditis (IE) is a rare condition and that research in this area in the UK would be facilitated by the availability of a national register of cases of IE that could offer data into the ‘case’ arm of proposed case–control studies.

Cardiac conditions and infective endocarditis (see section 2.1)

- What is the risk of developing IE in those with acquired valvular disease and structural congenital heart disease? Such research should use a population-based cohort study design to allow direct comparison between groups and allow estimation of both relative and absolute risk.

Interventional procedures and infective endocarditis (see section 2.3)

- What is the frequency and level of bacteraemia caused by non-oral daily activities (for example, urination or defaecation)? Such research should quantitatively determine the frequency and level of bacteraemia.

3 Glossary and abbreviations

3.1 Glossary

Case–control study

Comparative observational study in which the investigator selects individuals who have experienced an event (for example, developed a disease) and others who have not (controls), and then collects data to determine previous exposure to a possible cause.

Cohort study

(also known as follow-up, incidence, longitudinal, or prospective study): An observational study in which a defined group of people (the cohort) is followed over time. Outcomes are compared in subsets of the cohort who were exposed or not exposed (or exposed at different levels) to an intervention or other factor of interest.

Confidence interval

The range within which the 'true' values (for example, size of effect of an intervention) are expected to lie with a given degree of certainty (for example, 95% or 99%). (Note: confidence intervals represent the probability of random errors, but not systematic errors or bias).

Economic evaluation

Technique developed to assess both costs and consequences of alternative health strategies and to provide a decision making framework.

Guideline Development Group

A group of healthcare professionals, patients, carers and technical staff who develop the recommendations for a clinical guideline. The NICE Short Clinical Guidelines Team recruits the guideline development group, reviews the evidence and supports the guideline development group. The group writes draft guidance, and then revises it after a consultation with organisations registered as stakeholders.

Generalisability

The degree to which the results of a study or systematic review can be extrapolated to other circumstances, particularly routine healthcare situations in the NHS in England and Wales.

Heterogeneity

A term used to illustrate the variability or differences between studies in the estimates of effects.

Odds ratio

A measure of treatment effectiveness. The odds of an event happening in the intervention group, divided by the odds of it happening in the control group. The 'odds' is the ratio of non-events to events.

Quality-adjusted life year (QALY)

A statistical measure, representing 1 year of life, with full quality of life.

Randomised controlled trial

A form of clinical trial to assess the effectiveness of medicines or procedures. Considered reliable because it tends not to be biased.

Relative risk

Also known as risk ratio; the ratio of risk in the intervention group to the risk in the control group. The risk (proportion, probability or rate) is the ratio of people with an event in a group to the total in the group. A relative risk (RR) of 1 indicates no difference between comparison groups. For undesirable outcomes, an RR that is less than 1 indicates that the intervention was effective in reducing the risk of that outcome.

Sensitivity (of a test)

The proportion of people classified as positive by the gold standard who are correctly identified by the study test.

Systematic review

Research that summarises the evidence on a clearly formulated question according to a predefined protocol using systematic and explicit methods to

identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis.

3.2 Abbreviations

AHA	American Heart Association
ASD	Atrial septal defect
BE	Bacterial endocarditis
CFU	Colony-forming units
CHF	Congestive heart failure
CI	Confidence interval
CNS	Central nervous system
EIS	Endoscopic injection sclerotherapy
EVL	Endoscopic variceal ligation
EVS	Endoscopic variceal sclerotherapy
ENT	Ear, nose and throat
ERCP	Endoscopic retrograde cholangiopancreatography
ESWL	Extra corporeal shock wave lithotripsy
GI	Gastrointestinal
GU	Genitourinary
GUCH	Grown-up congenital heart
ICER	Incremental cost effectiveness ratio
IE	Infective endocarditis

IVDU	Intravenous drug user
MVP	Mitral valve prolapse
NVE	Native valve endocarditis
OR	Odds ratio
PCC	Predisposing cardiac conditions
PSA	Prostate-specific antigen
PVE	Prosthetic valve endocarditis
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RR	Relative risk
SE	Standard error
TOE	Transoesophageal echocardiography
TURP	Transurethral resection of the prostate
UTI	Urinary tract infection
VSD	Ventricular septal defect

4 Methods

4.1 Aim and scope of the guideline

4.1.1 Scope

NICE guidelines are developed in accordance with a scope that defines what the guideline will and will not cover (see appendix 1). The scope of this guideline is available from: http://www.nice.org.uk/guidance/index.jsp?action=download&o=37136

The aim of this guideline is to provide evidence-based recommendations to guide healthcare professionals in the appropriate care of people considered to be at risk of infective endocarditis (IE) who may require antimicrobial prophylaxis before an interventional procedure.

4.2 Development methods

This section sets out in detail the methods used to generate the recommendations for clinical practice that are presented in the previous chapters of this guideline. The methods used to develop the recommendations are in accordance with those set out by the National Institute for Health and Clinical Excellence ('NICE' or 'the Institute') in 'The guidelines manual' (2007) (available at: www.nice.org.uk/guidelinesmanual).

4.2.1 Developing the guideline scope

The draft scope, which defined the areas the guideline would and would not cover, was prepared by the Short Clinical Guidelines Technical Team on the basis of the remit from the Department of Health, consultation with relevant experts and a preliminary search of the literature to identify existing clinical practice guidelines, key systematic reviews and other relevant publications. The literature search gave an overview of the issues likely to be covered by the guideline and helped define key areas. It also informed the Short Clinical Guidelines Technical Team of the volume of literature likely to be available in the topic area, and therefore the amount of work required.

The draft scope was tightly focused and covered four clinical topic areas.

The draft scope was the subject of public consultation.

4.2.2 Forming and running the Short Clinical Guideline Development Group

The short clinical guideline on antimicrobial prophylaxis for IE was developed by a Guideline Development Group consisting of 12 members and the Short Clinical Guidelines Technical Team. In addition, 10 co-opted experts were invited to attend part of a Guideline Development Group meeting and prepared a short expert position paper. The Guideline Development Group had a chair, healthcare professional members and patient/carer members who were recruited through open advertisement. The co-opted experts were also recruited, where possible, by open advertisement. A clinical adviser, who had specific content expertise, was also appointed. Development took 4 months and the Guideline Development Group met on three occasions, every 4 to 6 weeks.

4.2.3 Developing key clinical questions

The third step in the development of the guidance was to refine the scope into a series of key clinical questions. The key clinical questions formed the starting point for the subsequent evidence reviews and facilitated the development of recommendations by the Guideline Development Group.

The key clinical questions were developed by the Guideline Development Group with assistance from the Short Clinical Guidelines Technical Team. As necessary, the questions were refined into specific research questions by the project teams to aid literature searching, appraisal and synthesis. The full list of key clinical questions is shown in appendix 6.2.

The Guideline Development Group and Short Clinical Guidelines Technical Team agreed appropriate review parameters (inclusion and exclusion criteria) for each question or topic area. A full table of the included and excluded studies is shown in appendix 6.4.

4.2.4 Developing recommendations

For each key question, recommendations were derived from the evidence summaries and statements presented to the Guideline Development Group.

4.2.5 Literature search

The evidence reviews used to develop the guideline recommendations were underpinned by systematic literature searches, following the methods described in 'The guidelines manual' (National Institute for Health and Clinical Excellence 2007). The purpose of systematically searching the literature is to attempt to comprehensively identify the published evidence to answer the key clinical questions developed by the Guideline Development Group and Short Clinical Guidelines Technical Team.

The search strategies for the key clinical questions were developed by the Information Services Team with advice from the Short Clinical Guidelines Technical Team. Structured clinical questions were developed using the PICO (population, intervention, comparison, outcome) model, and were translated into search strategies using subject heading and free text terms. The strategies were run across a number of databases with no date restrictions imposed on the searches. When required, filters to identify systematic reviews, randomised controlled trials and observational studies were appended to the search strategies to retrieve high quality evidence.

To identify economic evaluations the NHS Economic Evaluation Database (NHS EED) and the Health Economic Evaluations Database (HEED) were searched. Search filters to identify economic evaluations and quality of life studies were used to interrogate bibliographic databases. There were no date restrictions imposed on the searches.

In addition to the systematic literature searches, the Guideline Development Group was asked to alert the Short Clinical Guidelines Technical Team to any additional evidence, published, unpublished or in press, that met the inclusion criteria.

The searches were undertaken between May and September 2007. Full details of the systematic search, including the sources searched and the MEDLINE strategies for each evidence review, are presented in appendix 6.3.

4.2.6 Reviewing the evidence

The aim of the literature review was to systematically identify and synthesise relevant evidence in order to answer the specific key clinical questions developed from the guideline scope. The guideline recommendations were evidence based if possible; if evidence was not available, informal consensus of opinion within the Guideline Development Group was used. The need for future research was also specified. This process required four main tasks: selection of relevant studies; assessment of study quality; synthesis of the results; and grading of the evidence. The Technical Analyst had primary responsibility for reviewing the evidence but was supported by the Project Lead, Information Scientist and Health Economist.

After the scope was finalised, searches based on individual key clinical questions were undertaken. The searches were first sifted by the Short Clinical Guidelines Technical Team using title and abstract to exclude papers that did not address the specified key clinical question. After selection based on title and abstract, the full texts of the papers were obtained and reviewed by the Short Clinical Guidelines Technical Team in order to determine which studies should be included in the literature review. Studies suggested or submitted by the Guideline Development Group and expert advisers were also reviewed for relevance to the key clinical questions and included if they met the inclusion criteria.

The papers chosen for inclusion were then critically appraised by the Short Clinical Guidelines Technical Team for their methodological rigour against a number of criteria that determine the validity of the results. These criteria differed according to study type and were based on the checklists included in 'The guidelines manual' (2007) by NICE (available from www.nice.org.uk/guidelinesmanual). The checklists that were used in this particular guidance included Checklist C for randomised control trials,

Checklist B for cohort studies, Checklist F for diagnostic studies, and Checklist F for qualitative studies.

The data were extracted to standard evidence table templates. The findings were summarised by the Short Clinical Guidelines Technical Team into both a series of evidence statements and an accompanying narrative summary.

4.2.7 Grading the evidence

Intervention studies

Studies that meet the minimum quality criteria were ascribed a level of evidence to help the guideline developers and the eventual users of the guideline understand the type of evidence on which the recommendations have been based.

There are many different methods of assigning levels to the evidence and there has been considerable debate about what system is best. A number of initiatives are currently underway to find an international consensus on the subject. NICE has previously published guidelines using different systems and is now examining a number of systems in collaboration with the NCCs and academic groups throughout the world to identify the most appropriate system for future use.

Until a decision is reached on the most appropriate system for the NICE guidelines, the Short Clinical Guidelines Technical Team will use the system for evidence shown in table 11.

Table 11 Levels of evidence for intervention studies.

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Level of evidence	Type of evidence
1^{++}	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1^{+}	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias[a]

2^{++}	High-quality systematic reviews of case–control or cohort studies High-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2^{+}	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2^{-}	Case–control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal[a]
3	Non-analytic studies (for example, case reports, case series)
4	Expert opinion, formal consensus
[a] Studies with a level of evidence '–' should not be used as a basis for making a recommendation	

It was the responsibility of the Guideline Development Group to endorse the final levels given to the evidence.

4.2.8 Evidence to recommendations

The evidence tables and narrative summaries for the key clinical questions being discussed were made available to the Guideline Development Group 1 week before the scheduled Guideline Development Group meeting.

All Guideline Development Group members were expected to have read the evidence tables and narrative summaries before attending each meeting. The review of the evidence had three components. First, the Guideline Development Group discussed the evidence tables and narrative summaries and corrected any factual errors or incorrect interpretation of the evidence. Second, evidence statements, which had been drafted by the Short Clinical Guidelines Technical Team, were presented to the Guideline Development Group and the Guideline Development Group agreed the correct wording of these. Third, from a discussion of the evidence statements and the experience of Guideline Development Group members, recommendations were drafted. The Short Clinical Guidelines Technical Team explicitly flagged up with the Guideline Development Group that it should consider the following criteria (considered judgement) when developing the guideline recommendations from the evidence presented:

- internal validity
- consistency
- generalisability (external validity)
- clinical impact
- cost effectiveness
- ease of implementation
- patient's perspective
- social value judgments
- overall synthesis of evidence.

The Guideline Development Group was able to agree recommendations through informal consensus. The process by which the evidence statements informed the recommendations is summarised in an 'evidence to recommendations' section in the relevant evidence review. Each recommendation was linked to an evidence statement if possible. If there was a lack of evidence of effectiveness, but the Guideline Development Group was of the view that a recommendation was important based on the Guideline Development Group members' own experience, this was noted in the 'evidence to recommendations' section.

4.2.9 Health economics

An economic evaluation aims to integrate data on the benefits (ideally in terms of quality-adjusted life years [QALYs]), harms and costs of alternative options. An economic appraisal will consider not only whether a particular course of action is clinically effective, but also whether it is cost-effective (that is, value for money). If a particular treatment strategy were found to yield little health gain relative to the resources used, then it could be advantageous to redirect resources to other activities that yield greater health gain.

A systematic review of the economic literature relating to antibiotic prophylaxis for IE was also conducted. In addition, the Guideline Development Group and expert advisers were questioned over any potentially relevant unpublished data. The search of the published literature yielded five relevant economic studies. Only one UK study was found (Gould and Buckingham 1993). All but

one of the studies considered an adult population and the impact of antibiotic prophylaxis preceding dental procedures in people at risk of IE.

Given the potentially large resource implications of antibiotic prophylaxis – it has been estimated that approximately 3% of the population have a predisposing cardiac condition (Duval et al. 2006) – and the potential adverse consequences of widespread antibiotic use (for example, fatal anaphylaxis), a de novo model was developed that considered an at risk UK adult population undergoing dental procedures.

Health economics statements are made in the guideline in sections in which the use of NHS resources is considered.

4.2.10 Consultation

The draft of the full guideline was available on the website for consultation, and registered stakeholders were informed by NICE that the documents were available. Non-registered stakeholders could view the guideline on the NICE website.

4.2.11 Piloting and implementation

It is beyond the scope of the work to pilot the contents of this guideline or validate any approach to implementation. These limitations excepted, every effort has been made to maximise the relevance of recommendations to the intended audience through the use of a guideline development group with relevant professional and patient involvement, by use of relevant experienced expert reviewers and the stakeholder process facilitated by the NICE Short Clinical Guidelines Technical Team. Implementation support tools for this guideline will be available from the Implementation Team at NICE.

4.2.12 Audit methods

The guideline recommendations have been used to develop clinical audit criteria for use in practice. Audit criteria are essential implementation tools for monitoring the uptake and impact of guidelines and thus need to be clear and straightforward for organisations and professionals to use.

NICE has commissioned the Clinical Accountability, Service Planning and Evaluation (CASPE) Research Unit and Health Quality Service (HQS) to develop the audit criteria for all its guidance as part of its implementation strategy.

4.2.13 Scheduled review of this guideline

The guidance has been developed in accordance with the NICE guideline development process for short clinical guidelines. This included allowing registered stakeholders the opportunity to comment on the draft guidance. In addition, the first draft was reviewed by an independent Guideline Review Panel established by NICE.

The comments made by stakeholders, peer reviewers and the Guideline Review Panel were collated and presented anonymously for consideration by the Guideline Development Group. All comments were considered systematically by the Guideline Development Group and the Project Team recorded the agreed responses.

This guideline will be considered for an update following the current process (chapter 15 of 'The guidelines manual'). However, if the evidence available has not changed we will not update it. Any agreed update would be carried out by the Short Clinical Guidelines Technical Team in conjunction with the Guideline Development Group. Alternatively the topic may be referred to the NICE Topic Selection Panel for it to consider developing a standard clinical guideline.

5 Contributors

5.1 The Guideline Development Group

The Guideline Development Group was composed of relevant healthcare professionals, patient representatives and NICE technical staff.

The members of the Guideline Development Group are listed below.

Professor David Wray (Chair) – Professor of Oral Medicine

Mr Danny Keenan – Consultant Cardiothoracic Surgeon

Dr Deborah Franklin – Consultant Paediatric Dentist

Dr John Gibbs – Consultant Cardiologist

Dr Jonathan Sandoe – Consultant Microbiologist

Dr Kathy Orr – Consultant Microbiologist

Dr Martin Fulford – General Dental Practitioner

Dr Nicholas Brooks – Consultant Cardiologist

Mr Nick Cooley – Antibiotic Pharmacist

Dr Richard Oliver – Senior Lecturer and Honorary Consultant in Oral Surgery

Ms Suzannah Power – Patient representative

Ms Anne Keatley-Clarke – Patient representative

The following individuals were not full members of the Guideline Development Group but were co-opted onto the group as expert advisers:

Professor Graham Roberts – Professor of Paediatric Dentistry

Professor Kate Gould – Professor of Microbiology

Dr Bernard Prendergast – Consultant Cardiologist

Mr Ian Eardley – Consultant Urologist

Professor Mark Kilby – Professor of Maternal and Foetal Medicine

Dr Andrew Klein – Consultant Anaesthetist

Dr Pallav Shah – Consultant Chest Physician

Dr Miles Alison – Consultant Gastroenterologist

Mr Gerald McGarry – Consultant Otorhinolaryngologist (ENT surgeon)

Ms Alison Pottle – Cardiac Nurse

5.1.1 The Short Clinical Guidelines Technical Team

The Short Clinical Guidelines Technical Team was responsible for this guideline throughout its development. It was responsible for preparing information for the Guideline Development Group, for drafting the guideline and for responding to consultation comments. The following people, who are employees of NICE, made up the technical team working on this guideline.

Dr Tim Stokes – Guideline Lead and Associate Director

Francis Ruiz – Technical Adviser in Health Economics

Roberta Richey – Technical Analyst

Michael Heath – Project Manager

Toni Price – Information Specialist

Lynda Ayiku – Information Specialist

Nicole Elliott – Commissioning Manager

Emma Banks – Coordinator

5.1.2 Guideline Review Panel A

- Robert Walker
- Ailsa Donnelly

- John Harley
- John Young

5.1.3 List of stakeholders

- Addenbrookes NHS Trust
- Advisory Committee on Antimicrobial Resistance and Healthcare (ARHAI)
- Association of British Academic Oral & Maxillofacial Surgeons
- Association of Medical Microbiologists
- Association of the British Pharmaceuticals Industry (ABPI)
- Avon, Gloucestershire & Wiltshire Cardiac Network
- Hospital NHS Foundation Trust
- Berkshire Healthcare NHS Trust
- Birmingham, Sandwell and Solihull Cardiac Network
- Birmingham Women's Hospital
- Bolton Council
- Bournemouth & Poole PCT
- Britannia Pharmaceuticals Ltd
- British Association for the Study of Community Dentistry
- British Association of Oral and Maxillofacial Surgeons
- British Cardiovascular Society
- British Dental Association
- British Dental Health Foundation
- British Geriatrics Society
- British Heart Foundation
- British Infection Society
- British National Formulary (BNF)
- British Nuclear Medicine Society
- British Society for Antimicrobial Chemotherapy
- British Society of Disability and Oral Health
- British Society of Echocardiography
- British Society of Gastroenterology
- British Society of Oral Medicine
- British Society of Paediatric Dentistry

- British Society of Periodontology
- BUPA
- Calderdale PCT
- CASPE Research
- Coast to Coast Cardiac Health
- Cochrane Oral Health Group
- Commission for Social Care Inspection
- Connecting for Health
- Coventry and Warwickshire Cardiac Health
- Department of Health
- Dudley Group of Hospitals NHS Trust
- East & North Herts PCT & West Herts PCT
- Eastman Dental Institute
- European Delirium Association
- Faculty of General Dental Practice
- Faculty of Dental Surgery
- Greater Manchester and Cheshire Cardiac Network
- Health Commission Wales
- Healthcare Commission
- Heatherwood & Wexham Park Hospitals Trust
- Home Office
- Institute for Ageing and Health
- Institute of Biomedical Science
- King's College London Dental Institute
- Kirklees PCT
- Leeds PCT
- Liverpool Women's NHS Trust
- LNR Cardiac Network
- Medicines and Healthcare Products Regulatory Agency
- Mid Essex Hospitals NHS Trust
- National Patient Safety Agency
- National Public Health Service – Wales

- National Treatment Agency for Substance Misuse
- National Coordinating Centre for Health Technology Assessment (NCCHTA)
- Neonatal & Paediatric Pharmacists Group (NPPG)
- Newcastle Upon Tyne Hospitals NHS Foundation Trust
- NHS Health and Social Care Information Centre
- NHS Plus
- NHS Quality Improvement Scotland
- NHS South Central Vascular Network
- North and East Yorkshire & Northern Lincolnshire Cardiac Network
- North Tees PCT
- North West London Cardiac Network
- North Yorkshire and York PCT
- Papworth Hospital NHS Trust
- Peninsula Clinical Management Cardiac Network
- PERIGON Healthcare Ltd
- Phoenix Partnership, The
- PRIMIS+
- OCD Today
- Regional Public Health Group – London
- Royal Brompton & Harefield NHS Trust
- Royal College of General Practitioners
- Royal College of Midwives
- Royal College of Nursing
- Royal College of Obstetricians and Gynaecologists
- Royal College of Paediatrics and Child Health
- Royal College of Pathologists
- Royal College of Physicians of London
- Royal Pharmaceutical Society of Great Britain
- Sandwell PCT
- Scottish Intercollegiate Guidelines Network (SIGN)
- Scottish Oral Health Group

- Sheffield PCT
- Sheffield Teaching Hospitals NHS Foundation Trust
- Social Care Institute for Excellence (SCIE)
- Specialist Advisory Committee on Antimicrobial Resistance
- Stockport PCT
- Sussex Heart Network
- UK Clinical Pharmacy Association
- University Hospital Birmingham NHS Foundation Trust
- University of North Tess and Hartlepool NHS Trust
- Welsh Assembly Government
- Welsh Scientific Advisory Committee (WSAC)
- West Yorkshire Cardiac Network
- Western Cheshire PCT
- Wiltshire PCT
- Whipps Cross Hospital NHS Trust
- York NHS Trust

5.2 Declarations

5.2.1 Authorship and citation

Authorship of this full guideline document is attributed to the NICE Short Clinical Guidelines Technical Team and members of the Guideline Development Group under group authorship.

The guideline should be cited as: NICE Short Clinical Guidelines Technical Team (2008) Prophylaxis against infective endocarditis: antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures. London: National Institute for Health and Clinical Excellence.

5.2.2 Declarations of interest

A full list of all declarations of interest made by this Guideline Development Group is available on the NICE website (www.nice.org.uk).

6 Appendices

Available as a separate document:

6.1 Appendix 1 – The scope

6.2 Appendix 2 – Key clinical questions

6.3 Appendix 3 – Search strategies

6.4 Appendix 4 – Evidence flow charts and evidence tables

6.5 Appendix 5 – References

6.6 Appendix 6 – De novo economic analysis

6.7 Appendix 7 – Health economics evidence tables

National Institute for Health and Care Excellence

Final

Prophylaxis against infective endocarditis

Clinical Guideline 64.1

Methods, evidence and recommendations

September 2015

Final

Developed by the National Institute for Health and Care Excellence

Contents

Clinical guidelines update

The NICE Clinical Guidelines Update Team update discrete parts of published clinical guidelines as requested by NICE's Guidance Executive.

Suitable topics for update are identified through the new surveillance programme (see surveillance programme interim guide).

These guidelines are updated using a standing Committee of healthcare professionals, research methodologists and lay members from a range of disciplines and localities. For the duration of the update the core members of the Committee are joined by up to 5 additional members who are have specific expertise in the topic being updated, hereafter referred to as 'topic expert members'.

In this document where 'the Committee' is referred to, this means the entire Committee, both the core standing members and topic expert members.

Where 'standing committee members' is referred to, this means the core standing members of the Committee only.

Where 'topic expert members' is referred to this means the recruited group of members with topic expertise.

All of the core members and the topic expert members are fully voting members of the Committee.

Details of the Committee membership and the NICE team can be found in appendix A. The Committee members' declarations of interest can be found in appendix B.

1 Summary section

1.1 Update information

In 2008 NICE published a guideline (CG64) on prophylaxis against infective endocarditis. This 2015 guideline on the same topic updates and replaces the 2008 publication.

A UK study published in the BMJ in 2011 (Thornhill et al. 2011) looked at the impact of the NICE guideline and showed an 80% fall in antibiotic prescribing thereby indicating that the guideline had been effectively implemented. A longstanding increase in the incidence of IE was also noted but with no clear evidence of any additional increase following publication of the guideline. This increase in the incidence of IE was not well understood and there were a number of possible reasons for this.

The publication of further research by the same research group, covering the period 2000 to 2013 (Dayer et al. 2014), suggested that the incidence of IE increased in both low and high risk groups above the baseline trend, in contrast to the 2011 study, following the publication of NICE's guidance in 2008. Given the uncertainty of the association as suggested by the research, this has triggered an exceptional update to assess all new evidence relevant to this guidance.

The objective of this update is to assess new evidence since 2008 for all review questions covered by the original Scope, except the review question on the information needs of patients regarding the benefits and risks of antimicrobial prophylaxis for IE.

Strength of recommendations

Some recommendations can be made with more certainty than others. The Committee makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the Committee is confident that, given the information it has looked at, most people would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

For all recommendations, NICE expects that there is discussion with the person about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision (see also 'Patient-centred care').

Recommendations that must (or must not) be followed

We usually use 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Recommendations that should (or should not) be followed– a 'strong' recommendation

Recommendations that an intervention should be used are made when we are confident that for the vast majority of patients, an intervention will do more good than harm, and be cost effective. Similarly, we recommend that an intervention should not be used when we are confident that an intervention will not be of benefit for most patients.

Recommendations that could be followed

Recommendations that an intervention could be used are made when we are confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

1.21 Recommendations

Adults and children with structural cardiac defects at risk of developing infective endocarditis

1.1.1 Healthcare professionals should regard people with the following cardiac conditions as being at risk of developing infective endocarditis:

- **acquired valvular heart disease with stenosis or regurgitation**
- **valve replacement**
- **structural congenital heart disease, including surgically corrected or palliated structural conditions, but excluding isolated atrial septal defect, fully repaired ventricular septal defect or fully repaired patent ductus arteriosus, and closure devices that are judged to be endothelialised**
- **previous infective endocarditis**
- **hypertrophic cardiomyopathy.**

Patient advice

1.1.2 Healthcare professionals should offer people at risk of infective endocarditis clear and consistent information about prevention, including:

- **the benefits and risks of antibiotic prophylaxis, and an explanation of why antibiotic prophylaxis is no longer routinely recommended**
- **the importance of maintaining good oral health**
- **symptoms that may indicate infective endocarditis and when to seek expert advice**
- **the risks of undergoing invasive procedures, including non-medical procedures such as body piercing or tattooing.**

Prophylaxis against infective endocarditis

1.1.3 Antibiotic prophylaxis against infective endocarditis is not recommended:

- **for people undergoing dental procedures**
- **for people undergoing non-dental procedures at the following sites[1]**
    - **upper and lower gastrointestinal tract**
    - **genitourinary tract; this includes urological, gynaecological and obstetric procedures, and childbirth**
    - **upper and lower respiratory tract; this includes ear, nose and throat procedures and bronchoscopy.**

1.1.4 Chlorhexidine mouthwash should not be offered as prophylaxis against infective endocarditis to people at risk of infective endocarditis undergoing dental procedures.

Infection

1.1.5 Any episodes of infection in people at risk of infective endocarditis should be investigated and treated promptly to reduce the risk of endocarditis developing.

1.1.6 If a person at risk of infective endocarditis is receiving antimicrobial therapy because they are undergoing a gastrointestinal or genitourinary procedure at a site where there is a suspected infection, the person should receive an antibiotic that covers organisms that cause infective endocarditis.

[1] The evidence reviews for this guideline covered only procedures at the sites listed in this recommendation. Procedures at other sites are outside the scope of the guideline (see appendix Q for details).

1.3 Research recommendations

1.3.1 National register of IE

Infective endocarditis is a rare condition. The development of a national register of infective endocarditis in the UK to support research is recommended.

Why this is important

Such research would be facilitated by the availability of a national register that could offer data into the 'case' arm of proposed case-control studies and should be an anonymised database that would not require patient consent and hence more straightforward case ascertainment. Although it is a rare condition, it is likely that across the country there are enough patients to generate evidence from well conducted national studies.

1.3.2 Antibiotic prophylaxis against infective endocarditis

Does antibiotic prophylaxis in those at risk of developing infective endocarditis reduce the incidence of infective endocarditis when given before a defined interventional procedure?

Why this is important

There is limited evidence about the effectiveness of antibiotic prophylaxis in reducing the incidence of infective endocarditis in people at risk of developing infective endocarditis. The current evidence includes very limited data from observational studies with inconclusive findings. The study should be a randomised controlled trial with long-term follow-up comparing antibiotic prophylaxis with no antibiotic prophylaxis in adults and children with underlying structural cardiac defects undergoing interventional procedures. Outcomes should include the incidence infective endocarditis in those receiving prophylaxis compared to those not, and the incidence of adverse effects including anaphylaxis.

1.4 Patient-centred care

This guideline offers best practice advice on the care of adults, young people and children with infective endocarditis.

Patients and healthcare professionals have rights and responsibilities as set out in the NHS Constitution for England – all NICE guidance is written to reflect these. Treatment and care should take into account individual needs and preferences. Patients should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If the person is under 16, their family or carers should also be given information and support to help the child or young person make decisions about their treatment. Healthcare professionals should follow the Department of Health's advice on consent. If someone does not have the capacity to make decisions, healthcare professionals should follow the code of practice that accompanies the Mental Capacity Act and the supplementary code of practice on deprivation of liberty safeguards. In Wales, healthcare professionals should follow advice on consent from the Welsh Government.

If a young person is moving between paediatric and adult services, care should be planned and managed according to the best practice guidance described in the Department of Health's Transition: getting it right for young people.

Adult and paediatric healthcare teams should work jointly to provide assessment and services to young people with infective endocarditis. Diagnosis and management should be reviewed throughout the transition process, and there should be clarity about who is the lead clinician to ensure continuity of care.

1.5 Methods

This update was developed based on the process and methods described in the The Manual 2014. Where there are deviations from the process and methods, these are clearly stated in the interim process and methods guide for updates pilot programme 2013.

2 Evidence review and recommendations

2.1 Epidemiological review

2.1.1 Overview of epidemiology: incidence and trends of infective endocarditis

Infective endocarditis (IE) is an uncommon condition with an annual incidence of fewer than 10 per 100,000 cases in the general population. Despite advances in diagnosis and treatment, IE remains a life-threatening disease with significant mortality (approximately 20%) and morbidity. IE may arise following bacteraemia in any patient but most often affects those with a predisposing cardiac lesion. It can affect any part of the endocardium but most often affects heart valves. . The predisposing factors for the development of IE have changed in the past 50 years, mainly with the decreasing incidence of rheumatic heart disease and the increasing impact of prosthetic heart valves, nosocomial infection and intravenous drug misuse. However, the potentially serious impact of IE on the individual has not changed (Prendergast 2006). In an attempt to prevent this disease, over the past 50 years, at-risk patients have been given antibiotic prophylaxis before dental and certain non-dental interventional procedures, as recommended by different national and international clinical guidelines formed by expert groups based on their expert opinions [American Heart Association (AHA) 2007 (Wilson et al. 2007), British Society for Antimicrobial Chemotherapy (BSAC) 2006 (Gould et al. 2006), European Society of Cardiology (ESC) 2009 (Habib et al. 2009) and British Cardiac Society (BCS)/Royal College of Physicians (RCP) 2004 (Advisory Group of the British Cardiac Society Clinical Practice Committee 2004)].

Despite guidelines on antibiotic prophylaxis to prevent IE, the incidence of IE continues to increase across the world. A recent UK study in England from 2000 to 2013 (Dayer et al. 2014) showed that prescriptions of antibiotic prophylaxis for the prevention of infective endocarditis fell substantially after introduction of the NICE guideline in 2008, and suggested that the number of cases of IE increased significantly above the projected historical trend, by 0·11 cases per 10 million people per month (95% CI 0·05–0·16, p<0·0001). This increase in the incidence of IE was significant for both individuals at high risk of IE and those at lower risk. The study postulated that the significant increase of incidence of IE in England may be due to the introduction of the 2008 NICE guideline, although the authors stated the study could not establish a causal association based on the data from the study.

For the critique of this particular study (Dayer et al. 2014) please see section 2.1.2.

To further investigate the incidence of IE across the world for the past 2 decades, a literature search for published studies on the trend or incidence of IE in general, and the possible impact of other published guidelines on the incidence of IE was conducted. For the search strategy, please see appendix D. From this literature search, 2827 studies have been retrieved and full papers of 64 studies have been obtained for assessment. Out of the 64 studies, 8 studies were included for this review (1 after consultation). The descriptive summary of these identified studies is summarised in Table 1 below.

Overall, 7 out of the 8 studies have suggested statistical significant upward trends of incidence of IE from 1980s to 2000s in different countries. Out of the 8 studies, 5 were from the USA and the findings from these 5 studies were as below:

- A study from 1970 to 2006 on adults in Olmsted county, USA suggested that there was a statistical significant increase in the incidence of IE from the period of 1970-1974 to the period of 2001-2006 (trend, p=0.02) (Correa et al. 2010).
- A study from 1999 to 2008 on adults and children in the USA (using the Nationwide Inpatient Sample [NIS], produced by the Agency for Healthcare Research and Quality, with approximately 8 million hospital records per year) suggested that there was a

statistical significant increase in the incidence of IE from 1999 to 2008 (trend, p<0.001) (Federspiel et al. 2012).

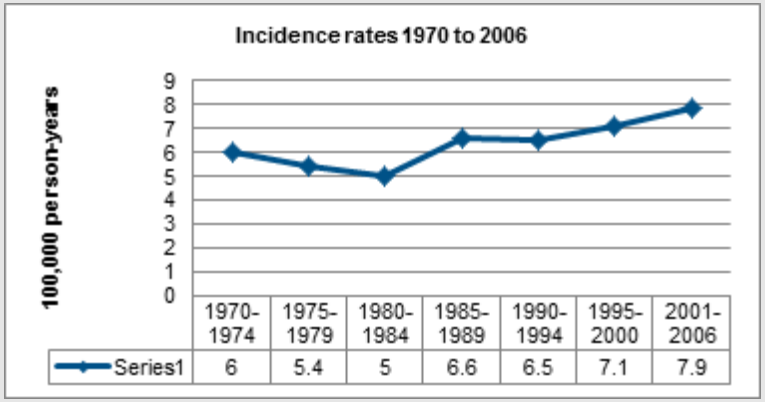
- Another study from 1998 to 2009 on adults and children in the USA (also using the NIS) suggested that there was again a statistical significant increase in the incidence of IE from 1998 to 2001 (trend, p<0.001) (Bor et al. 2013).
- The fourth study, from 2003 to 2010, which also assessed the impact of the AHA guideline (Wilson et al. 2007) on children using the Paediatric Health Information System (PHIS) Database (hospital n = 37) suggested that there was an upward increase in the raw number of IE cases over time but the increase before and after the AHA guidelines were published in 2007 was not statistically significant (p=0.7) (Pasquali et al. 2012).
- The fifth study, from 2007 to 2011, assessed the temporal trends in IE incidence, microbiology, and outcomes before and after the change in the 2007 IE prophylaxis guideline (AHA guideline) in the United States (Pant et al. 2015). The results suggested that IE incidence has increased in the United States over the past decade. With regard to the microbiology of IE, there has been a significant rise in the incidence of Streptococcus IE since the 2007 guideline revisions. However, the rates of hospitalization and valve surgery for IE have not increased since the change in IE prophylaxis guideline in 2007.

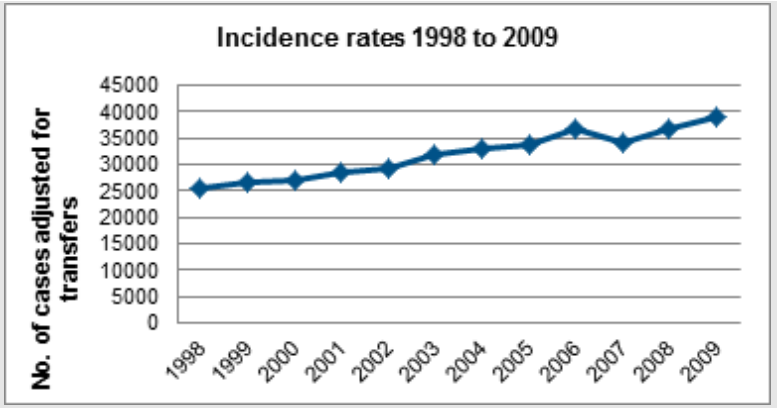
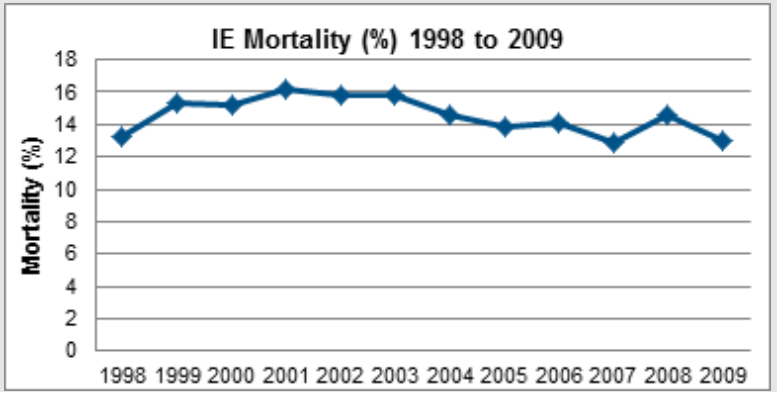
The other 3 studies were from Italy, Sweden and Taiwan. The findings from these 3 studies were as below:

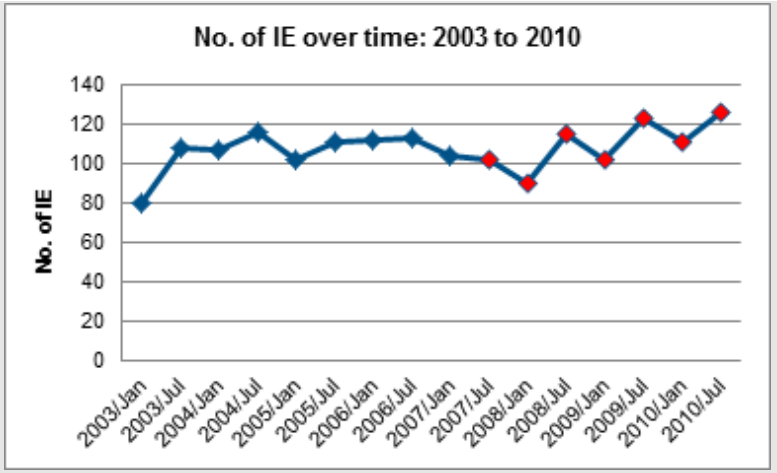
- An Italian study in the Veneto Region from 2000 to 2008 on adults and children suggested that there was a statistically significant increase in the number of cases of IE from the period of 2000-2002 to the period of 2006-2008 (trend, p=0.003) (Fedeli et al. 2011).
- A Swedish nationwide population-based study from 1997 to 2007 on adults and children suggested that there was a statistically significant increase in the incidence of IE from 1997 to 2007 (trend, p=0.01) (Ternhag et al. 2013).
- A Taiwanese population-based study (using the NHI database, which contained >96% health data of all hospitals in Taiwan) from 1997 to 2002 on adults only suggested that there was a statistically significant increase in the incidence of IE from 1997 to 2002 (trend, p<0.001) (Lee et al. 2007).

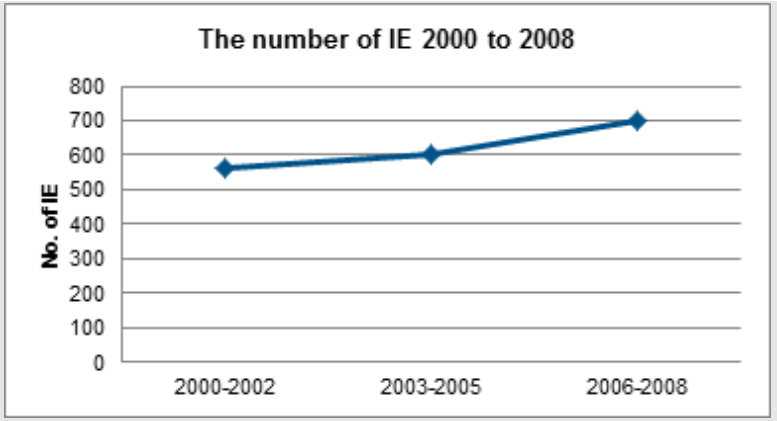
Generally, 6 out of the 7 studies have suggested statistically significant upward trends of incidence of IE over time. These findings are particularly interesting because in the USA studies and the European studies, the incidence of IE continues to increase despite the fact that these countries have more conservative antibiotic prophylaxis guidelines compared to the UK NICE guideline (NICE CG64). The authors of these studies postulated that, the increase of the incidence of IE may be due to aging populations with multi-morbidity, increase of degenerative valves, increase of hemodialysis, an increasing population of intravenous drug users and people with HIV and change of microbiology. To further validate these postulations, a well-designed longitudinal epidemiology study will need to be conducted to provide valid evidence to explain such phenomena.

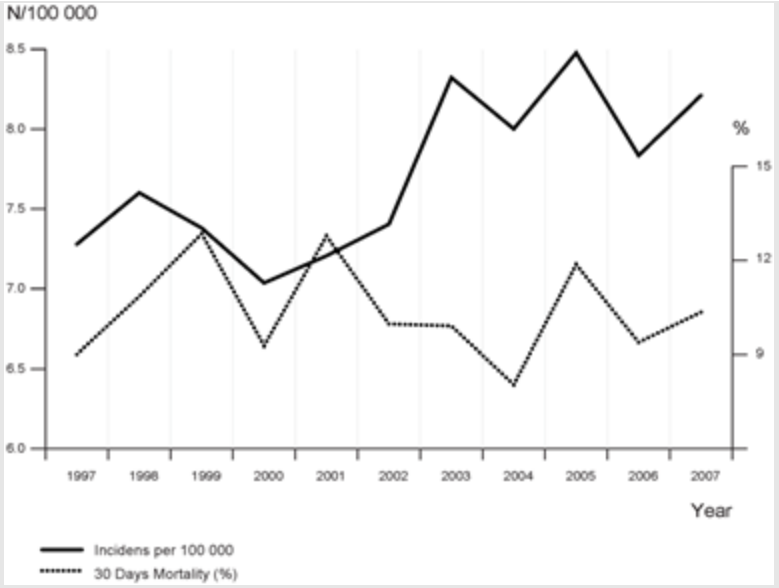
1 **Table 1: Summary of included studies**

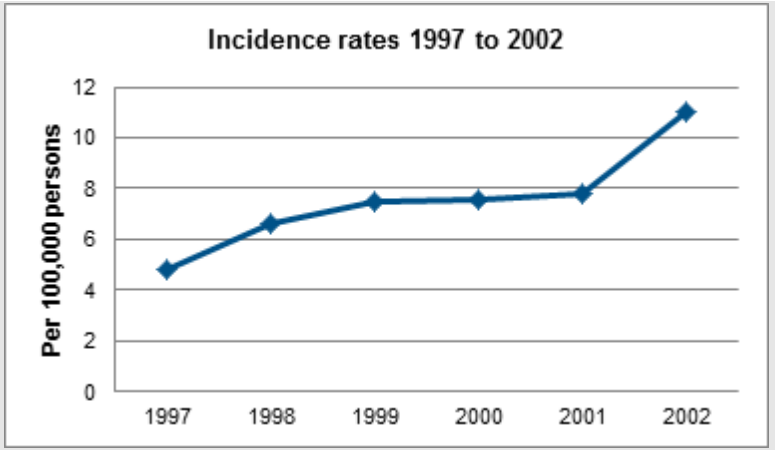
Study reference	Study population/ country	Time period	Methods	Results
Correa (2010) ID: 699	The Endocarditis Registry of the Division of Infectious Diseases of Olmsted county, USA. Residents 18 years or older.	1970 to 2006	Multivariable Poisson regression was used to examine temporal trends in the incidence of IE from 1970 to 2006, with the period grouped into 5-year intervals and fit as continuous, adjusted for age and gender.	The age- and gender-adjusted incidence rates of IE ranged from 6.0 cases per 100,000 person-years (1970-1974) to 7.9 cases per 100,000 person-years (2001-2006). 
Bor (2013) ID: 241	Agency for Healthcare Research and Quality's Nationwide Inpatient Sample (NIS) for hospital discharge data for about 8 million inpatient stays annually. The NIS provides weights to allow extrapolation to all US hospitalizations. USA. Adults and children	1998 to 2009	Changes in endocarditis hospitalization rates between 1998 and 2009 were compared using Census Bureau figures and the direct method to adjust for population growth and aging. Cochran-Armitage tests were used to evaluate time trends.	After adjustment for transfer to another hospital within the NIS sampling frame, the number of unique IE hospitalizations was 25,511 in 1998 (9.3 per 100,000 population) rising to 38, 976 in 2009 (12.7 per 100,000 population) (trend: p<0001). After adjustment for population aging and growth, IE hospitalizations increased by 2.4% annually.

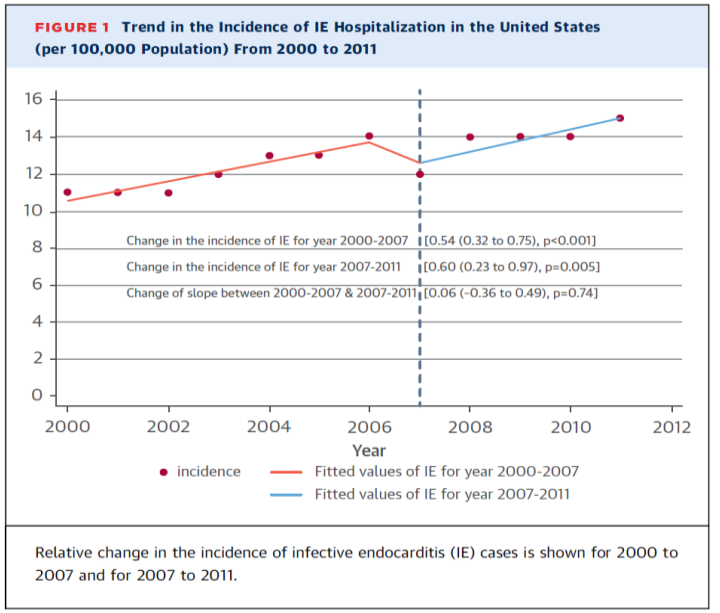
Study reference	Study population/ country	Time period	Methods	Results
				 
Pasquali (2012) ID: 368	The Paediatric Health Information System (PHIS) Database, containing inpatient data from 41 children's hospitals in the US affiliated with the Child Health Corporation of America. The	2003 to 2010	Poisson regression was used to estimate the rate of change in the annual number of IE hospitalizations over time (both raw and indexed to the total number of annual hospital admissions). Time was modelled in 6 month intervals as a linear trend allowing for change in slope at the time when the new AHA guidelines were published	A total of 1157 cases of hospitalization for IE during the study period were identified. Analysis did not detect a significant change in the raw number of IE cases over time, before and after the new guidelines were published in 2007: +1.6% difference post vs. pre guidelines (95% CI −6.4 to +10.3%, p=0.7).

Study reference	Study population/ country	Time period	Methods	Results
	database contains information from >5 million inpatient discharges. USA, children <18 years of age hospitalized with IE were included. (n=37 hospitals)		in 2007.	
Federspiel (2012) ID: 403	The Nationwide Inpatient Sample (NIS), produced by the Agency for Healthcare Research and Quality. The NIS is the largest all-payer inpatient database in the United States (approx.8 million records per year). USA. Adults and children.	1999 to 2008	Incidence was estimated using the rate of IE-related discharges per 100,000 US population years. Data were calculated quarterly based on discharge date; the denominator was adjusted annually based on the US population. Trends in admission rate were evaluated using joinpoint methods, allowing the trend to change over time	Of the 78.2 million records in the 1999–2008 NIS, 93,511 met inclusion criteria. Using weights, these records correspond to 457,690 discharges nationwide. After exclusion of 9,538 admissions ending in inpatient transfer and 273 (0.3%) with unknown disposition, the main study sample consisted of 83,700 discharges (409,665 weighted). Between the first quarter of 1999 and the first quarter of 2006, the rate of bacterial IE-related hospitalizations increased from 11.4 per 100,000 population-years to 16.6 per 100,000 population-years (trend, $p < 0.001$). This trend corresponds to an average percent change (APC) of 1.1% per quarter (95% CI: 0.9% to 1.3%).
Fedeli (2011) ID: 555	The total population of the Veneto Region was 4,885,548 in 2009, with 65 hospitals, there were	2000 to 2008	The first hospitalization (day-case excluded) for IE in the years 2000-2008 was selected The presence of time trends across the time periods was assessed by means of the Chi-	1,863 residents in the Veneto Region were hospitalized for IE in the period 2000-2008. The number of incident IE increased from 562 in 2000-2002 to 700 in 2006-2008 (+25%), with a corresponding crude rate rising from 4.1 to 4.9 per 100,000 person-years (+17%; $p = 0.003$).

Study reference	Study population/ country	Time period	Methods	Results
	approximately 900,000 discharges from these hospitals each year. Veneto region, Italy. Adults and children.		square test for linear trend or a non-parametric trend test derived from the Wilcoxon rank-sum test, as appropriate.	 
Ternhag (2013) ID: 187	A nation-wide population-based register study of patients with IE (hospitalized and treated for IE during 1997 to 2007 in Sweden). The Swedish Hospital	1997 to 2007	In order to explore possible increases in long-term relative mortality risks, the crude mortality rates were directly standardised using age- and gender-stratified mortality rates from the general population of Sweden as the reference population.	There were 7817 cases of IE, with an average annual incidence of 7.7 per 100000. The incidence rate has increased during the study period (slope of the line 0.01, p-value for trend 0.01).

Study reference	Study population/ country	Time period	Methods	Results
	Discharge Register collects individual data from all hospitals and more than 99% of the discharges in somatic care are covered by the register. Sweden. Adults and children		The time trend for the annual incidence and mortality rate of IE was explored in a linear regression model using a quasi-Poisson distribution and t-test for significance.	 Figure: Incidence Rate and 30-days Mortality (%) of Infective endocarditis (IE) hospitalizations in Sweden during 1997 through 2007. The all-cause 30-days crude mortality rate was 10.4%. The mortality rate fluctuates annually during 1997–2007 with no obvious trend through the years (slope of the line 20.006, p-value for trend 0.7).
Lee (2007) ID: 1082	Hospitalization data from the NHI database, which contained >96% health data of all hospitals in Taiwan. The population in Taiwan was approx. 22 million for all 6 years study period. Population	1997 to 2002	The annual incidence of IE was calculated by dividing the number of IE-associated hospitalizations by the general population of the same age as reported between 1997 and 2002. A Poisson regression model was used to examine the temporal trend in the incidence of IE.	7240 hospitalized patients>18 years of age with a principal discharge diagnosis of IE were identified. The mean annual incidence of IE was 7.6 per 100,000 inhabitants during the 6-year period, which significantly increased from 4.8 per 100,000 persons in 1997 to 11 per 100,000 persons in 2002 (linear trend, p<0.001).

Study reference	Study population/ country	Time period	Methods	Results
	data also obtained from the Department of Statistics of the Ministry of the Interior of Taiwan. Taiwan. Adults >18 years of age			
Pant (2015)	Healthcare Cost and Utilization Project NIS (Nationwide Inpatient Sample) database, sponsored by the Agency for Healthcare Research and Quality. Each year, the NIS data are updated to approximately represent a 20% stratified sample of U.S. hospitals. U.S Adults and children	2007 to 2011	To estimate the annual rates of IE hospitalizations, the study divided the total number of IE cases in a given year by the U.S. census population for that year, which were represented in tables and graphs per 100,000 or per million population. The proportion of IE hospitalizations due to each organism was expressed in 2 ways: 1) as a proportion of all IE hospitalizations; and 2) per population for that year. We compared the estimated mean annual rates of IE for data from before and after the introduction of the 2007 ACC/ AHA IE antibiotic prophylaxis guidelines using piecewise regression analysis (also known as segmented regression analysis)	A total of 457,052 estimated IE hospitalizations were identified during the study period (2000 to 2011). The annual IE hospitalization rate, microbiology, and valve replacement rates in the United States from 2000 to 2011 are summarized.

Study reference	Study population/ country	Time period	Methods	Results
			of the interrupted time series.	

Pasquali (2012): Red diamonds in the graph indicated time period after the introduction of the AHA guideline.
Pant (2015): Figure 1 is directly extracted from the Pant el al. (2015) study.

2.1.21 Critique of Dayer et al. (2014) study

In response to the Dayer et al. (2014) study, an independent critical review of the study has been conducted as part of this update by a non-voting topic expert on interrupted time series analysis (Ramsay 2015). A brief summary of the critique is below:

- There were no factual errors with the modelling approach undertaken in the paper.
- Data for incidence of endocarditis (Figure 2 in the original paper) and incidence of high and low risk cases (Figure 3 in the original paper) were abstracted from the graph and original paper analysis confirmed.
- Exploratory investigation (sensitivity analyses) of the data suggested that two straight lines (a single change point during the time period) might not be an adequate description of the series, implying that the change in slope (different trends between 2 time period) in original paper is likely to be unstable depending on the assumptions used in the analysis.
- Multiple change-points throughout the time period seem possible rather than only one at the point of guideline publication in 2008.
- Reanalysis of the series suggests the change in slope estimate is primarily driven by whether the post-intervention data is a straight line (as in the original paper) or not.
- If an additional interruption (increase of cases) occurs at June 2011, the change in slope at guideline introduction is reduced to zero, suggesting no effect of guidance publication on trends.
- Applying the Cochrane Effective Practice and Organisation of Care risk of bias assessment for interrupted time series suggests the study is at high risk of bias.

For the full critical review paper from Ramsay (2015), please see appendix O .

2.2 Review question 1a, 1b and 2

1a) Which pre-existing cardiac conditions, in adults and children increase the risk of developing infective endocarditis (IE)?

1b) Which pre-existing cardiac conditions are not associated with increased risk of developing IE?

2) Which pre-existing cardiac conditions are associated with relatively poorer outcomes from IE?

2.2.1 Clinical evidence review

Patients with certain cardiac conditions are known to be at risk of developing IE. Guidelines and discussion on prophylaxis against IE start from the principle that it is possible to classify those with underlying cardiac conditions into those who are at increased risk and those whose risk is considered to be the same as, or little greater than the general population. We therefore sought to review which underlying cardiac conditions affect a person's risk of developing IE/outcome of IE because it will influence decisions made about offering prophylaxis.

A systematic search was conducted (see appendix D) for question 1a, 1b and 2 which identified 4566 articles in total. The titles and abstracts were screened and 156 articles were identified as potentially relevant. Full-text versions of these articles were obtained, and reviewed against the criteria specified in the review protocol (appendix C). Of these, 131 were excluded as they did not meet the criteria and 25 met the criteria and were included. In addition all 12 of the studies included in CG64 were reviewed against the protocol criteria. Of these 8 were excluded as they did not meet the criteria and 4 were included. This gave a final total of 29 included studies.

Question 1a and b included 4 new studies plus 3 from the original 7 (total 7) and question 2 includes 21 new studies plus 1 study from the original 5 (total 22). One study has been included for both questions (double counted).

A review flowchart is provided in appendix E, and the excluded studies (with reasons for exclusion) are shown in appendix F.

2.2.2 Methods

Summary of review protocols

The population included adults and children with/without underlying structural cardiac conditions and a history of IE, or adults and children who have previous had IE irrespective of whether they had a known underlying cardiac condition. It did not include people with rhythmic disorders and/or pacemakers, people at increased risk of IE who do not have underlying cardiac conditions (such as intravenous drug users or people on haemodialysis) and people with fungal IE and non-infective causes of endocarditis.

The topic expert members identified the following outcomes of interest, ranked in order of importance, for question 2: mortality, cardiac surgery, recurrence, stroke, length of stay and acute kidney injury.

Single case reports, case series and qualitative studies were excluded.

Quality assessment - risk of bias

As this is a review question on assessing associations between different risk factors and IE, GRADE methodology is not appropriate for quality assessment for this particular question.

The quality of individual studies was assessed using the checklist for prognostic/prediction/association studies by Hayden et al., 2006, as guided in Developing NICE guidelines - the Manual, 2014This checklist addresses 6 main areas including study participation, study attrition, prognostic factor measurement, outcome measurement, confounding measurement and account and finally the analysis used in the study. We assessed each individual study against this criteria and assigned an overall quality rating using the following thresholds:

- all 6 criteria on checklist met: no risk of bias
- at least 4 out of 6 criteria met: low risk of bias
- anything else: high risk of bias

Statistical analysis

Conventional meta-analyses were not conducted due to the variations and heterogeneity in population and outcome measures from study to study.

Where appropriate, summary measures such as adjusted or unadjusted odds ratios (with 95% confidence intervals, where available) were presented in the evidence summary. Where the reviewer calculated these, this has been footnoted.

All findings are based on statistical significance as the aim of review question is to investigate whether there are any statistically significant associations between the risk factors and outcomes of interest.

Overall Summary

For a summary of included studies please see table 2 below (for the full evidence tables and full result summary tables please see appendix G and appendix H respectively).

The body of evidence for each risk factor is of variable quality and consistency, making it difficult to rate risk factors for IE/IE outcome.

The following reasons are examples of potential bias in the included studies:

- Just under half of the included studies were retrospective in design (potential selection bias) and several studies were conducted in tertiary centres (potential referral bias).
- Often the data for adults and children were combined.
- Often there was insufficient detail about the recruitment of control participants.
- In some cases both definite and possible diagnoses of IE (according to Duke/modified Duke criteria) were combined.
- Unclear statistical analyses or omission of results - even where multivariate analysis was conducted, it was often with small sample size and hence lack of power.

Please see the comments section of individual evidence tables (Appendix G) for individual study ratings for risk of bias.

1a) Which pre-existing cardiac conditions, in adults and children increase the risk of developing infective endocarditis (IE)?

1b) Which pre-existing cardiac conditions are not associated with increased risk of developing IE?

Table 2: Summary of included studies

Study reference (including study design)	Study population	Predictors (or risk factors)	Outcomes	Effect estimates (including analysis used)	Comments
Alagna et al 2014 Prospective cohort	1874 Adult patients with definite IE enrolled onto International Collaboration on Endocarditis Prospective Cohort Study.	• Prosthetic Valve • Previous IE • Congenital heart disease	IE (single episodes and repeat episodes (recurrent or relapse)).	**Univariate analysis** Congenital heart disease – OR 1.06 (0.50-2.22)* Prosthetic valve – OR 1.49 (0.86-2.59)* Multivariate analysis results not reported for congenital heart disease and prosthetic valve. **Multivariate analysis** History of Previous endocarditis – adjusted OR 2.8 (1.5-5.1) *calculated by reviewer	High risk of bias 3/6 criteria met See Evidence table Study not designed to determine the risk of IE relative to the general population.
Ammar et al 2013 Retrospective case-control study	175 Adult patients with definite IE from an IE database at Cardiology Dept, Cairo University Hospital. Plus 175 control cases without IE matched for age, sex and underlying heart disease.	• Known structural heart disease • Congenital heart disease • Valvular heart disease • Prosthetic valve • Previous IE	IE	**Univariate analysis** Known structural heart disease – OR 1.16 (0.74-1.80)* Congenital heart disease – OR 1.26 (0.58-2.73)* Valvuar heart disease – OR 0.97 (0.62-1.53)* Prosthetic Valve – OR 1.12 (0.70-1.80)* Previous IE – OR 4.69 (0.998-22.03) **Multivariate analysis** Previous IE – adjusted OR - 5.841 (1.2-28.4) P=0.029 *calculated by reviewer	High risk of bias 3/6 criteria met See Evidence table. Study not designed to determine the risk of IE relative to the general population

Study reference (including study design)	Study population	Predictors (or risk factors)	Outcomes	Effect estimates (including analysis used)	Comments
Clemens et al 1992 [from CG64] Case-control study	51 Adult hospital inpatients with IE (with echo, lacking any known cardiovascular risk factors for endocarditis except mitral valve prolapse). 153 Controls without (adult inpatients).	Mitral valve prolapse	IE	**Univariate analysis** Mitral valve prolapse - Matched OR - 4.7 (1.1-19.5)	Low risk of bias 4/6 criteria met See Evidence table.
Hickey et al 1985 [from CG64] Case-control study	56 Cases - People age >15 admitted to hospital who met diagnostic criteria for IE. 168 Controls without IE Matched for age, sex and date of echo.	Mitral valve prolapse	IE	Mitral valve prolapse - Matched OR - 6.8 (2.1-22.0)	High risk of bias 3/6 criteria met See Evidence table.
Richet et al 2008 Case-control study	402 Adult and paediatric patients consulting hospital or hospitalised with definite IE. Patients with rejected IE	Prior Valve Damage (Prosthetic valves, pacemaker or congenital heart disease)	IE	**Multivariate analysis** Prior Valve Damage – adjusted OR 8.2 (5-13.3)	Low risk of bias 4/6 criteria met See Evidence table.

Study reference (including study design)	Study population	Predictors (or risk factors)	Outcomes	Effect estimates (including analysis used)	Comments
	served as controls.				
Rushani et al 2013 Population based cohort	47,518 children with CHD followed for 458109 pt/years generating 185 cases of IE. (matched on calendar time with 20 controls (who also had congenital heart diseases)	Congenital Heart Diseases (CHD) incl. • Cyanotic CHD • Endocardial cushion defects • L/R sided lesions • Patent ductus arteriosus • Ventricular septal defect • Atrial septal defect Cardiac Surgery in past 6 months.	IE	**Univariate and multivariate analysis** Cyanotic CHD – OR 6.38 (4.02-10.13), adjusted OR 6.44 (3.95-10.5) Endocardial cushion – OR 4.37 (2.35-8.15) adjusted OR 5.47 (2.89-10.36) L sided lesions - OR 1.57 (0.86-2.88) adjusted OR 1.88 (1.01-3.49) R sided lesions - OR 1.12 (0.49-2.59) adjusted OR 1.22 (0.52-2.86) Patent ductus arteriosus - OR 1.33 (0.54-3.27) adjusted OR 1.25 (0.50-3.13) Ventricular septal defect - OR 0.95 (0.56-1.62) adjusted OR 0.97 (0.56-1.66) Atrial septal defect – OR 0.449 (0.33-0.75)* Cardiac Surgery in past 6 months – OR 15.52 (8.08-29.80 adjusted OR 5.34 (2.49-11.43) *Calculated by reviewer	Low risk of bias 5/6 criteria met See Evidence table. Study not designed to determine the risk of IE relative to the general population
Strom et al 1998 [from CG64] Population based case-control.	273 Adults with Community acquired IE (not associated with IVDU) and 270 matched controls without IE (community residents).	• Mitral valve prolapse • Valvular heart disease • Congenital heart disease • Rheumatic fever • Previous IE	IE	**Univariate and multivariate analysis** Mitral valve prolapse – matched OR 19.4 (6.4-58.4) Valvular heart disease – adjusted OR 0.62 (0.34-1.14) Congenital heart disease – adjusted OR 6.7 (2.3-19.4) Rheumatic fever – adjusted OR 13.4 (4.5-39.5) Previous IE – adjusted OR 37.2 (4.4-317)	Low risk of bias 5/6 criteria met See Evidence table.

2) Which pre-existing cardiac conditions are associated with relatively poorer outcomes from IE?

Table 3: Summary of included studies

Study reference (including study design)	Study population	Predictors (or risk factors)	Outcomes	Effect estimates (including analysis used)	Comments
Alagna et al 2014 Prospective cohort	1874 Adult patients with definite IE enrolled onto International Collaboration on Endocarditis Prospective Cohort Study.	• Prosthetic Valve • Previous IE • Congenital heart disease	Recurrence	**Univariate analysis** Prosthetic valve – OR 0.73 (0.42-1.25)* Congenital heart disease - OR 1.49 (0.86-2.59)* *Calculated by reviewer	High risk of bias 3/6 criteria met See Evidence table. Study not designed to determine the risk of IE relative to the general population
Aksoy et al 2007 Longitudinal cohort study	333 Adult patients with IE.	• Congenital heart disease. • Aortic valve involvement	Cardiac surgery	**Univariate analysis** Congenital heart disease – OR 0.41 (0.19-0.87)* Aortic valve involvement – OR 11.61 (0.64-211.63)* *Calculated by reviewer	Low risk of bias 4/6 criteria met See Evidence table. Study not designed to determine the risk of IE relative to the general population
Alonso-Valle et al 2010 Retrospective cohort study	133 cases of IE (in 122 patients) of the prosthetic valve.	• Previous IE • Previous valve replacement • Mechanical prosthesis implantation	Mortality	**Univariate analysis** Previous IE - (RR) 1.7 (0.7-4.4) Previous valve replacement - (RR) 0.9 (0.4-2.1). Mechanical prosthesis implantation - (RR) 1.1 (0.5-2.4).	High risk of bias 3/6 criteria met See Evidence table. Study not designed to determine the risk of IE relative to the general population

Study reference (including study design)	Study population	Predictors (or risk factors)	Outcomes	Effect estimates (including analysis used)	Comments
Bannay et al 2011 Long term prospective follow-up study	449 Adults with Left sided IE selected from a prospective, population based study.	• Predisposing cardiac diseases (Valvular diseases with/without prosthesis) • Valvular prosthesis • Previous IE	Mortality, cardiac surgery	**Mortality** Previous valve replacement/prosthetic valve – HR 1.09 (0.72-1.67) **Univariate analysis** **Cardiac surgery** Valvular prosthesis only - OR 0.95 (0.57-1.56)* Native and prosthetic valves OR1.08 (0.79-1.46)* Previous IE – OR 1.49 (0.75-2.96)* *calculated by reviewer	Low risk of bias 4/6 criteria met See Evidence table. Study not designed to determine the risk of IE relative to the general population
Da costa et al 2007 Retrospective observational study	186 Adults and children with IE.	• Prosthetic heart valve • Rheumatic disease	Mortality	**Univariate and Multivariate analysis** Prosthetic heart valve – OR 4.57 (1.89-11.07), Adjusted OR 4.77 (1.44, 15.76). **Univariate analysis** Rheumatic disease – OR 0.70 (0.31-1.56)* *Calculated by reviewer	Low risk of bias 4/6 criteria met See evidence table. Study not designed to determine the risk of IE relative to the general population
Delahaye et al 2007 Population based survey	653 Adults with IE living in one of the study regions.	• Prosthetic valve • Rheumatological manifestations	Mortality	Prosthetic valve - Reported as significant p value only (p=0.004) after univariate analysis. Not possible to back calculate due to missing data. Rheumatological manifestations - Reported as significant p value only (p=0.001) after univariate analysis. Not possible to back calculate due to missing data.	High risk of bias 3/6 criteria met See evidence table. Study not designed to determine the risk of IE relative to the general population
Erbay et al 2010 Retrospective cohort design	107 Adults with IE admitted to hospital.	• Congenital heart disease • Predisposing heart disease	Mortality	**Univariate analysis** Congenital heart disease - OR 1.08 (0.20-5.86)* Predisposing heart disease – OR 1.09 (0.58-2.04)*	Low risk of bias 4/6 criteria met. See evidence table.

Study reference (including study design)	Study population	Predictors (or risk factors)	Outcomes	Effect estimates (including analysis used)	Comments
		• Rheumatic heart disease • Degenerative heart disease • Bicuspid aortic valve • Prosthetic valve • Previous IE		Rheumatic heart disease – OR 2.24 (0.64-7.91)* Degenerative heart disease – OR 0.98 (0.29-3.32)* Bicuspid aortic valve – OR 5.38 (0.47-61.60)* Prosthetic valve – OR 0.73 (0.32-1.65)* Previous IE - HR 3.5 (1.2-11.0) p=0.026 *Calculated by reviewer	Study not designed to determine the risk of IE relative to the general population
Fenandez-Guerrero et al 2007 Retrospective cohort study	44 Adults with IE (enterococcal) (hospital based)	Prosthetic valve	Mortality, surgery, stroke	**Univariate analysis** **Mortality** Prosthetic valve – OR 0.21 (0.04-1.04)* **Surgery** Prosthetic valve – OR 0.87 (0.27-2.78)* **Stroke** Prosthetic valve – OR 1.27 (0.30-5.41)* *Calculated by reviewer	High risk of bias 3/6 criteria met. See evidence table. Study not designed to determine the risk of IE relative to the general population
Fernandez-Guerrero et al 2010 Retrospective cohort study	84 Adults (?) with IE (staphylococcal) with data recorded on a patient records database.	Prosthetic valve	Mortality, surgery, stroke	**Univariate analysis** **Mortality** Prosthetic valve – OR 0.53 (0.21-1.37) **Surgery** Prosthetic valve – OR 0.24 (0.09-0.64) **Stroke** Prosthetic valve – OR 0.72 (0.27-1.89)	High risk of bias. 2/6 criteria met. See evidence table.
Galvez-Acebal et al 2010 Observational multi-centre study	705 Adults and children with Left sided IE	Prosthetic valve	Mortality	**Univariate and multivariate analysis** Prosthetic valve - OR 1.48 (1.17-1.87). Adjusted OR 1.99 (1.26-3.14)	Low risk of bias. 4/6 criteria met. See evidence table. Study not designed to determine the

Study reference (including study design)	Study population	Predictors (or risk factors)	Outcomes	Effect estimates (including analysis used)	Comments
					risk of IE relative to the general population
Lin et al 2013 Retrospective analysis	47 Children with IE (consecutive patients)	Congenital heart disease (cyanotic only)	Mortality, surgery.	**Univariate analysis** **Mortality** Cyanotic CHD – OR 1.41 (0.42-4.66)* **Surgery (all cardiac)** Cyanotic CHD – OR 0.75 (0.28-1.98)* **Valve replacement surgery** Cyanotic CHD – OR 0.36 (0.09-1.42)* *Calculated by reviewer	High risk of bias. 3/6 criteria met. See evidence table. Study not designed to determine the risk of IE relative to the general population
Murakami et al 2012 Retrospective observational Cohort	239 Adults and children with IE	• Congenital heart disease (plus cardiac surgery) • Previous IE	Surgery	**Univariate analysis** Congenital heart disease (plus cardiac surgery) – OR 0.27 (0.11-0.65) Previous cardiac surgery - OR 0.68 (0.38-1.22) Previous IE – OR 0.67 (0.22-2.06)	Low risk of bias. 4/6 criteria met. See evidence table.
Murdoch et al 2009 Prospective cohort study	2781 Adults with IE	• Congenital heart disease • Prosthetic valve	Mortality	**Multivariate analysis** Congenital heart disease – Adjusted OR 1.22 (0.74-2.02) Prosthetic valve - Adjusted OR 1.47 (1.13-1.90)	Low risk of bias. 4/6 criteria met. See evidence table
San Roman et al 2007 Prospective study	317 Adults with left sided IE (consecutive patients)	Prosthetic valve Rheumatic heart disease Degenerative heart disease	Events (death or surgery)	**Univariate analysis** Prosthetic valve – OR 0.96 (0.63-1.47)* RHD – OR 0.79 (0.38-1.63)* DHD – OR 0.86 (0.40-1.84)* *Calculated by reviewer	High risk of bias. 3/6 criteria met. See evidence table. Study not designed to determine the risk of IE relative to the general population
Smith et al 2007	87 Adults with IE	Previous cardiac	Mortality	**Univariate analysis**	Low risk of bias.

Study reference (including study design)	Study population	Predictors (or risk factors)	Outcomes	Effect estimates (including analysis used)	Comments
Prospective cohort	(hospitalised patients)	surgery Mechanical prosthesis		Mechanical prosthesis – OR 0.77 (0.16-3.80)* Previous cardiac surgery - OR 1.10 (0.28-4.36)* *Calculated by reviewer	4/6 criteria met. See evidence table.
Ternhag et al 2013 Retrospective cohort	7063 Adults with IE (hospitalised and treated patients) from Swedish National inpatient register.	Prosthetic valve	Mortality	Standardised mortality ratio – 2.3 (1.9-2.7)	Low risk of bias. 4/6 criteria met. See evidence table.
Thuny et al 2012 Observational cohort	328 Adults with IE (consecutive hospitalised patients)	Underlying heart disease Prosthetic valve	Mortality	**Univariate analysis** Underlying heart disease - OR 0.85 (0.52-1.37)* Prosthetic valve – OR 0.85 (0.52-1.37)* *Calculated by reviewer	Low risk of bias. 4/6 criteria met. See evidence table.
Thuny et al 2007 Prospective study	496 Adults with IE (consecutive hospitalised patients)	Prosthetic valve Underlying heart disease	Stroke	**Univariate analysis** Underlying heart disease – OR 0.97 (0.68-1.39)* Prosthetic valve – OR 0.99 (0.60-1.63)* *Calculated by reviewer	Low risk of bias. 4/6 criteria met. See evidence table.
Tleyjeh et al 2007 Retrospective/Prospective study	546 Adults with IE (consecutive patients diagnosed and treated)	Previous IE	Surgery	**Univariate analysis** Previous IE – OR 1.20 (0.66-2.21)* *Calculated by reviewer	High risk of bias. 3/6 criteria met. See evidence table.
Wang et al 2007 [from CG64] Observational cohort	2670 Adults with IE (of whom had prosthetic valve endocarditis n=556) enrolled in ICE-PCS (International Collaboration on Endocarditis-Prospective Cohort	Prosthetic valve Endocarditis	Mortality	**Univariate analysis** Prosthetic valve – unadjusted OR) 1.51 (1.2-1.91)*. *Calculated by reviewer	Low risk of bias. 4/6 criteria met. See evidence table.

Study reference (including study design)	Study population	Predictors (or risk factors)	Outcomes	Effect estimates (including analysis used)	Comments
	study)				
Wong et al 2009 Retrospective review	47 Adults with IE	Rheumatic heart disease (RHD) Aortic stenosis Mitral valve prolapse Prosthetic valve	Recurrence	**Univariate analysis** RHD – OR 0.61 (0.07-5.58)* Aortic stenosis – OR 4.88 (0.60-39.91)* Mitral valve prolapse – OR 0.70 (0.08-6.47)* 0.41 (0.05-3.58)* *Calculated by reviewer	Low risk of bias. 3/6 criteria met. See evidence table.
Yoshinaga et al 2008. Retrospective observational review	137 Adults and children with congenital heart disease and IE	Cyanotic CHD Prosthetic heart valve Previous cardiac surgery (for CHD) Previous IE	Mortality	**Univariate analysis** Cyanotic CHD – OR 5.34 (1.66-17.2) Prosthetic heart valve – OR not reported Previous cardiac surgery – OR 4.69 (1.25-17.6) Previous IE – OR 3.46 (0.81-14.7)	High risk of bias. 2/6 criteria met. See evidence table.

2.2.31 Clinical evidence statements

2 **Question 1:**

3 Particular types of congenital heart disease (cyanotic congenital heart disease, endocardial
4 cushion defects and left sided lesions in children), rheumatic heart disease, previous cardiac
5 surgery and previous IE appear to be significantly associated with increased odds of
6 developing IE (low to high risk of bias).

7 Pre-existing cardiac conditions that do not appear to increase risk of IE include particular
8 types of congenital heart disease in children (patent ductus arteriosus and ventricular and
9 atrial septal defects (one study of low risk of bias).

10 There is a lack of good quality case-control studies that illustrate the association between
11 prosthetic valves and the risk of IE compared to the general population.

12 People with mitral valve prolapse may have an increased risk of IE (based on three studies,
13 two with low and one with high risk of bias).

14 **Congenital heart disease**

15 People with congenital heart disease appear to have significantly increased odds of getting
16 IE than people without congenital heart disease, based on one study with low risk of bias,
17 however this finding was not consistent across all studies.

18 Particular types of congenital heart disease in children appear to significantly increase the
19 odds of IE. These include cyanotic CHD, endocardial cushion defects and left sided lesions
20 (based on one study with low risk of bias).

21 **Rheumatic heart Disease (RHD)**

22 People with RHD have significantly increased odds of getting IE than people without RHD,
23 based on one study of low risk of bias.

24 **Valvular heart disease**

25 People with valvular heart disease (when dealt with collectively) may have significantly
26 increased odds of developing IE than people without valvular heart disease, based on one
27 study with low risk of bias, however two studies found no significant difference in odds (high
28 and low risk of bias respectively)

29 **Mitral valve prolapse (MVP)**

30 People with MVP appear to have significantly increased odds of developing IE than people
31 without MVP, based on 3 studies with variable risk of bias (2 low risk and 1 high risk of bias),
32 however these odds are unadjusted for other factors that may predispose to IE

33 **Prosthetic heart valve**

34 There is a lack of good quality case-control studies that illustrate the association between
35 prosthetic valves and the risk of IE. People with prosthetic heart valves do not appear to be
36 at increased odds of developing IE than people without prosthetic heart valves, based on two
37 studies (one cohort study and one retrospective case-control study) of high risk of bias.[a]

38 **Previous IE**

a Please refer to the LETR table (table p.35/36 for further comment.

People who have had previous infective endocarditis appear to have significantly increased odds of developing a further IE than people who have not had previous IE, based on three studies (one low and two high risk of bias).

Question 2:

In people with certain pre-existing cardiac conditions, the evidence for having a poorer outcome after IE is inconsistent and based on studies of low and high risk of bias.

People with prosthetic valves are at increased risk of in-hospital death (five studies of low risk of bias).

Pre-existing cardiac conditions where there is no evidence of an increased risk of death or recurrence include rheumatic heart disease, degenerative heart disease, aortic valve disease and mitral valve prolapse (based on evidence of predominantly low risk of bias).

Congenital heart disease

The evidence for risk of mortality in people with congenital heart disease is inconsistent. (Three studies indicating no increased risk, low and high risk of bias, one study indicating increased risk of in hospital death and one study indicating reduced risk of death at 5 years (high and low risk of bias).

In people with CHD who get IE there is evidence of a reduced odds of cardiac surgery (based on one study with low risk of bias, but is unadjusted for other factors leading to surgery).

In people with CHD who get IE, there is no evidence of a difference in IE recurrence (based on one study with high risk of bias).

Rheumatic Heart Disease and Degenerative Heart Disease

In people with rheumatic heart disease or degenerative heart disease who get IE, there are no significantly increased odds of death, recurrence or cardiac surgery (based on five studies, four with low and one with high risk of bias).

Aortic Valve Disease / Mitral Valve prolapse

In people with aortic valve disease or mitral valve prolapse who get IE, there are no significantly increased odds of death or recurrence (based on three studies, all with low risk of bias).

Previous Valve Replacement/Prosthetic Valve

In people with previous valve replacement (prosthetic valve) who get IE, the odds of death areincreased. Five studies (n-=7087) of low risk of bias indicate a significantly increased odds of in-hospital death and 4 studies (n=936, 3 of high and 1 of low risk of bias) suggest there is no difference.

In people with previous valve replacement who get IE, there is no significantly increased odds of death beyond the hospital stay, need for cardiac surgery, recurrence or stroke.

Previous cardiac surgery

In people who have had previous cardiac surgery who get IE, there may be increased odds of death (based on one study with high risk of bias). Two further studies indicate no difference in the odds of further cardiac surgery (low risk of bias).

Previous IE

In people who have had IE previously, who get it again, there may be a significantly increased likelihood of death but the evidence is inconsistent (based on four studies, two with low and two with high risk of bias). There are no increased odds of further cardiac surgery (based on three studies, two with low and one with high risk of bias).

2.2.46 Evidence to recommendations

	Committee discussions
Relative value of different outcomes	The committee noted the presented limitations around the outcome of IE and the outcomes associated with IE but had no further comment about this point. The Committee discussed and agreed that the critical outcome for review question 1a and 1b was to establish whether there is a clear relationship between having a pre-existing cardiac condition and the risk of developing IE. Therefore, the only critical outcome is the measurement of such an association and the precision and certainty for these measurements reported in the included studies (i.e. odds ratios and risk ratios, adjusted or unadjusted). The Committee also discussed review question 2. As the aim of this question was to identify who would have poorer outcomes within this patient pathway: • People with a pre-existing cardiac condition/or have had IE before --> experienced an episode of IE --> who are likely to die; and for those who survived, who would have the poorer outcomes. The Committee agreed that the critical outcomes for review question 2 are mortality; cardiac surgery; stroke/systemic embolism; length of hospital stay; recurrent attacks of IE; and acute kidney injury.
Quality of evidence	The committee sought clarification on the quality assessment criteria used to identify risk of bias and we invited the topic experts to identify any ratings that they felt might need amending. None were received. The Committee discussed the quality assessment tool (Hayden's checklist) used to assess the quality of included studies. The Committee commented that the criteria in the checklist did not account for other important complex elements that were relevant to this review question, for example, how different cardiac conditions are diagnosed and how this has changed over time; aging population and its associated multi-morbidity; and others. The committee expressed some surprise at the effect estimates and associated quality levels for pre-existing cardiac conditions in that the findings did not indicate as much of an increased risk of IE or as much of an increase in poorer outcomes as had been previously widely accepted. The Committee noted that the majority of the evidence was of high risk of bias, and that it was difficult to draw conclusions on whether people with a pre-existing cardiac condition, were more at risk of developing IE over time, though there was some evidence that suggested people who have previously had IE may be more at risk of developing further IE. Post consultation, consistent with stakeholder comments, topic experts were keen to note that the evidence for risk of IE in people with prosthetic valves was poor. This they felt was in part due to the lack of high quality case-control studies comparing people with prosthetic valves with the general population. In practice, people with prosthetic valves are consistently and widely accepted to be at increased risk, but the evidence found was scant and does not support this claim thus they found it difficult

	Committee discussions
	to believe. They supposed this could be due to the lack of perceived need to conduct studies to prove an association. Regardless, it was noted that it is beyond the remit of the Committee to change the current recommendations in the absence of high quality evidence to over-rule it. As such, recommendation 1.1.1. still cites people with prosthetic valves as at increased risk. The Committee also noted that, from this particular update, the evidence is still inconclusive to assess for those within the potential high-risk groups, who would have poorer outcomes (e.g. there was inconsistent evidence on mortality, cardiac surgery, stroke and recurrent IE, however the increased risk of mortality in people with prosthetic valves was noted). The topic experts commented on the generalisability of older studies. For example, these may have included older or obsolete practices, diagnostic criteria that no longer used and altered causative organism profiles that could affect the study quality and potentially the uncertainty around the effect estimates. In particular, this point was made in relation to the three studies cited for mitral valve prolapse (published in 1992, 1985 and 1998 respectively) which were all included in the original guideline.
Trade-off between benefits and harms	As the aim of this review question is to investigate the relationship between having a pre-existing cardiac condition and the risk of developing IE (to explore the pathogenesis of IE) , the discussion of trade-off between benefits and harms was not relevant for this question.
Trade-off between net health benefits and resource use	There is no impact on resource use related to these review questions per se. Section 2.6.4 contains a systematic review of economic evaluations that investigate the cost-effectiveness of antibiotic prophylaxis.
Other considerations	The Committee discussed the exclusion of people with implantable cardiac electronic devices and agreed that the exclusion is appropriate, as this population will merit their own separate clinical guideline on antibiotic prophylaxis. Due to the inconsistencies in the evidence and the number of studies that were deemed to be at high risk of bias or of questionable quality the Committee felt there was insufficient evidence to justify making an amendment to the current recommendation on high risk groups (please see recommendation 1.1.1).

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2.3 Review question 3

Which dental and other interventional procedures are associated with increased incidence of IE in those considered at risk of IE?

2.3.1 Clinical evidence review

Infective endocarditis (IE) is a rare condition and therefore it is difficult to determine which interventional procedures may be associated with an increased incidence of IE in those with defined pre-existing cardiac conditions. It has been suggested that some interventional procedures can cause bacteraemia, eliminated naturally in most people, most of the time. However, those with certain conditions may be at risk of this bacteraemia leading to the development of IE. It is therefore important to consider any evidence of significant post-procedure bacteraemia that may be potentially contribute to the risk of developing IE.

The aim of this review is to identify which interventional procedures are associated with increased incidence of IE in those considered at risk of IE (those with pre-existing cardiac conditions and those who have had IE previously). The interventional procedures covered by this review are listed below (defined by the original scope – appendix Q):

- Dental procedures
- Interventional procedures that cover the following sites:
  - Upper and lower gastrointestinal (GI) tract
  - Genitourinary tract (includes urological, gynaecological and obstetric procedures)
  - Upper and lower respiratory tract (includes ENT and bronchoscopy procedures)

A systematic update search using the original search strategy from CG64 was conducted (see appendix D) which identified 1081 articles. The titles and abstracts were screened and 13 articles were identified as potentially relevant. Full-text versions of these articles were obtained and reviewed against the criteria specified in the review protocol (appendix C). Of these, 12 were excluded as they did not meet the criteria. One study met the criteria and was included. Due to the substantial overlaps between this particular question and question 1 and 2, a very broad inclusive search with only endocarditis terms was also sifted for this review question to ensure no potential studies were missed. This additional search identified 2 more studies that met the inclusion criteria. With the 3 included studies from the original guideline CG64, there are 6 total included studies for this review question.

A review flowchart is provided in appendix E, and the excluded studies (with reasons for exclusion) are shown in appendix F.

2.3.21 Methods

2 Summary of review protocols

3 The population included adults and children undergoing interventional procedures (with
4 underlying cardiac condition, or who have had previous IE) including dental, upper and lower
5 gastrointestinal tract, genitourinary tract (this includes urological, gynaecological and
6 obstetric procedures including childbirth), upper and lower respiratory tract (includes ear
7 nose and throat and bronchoscopy procedures). No subgroups were identified for this
8 question.

9 The topic experts identified the following outcome as of interest for this review:

10 • Any statistical tests that assessed the association between the interventional procedures
11 mentioned above and the outcome of interest (number of IE).

12 Quality assessment - risk of bias

13 As this is a review question on assessing the association between different risk factors and
14 IE, GRADE methodology is not appropriate for quality assessment for this particular
15 question. The quality of individual studies was assessed using the checklist for
16 prognostic/prediction/association studies by Hayden et al., 2006, as guided in Developing
17 NICE guidelines - the Manual, 2014. This checklist addresses 6 main areas including study
18 participation, study attrition, prognostic factor measurement, outcome measurement,
19 confounding measurement and account and finally the analysis used in the study. Each
20 individual study was assessed against this criteria and an overall quality rating was assigned
21 using the following thresholds:

22 • all 6 criteria on checklist met: no risk of bias

23 • at least 4 out of 6 criteria met: low risk of bias

24 • anything else: high risk of bias

25 Statistical analysis

26 Conventional meta-analyses were not conducted due to the variations and heterogeneity in
27 population and outcome measures from study to study.

28 Where appropriate, summary measures such as adjusted or unadjusted odds ratios (with
29 95% confidence intervals, where available) were presented in the evidence summary.

30 All findings are based on statistical significance, as the aim of review question is to
31 investigate whether there are any statistical significant associations between rsk factors and
32 outcome of interest.

33 Overall summary of evidence

34 For a summary of included studies please see below table 4 (for the full evidence tables
35 please see appendix G). For the full details on quality assessment of the individual included
36 studies using the Hayden's checklist please see appendix M.

37 Overall, 6 studies were included in this review (3 from the update search, 3 from the original
38 guideline). All 6 included studies were of various degrees of risk of bias due to the following
39 reasons:

40 • Most included studies had unclear loss to follow-up due to the retrospective nature of the
41 study design (e.g. the quality of the databases data retrieved from).

- Most included studies did not report clearly how they accounted for potential confounders that may impact on the association between the risk factors (interventional procedures) and the outcome of interest (development of IE).
- Unclear statistical analyses that were used in the included studies, and even if multivariate analysis was conducted, it was of small sample size and therefore lacked power.

Table 4: Summary of included studies

Study reference (including study design)	Study population	Predictors (or risk factors)	Outcomes	Effect estimates (including analysis used)	Quality
Mohee (2014) Case-control study	384 adult patients treated for IE split into 4 groups: -Enterococcal IE group -CoNS IE group -Streptococcus bovis group -Oral streptococcal IE group (N=384)	Procedure related risk factors were identified from the data (procedures undertaken ≤1 year before the development of IE).	Odds of IE	Univariate ananlysis in patients with IE: *Enterococcal IE group (n=111)* Upper GI procedures: OR = 0.95 (95%CI: 0.33 to 2.72) Lower GI procedures: OR = 1.25 (95%CI: 0.41 to 3.73) Urological procedures: OR = 7.28 (95%CI: 3.35 to 15.8) *CoNS IE group (n=86)* Upper GI procedures: OR = 1.19 (95%CI: 0.65 to 4.93) Lower GI procedures: OR = 0.86 (95%CI: 0.24 to 3.14) Urological procedures: OR = 0.44 (95%CI: 0.15 to 1.28) *Streptococcus bovis group (n=36)* Upper GI procedures: OR = 1.22 (95%CI: 0.27 to 5.55) Lower GI procedures: OR = 0.68 (95%CI: 0.09 to 5.36) Urological procedures: OR = 0.58 (95%CI: 0.13 to 2.54) *Oral streptococcal IE group (n=151)* Upper GI procedures: OR = 0.43 (95%CI: 0.14 to 1.33) Lower GI procedures: OR = 0.77 (95%CI: 0.26 to 2.29) Urological procedures: OR = 0.19 (95%CI: 0.06 to 0.54) Multivariate analysis in patients with enterococcal IE: Urological procedures: adj OR = 8.56 (95%CI: 3.69 to 19.85)	Low risk of bias
Chen (2013) Case-control study	736 adult patients diagnosed with IE, and 7360 matched controls without IE.	The frequency of dental scaling within 2 years before the	Odds of IE	Logistic regression was used to analysis the associations between procedures and IE.	Low risk of bias

Study reference (including study design)	Study population	Predictors (or risk factors)	Outcomes	Effect estimates (including analysis used)	Quality
	(N=8096)	enrolment of the study.		*Frequency of dental scaling:* 1 time in 2 years: adj OR = 0.845 (95%CI: 0.693 to 1.012) At lease 1 time per year: adj OR = 0.696 (95%CI: 0.542 to 0.894)	
Ammar (2013) Case-control study	175 adult patients with definite IE according to modified Duke Criteria for diagnosis of IE and 175 adult controls without IE were identified. (N=350)	Procedure related risk factors were identified from data collected from the cases and control.	Odds of IE	Simple Pearson's chi-square test was used to analysis the associations between procedures and IE. Procedure-related risk factors: *Dental procedures:* Cases = 6 (3.4%); control = 8 (4.6%), P>0.05 *Gynaecological procedures:* Cases = 1 (0.6%); control = 4 (2.3%), P>0.05 *Urinary catheterization:* Cases = 2 (1.1%); control = 6 (3.4%), P>0.05	High risk of bias
Duval (2006) Cross sectional study (epidemiological study) [from CG64]	Of the 2805 interviewed adults, there were 182 cases of IE, 12 occurred in adults with known PCC after dental procedures and were considered to be caused by an oral microorganism (n = 10 unprotected). (N=2805)	Investigated the estimated risk of endocarditis in adults with predisposing cardiac conditions (PCC) undergoing dental procedures with or without antibiotic prophylaxis.	Odds of IE	The risk was estimated using the formula: risk = annual number of IE cases after at-risk dental procedures in adults with known PCC /annual number of at-risk dental procedures in adults with known PCC. The prevalence of PCC from the data from the study was 104 native valve and 24 prosthetic valve conditions. The estimated risk of IE after dental procedure in adults with known PCC was as follow: • 1 case per 46,000 (95% CI 36,236 to 63,103) for unprotected dental procedures • 1 case per 54,300 (95% CI 41,717 to 77,725) for unprotected dental procedures in those with native valve PCC • 1 case per 10,700 (95% CI 6000 to 25,149) for unprotected dental procedures in those with prosthetic valve PCC • 1 case per 149,000 (95% CI 88,988 to 347,509) for	High risk of bias

Study reference (including study design)	Study population	Predictors (or risk factors)	Outcomes	Effect estimates (including analysis used)	Quality
				protected dental procedures	
Lacassin (1995) Case-control study [from CG64]	A case–control study interviewed 171 adults following diagnosis of IE (based on the Von Reyn's criteria) within 180 days of the onset of symptoms, with one control identified for each case. Of the cases, with 89 (20.8%) having undergone a procedure for which prophylaxis was indicated. 88 (51.5%) of the cases and 70 (41%) of the controls had undergone at least one procedure. (N=342)	Procedure related risk factors were identified from data collected from the cases and control.	Odds of IE	The results of the association are as follow: Univariate analysis adjusted for other procedures: *Any dental procedures:* Cases = 37 (22%); control = 33 (19%); OR = 1.2 (95%CI: 0.7 to 2.1) *Any urological procedures:* Cases = 6 (3.5%); control = 2 (11%); OR = 3.1 (95%CI: 0.6 to 15.7) *Any GI procedures:* Cases = 14 (8.2%); control = 8 (4.7%); OR = 1.2 (95%CI: 0.7 to 4.1) *Multivariate analysis:* Urological procedure: adj OR = 6.1 (95%CI: 0.9 to 39.7) Scaling: adj OR = 2.7 (95%CI: 0.8 to 9.0) Canal treatment: adj OR = 1.7 (95%CI: 0.5 to 5.2) Both the univariate and multivariate analyses suggested that none of the interventional procedures being investigated were significantly associated with increased risk of IE.	High risk of bias
Strom (1998) Case-control study [from CG64]	273 adult patients who had definite, probableor possible IE were identified as cases. There was one control for each case matched for age, sex, ethnicity, education, occupation and dental insurance status; controls were selected	A case–control study that considered dental risk factors and the risk factors of oral hygiene and non-dental procedures.	Odds of IE	In the multivariate analysis, the associations of interventional procedures and risk of IE were as below: *Multivariable adjusted OR (in previous 3 months):* *Pulmonary procedures (inc. lung biopsy & bronchoscopy):* Cases = 3 (1.1%); control = 3 (1.1%); adj OR = 0.27 (95%CI: 0.01 to 5.46) *Barium enema:* Cases = 11 (4%); control = 1 (0.4%); adj OR = 11.9	High risk of bias

Study reference (including study design)	Study population	Predictors (or risk factors)	Outcomes	Effect estimates (including analysis used)	Quality
	from the community for each case patient using a modified random-digit method. (N=546)			(95%CI: 1.34 to 106) *Lower GI endoscopy:* Cases = 14 (5.1%); control = 8 (2.9%); adj OR = 1.95 (95%CI: 0.58 to 6.53) *Upper GI endoscopy:* Cases = 8 (2.9%); control = 4 (1.5%); adj OR = 1.36 (95%CI: 0.26 to 6.99) *Urinary catheterization:* Cases = 12 (4.4%); control = 4 (1.5%); adj OR = 0.58 (95%CI: 0.11 to 3.10) *Gynecological surgery:* Cases =3 (1.1%); control = 0 (0.0%); adj OR = N/A *Other genitourinary procedures (inc. cystoscopy, lithotripsy, vasectomy):* Cases = 4 (1.5%); control = 3 (1.1%); adj OR = 0.61 (95%CI: 0.06 to 5.80) Only barium enema remained significant after multivariate adjustment OR 11.9 (CI; 1.34 to 106), p=0.026	

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2.3.31 Clinical evidence statements

One case-control study with low risk of bias (n=111) suggested that enterococcal IE was significantly associated with urological procedures (positive association) but a negative significant association was also identified between oral streptococcal IE and urological procedures (n=151). Another case-control study suggested a negative significant association between dental scaling (at least 1 time per year) and IE (n=8096, low risk of bias).

However, there were also 3 case-control studies with high risk of bias (N = 350, 341, 546) that showed conflicting evidence. With the exception of barium enema, these 3 studies have suggested there were no statistical significant association between dental procedures, gynaecological procedures, urinary/urological procedures, pulmonary procedures, GI procedures and the development of infective endocarditis in adults.

Another cross sectional study with high risk of bias (N = 2805) also suggested the estimated risk of IE after dental procedure in adults with known pre-existing cardiac conditions was very low:

- 1 case per 46,000 (95% CI 36,236 to 63,103) for unprotected dental procedures
- 1 case per 54,300 (95% CI 41,717 to 77,725) for unprotected dental procedures in those with native valve pre-existing cardiac conditions
- 1 case per 10,700 (95% CI 6000 to 25,149) for unprotected dental procedures in those with prosthetic valve pre-existing cardiac conditions

2.3.40 Evidence to recommendations

	Committee discussions
Relative value of different outcomes	The Committee discussed and agreed that the critical outcome for this review question was to establish whether there is a clear relationship between specific interventional procedures and the development of IE in people who have pre-existing cardiac conditions or have had an episode of IE before (with or without known origin). Therefore, the only critical outcome is the measurement of such an association and the precision and certainty for these measurements reported in the included studies.
Quality of evidence	The Committee discussed the utility of the Hayden's checklist (2007) to assess the quality of evidence for this particular review question. It was acknowledged and agreed that the 6 criteria in the Hayden's checklist were not comprehensive nor detailed enough to fully assess the complex methodology and assumptions used in the included studies for this particular question. The Committee further discussed and acknowledged that the study design of Mohee (2014) study was different to the other included studies, and that the study investigated the relationship between the actual bacteria that caused IE and the interventional procedures (instead of just the events of IE). The Committee further noted that data on *staphylococcus aureus* was omitted from this particular study, which may or may not be a source of bias. The Committee also discussed and commented that baseline oral hygiene of the study population in the included studies on dental procedures could be a major confounder for the presence or absence of an association in this review question. As all the studies are retrospective and the baseline characteristic data is unclear, it was difficult to assess whether the association (or lack of association) was due to the specific dental procedures at index time, or the different degrees of oral hygiene of the individuals in the studies. This same concern also applied to the Chen (2013) study on scaling. Finally, the Committee commented that the estimated risk of IE after dental procedures in adults reported in the Duval (2006) study was based on a

	Committee discussions
	huge assumption that antibiotic prophylaxis is effective, which is still an area of high uncertainty (please see question 6). In addition, the pre-existing cardiac conditions were not clearly defined in the study. The Committee also further noted that the study on barium enema (Strom 1998) is relatively old, and that barium enema is seldom carried out in current practice. Overall, the Committee felt there is very limited evidence on this subject and there was high uncertainty due to the poor quality of the majority of the included studies.
Trade-off between benefits and harms	As the aim of this review question is to investigate the relationship between interventional procedures and the development of IE (to explore the pathogenesis of IE to inform the model structure of the health economic evaluation [please sections for question 6]), the discussion of trade-off between benefits and harms was not relevant for this question.
Trade-off between net health benefits and resource use	There is no impact on resource use related to this review question per se. Section 2.6.4 contains a systematic review of economic evaluations that investigate the cost-effectiveness of antibiotic prophylaxis.
Other considerations	For dental and non-dental procedures assessed in this review questions, the Committee felt that the studies have provided inconclusive evidence on the association between interventional procedures and the development of IE. The Committee agreed that current evidence is still insufficient to support the hypothesis that interventional procedures lead to the development of IE in people with pre-existing cardiac conditions. To answer this review question, a complex longitudinal study on the pathogenesis of IE (with a large sample size) needs to be conducted. The study may involve genetic sampling to investigate the origin of IE.

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2.4 Review question 4

What levels of bacteraemia are associated with interventional procedures, both pre and post-procedure (including consideration of what is considered significant bacteraemia)?

2.4.1 Clinical evidence review

In current practice, decisions on which interventional procedures merit antibiotic prophylaxis for people who are at risk of IE are drawn from the postulation that, bacteraemia that arises following interventional procedures could be part of the causative process in the development of IE. The aim of this review is to identify what levels of bacteraemia are associated with the following interventional procedures as defined in the guideline scope (appendix Q):

- Dental procedures
- Interventional procedures that cover the following sites:
  - Upper and lower gastrointestinal (GI) tract
  - Genitourinary tract (includes urological, gynaecological and obstetric procedures)
  - Upper and lower respiratory tract (includes ENT and bronchoscopy procedures)

A systematic update search using the original search strategy from CG64 was conducted (see appendix D) which identified 1081 articles. The titles and abstracts were screened and 74 articles were identified as potentially relevant. Full-text versions of these articles were obtained and reviewed against the criteria specified in the review protocol (appendix C). Of these, 58 were excluded as they did not meet the criteria and 16 met the criteria and were included. With the 14 included studies from the original guideline CG64, there are 30 total included studies for this review question.

A review flowchart is provided in appendix E, and the excluded studies (with reasons for exclusion) are shown in appendix F.

2.4.2 Methods

Summary of review protocols

The population included adults and children undergoing interventional procedures (irrespective whether they have underlying cardiac condition, or whether they have had previous IE) including dental, upper and lower gastrointestinal tract, genitourinary tract (this includes urological, gynaecological and obstetric procedures including childbirth), upper and lower respiratory tract (includes ear nose and throat and bronchoscopy procedures). No subgroups were identified for this question.

The topic experts identified the following outcomes of interest for this review:

- Bacteraemia levels/intensity/bacterial counts per unit volume at one or more time points following the procedure (definition of intensity may vary by study)
- Duration of bacteraemia following a procedure
- Number/incidence/odds of having positive blood samples before and after procedure

In order to establish any possible association between an interventional procedure and bacteraemia, only studies that had compared bacteraemia before and after a procedure, or compared bacteraemia between 2 groups (bacteraemia in interventional procedure group vs control group) were included.

Quality assessment - risk of bias

As this is a review question on assessing associations between interventional procedures and bacteraemia, GRADE methodology is not appropriate for quality assessment for this particular question. The quality of individual studies was assessed using the checklists as guided in Developing NICE guidelines - the Manua, 2014 based on the study designs. Of the total 30 included studies, 14 studies were intervention studies where the control arm data could be extracted for this particular question. As only the control arm data was used in these 14 studies (comparing the baseline pre-procedure data to the post-procedure data within the control group only), these 14 studies were re-assessed as before-and-after studies. The other 16 included studies were of primary within-subject before-and-after studies. Together, the risk of bias of these 30 included studies were assessed using the Cochrane effective and organisation of care review group (EPOC) checklist for before-and-after studies (as guided in Developing NICE guidelines - the Manual, , 2014). For more information for quality assessment, please see appendix M. Each individual study was assessed against the 7 criteria and an overall quality rating was assigned using the following thresholds:

- The EPOC tool (7 criteria)
  - Studies that have met all 7 criteria: no risk of bias
  - Studies that have met at least 4 out of the 7 criteria: low risk of bias
  - Studies that have met less than 4 out of the 7 criteria: high risk of bias

Statistical analysis

Conventional meta-analyses were not conducted, due to the variations and heterogeneity in population and outcome measures from study to study.

All findings are based on statistical significance, as the aim of review question is to investigate whether there are any statistical significant associations between interventional procedures and bacteraemia.

Overall summary of evidence

For a summary of included studies please see below table 5 (for the full evidence tables please see appendix G). For the full details on quality assessment of the individual included studies please see appendix N.

There are 30 included studies in total for this particular review question. Only 5 out of the 29 studies were on children (Lucas 2002; Roberts 1998, 2000, 2006; Sonbol 2009). The number of included studies for different interventional procedures are as follow:

- Dental procedures: 15 studies (5 old, 10 new)
- Upper and lower respiratory tract procedures: 4 studies (1 old, 3 new)
- Upper and lower GI procedures: 11 studies (8 old, 3 new)
- Genitourinary tract procedures: no study identified met the inclusion criteria

16 of the included studies were within-subjects before-and-after studies, 13 were randomised controlled trials (where the data from the control arm was extracted), and 1 cohort study. The majority of the included studies were of high risk of bias due to the following reasons:

- Unclear baseline characteristics
- Risk of selection bias and unclear data on those who withdrew from the studies
- Difficulty in establishing the association between procedures and bacteraemia (where multiple time points of blood samples were obtained, it was not clear whether the number of positive bacteraemia at different time points were from the same patients during the study).
- Small sample size and short follow-ups

- Inappropriate or lack of statistical comparison (only provided p-values from various non-parametric tests).

Table 5: Summary of included studies

Study reference (including study design)	Study population	Procedures	Outcomes	Effect estimates (including analysis used)
Tuna (2012), ID: 165 RCT	Total number = 34; control group = 10 (group of interest) [the other 24 patients had povidone iodine or chlorhexidine prophylaxis]. Adults: Gender: 5 males; 5 females Mean age: 26.8 years old (SD: 4.8)	Dental: Third molar extraction.	Bacteraemia Peripheral venous blood samples were collected from each patient at baseline (before the injection of local anaesthesia with articaine and adrenaline), 1 minute and 15 minutes after completion of the extraction.	Prevalence of bacteraemia: Baseline= 5/10 (50%); 1st min = 4/10 (40%); 15th min = 3/10 (30%); McNemar's p = 0.810.
DuVall (2013), ID: 80 RCT	Total number = 30; control group = 10 (group of interest) [the other 20 patients had amoxicilin or chlorhexidine prophylaxis]. Adults: Gender (total): 23 males; 7 females Mean age (total): 21.8 years old (range: 18 to 29)	Dental: Third molar extraction	Bacteraemia 4 blood samples (BS) were obtained through IV access line for each patient in the following manner: • Baseline (before placebo tablet) (BS1) • 1.5 min following initiation of the mucogingival flap #32 (BS2) • 1.5 min following initiation of the mucogingival flap #17 (BS3) • 10 min following initiation of the mucogingival flap #17 (BS4)	Incidence of bacteraemia (defined as at least one positive culture of the 4 BS per patient): 6/10 (60%) Magnitude of bacteraemia (mean CFU/ml per BS with SD): BS1 = 0.00 (SD:0.00); BS2 = 1.26 (SD: 3.67); BS3 = 1.90 (SD: 5.36); BS4 = 0.45 (SD: 0.83); Kruskal-Wallis P = 0.031
Lockhart (2008), ID: 457	Total number = 290; control group = 96 (group of interest)	Dental: Tooth extraction	Bacteraemia	Prevalence and duration of bacteraemia:

Study reference (including study design)	Study population	Procedures	Outcomes	Effect estimates (including analysis used)
RCT	[the other 194 patients either had amoxicilin prophylaxis or on brushing intervention]. Adults: Mean age = 40.5 years old (SD: 10.9) Gender = 51 males; 45 females.		6 blood samples (BS) were drawn as follow: • The baseline blood sample (20 mL) was then drawn and 7-8 mL was inoculated directly into both aerobic and anaerobic BACTEC® bottles for bacterial culturing. • Subsequent blood draws of 20 mL were taken at 1.5 min and at 5 min after the initiation of surgery. • Additional blood samples (20 mL) were drawn 20, 40, and 60 min following the end of the procedure.	Baseline = 0/89 (0%); 1.5 min = /84 (45%); 5 min = 42/84 (50%); 20 min = 8/83 (10%); 40 min = 4/83 (5%); 60 min = 4/82 (5%), p=0.03
Assaf (2007), ID: 687 Split-mouth trial	Total number = 22 Adults: Gender: 14 females; 8 males Age range: from 21 years to 50 years Mean age: 31.8 years for females; 33 years for males.	Dental: Ultrasonic scaling (US) with or without diode lasers (DL) (on all patients, split-mouth design)	Bacteraemia Blood sample of 10 mL was drawn just before and 3 min after initiation of US on the control side. Following the completion of US on the control side, laser energy was applied to the gingival crevices of the teeth present on the experimental side (DL+US). Thirty minutes later, blood was drawn again just before and 3 min after initiation of US in the previously lased teeth.	Prevalence of bacteraemia: US: Baseline = 0/22 (0%); 3 min = 15/22 (68%), p<0.05 US+DL: Baseline = 0/22 (0%); 3 min = 8/22 (36%); RR = 1.87 (95%CI: 1.01 to 3.49), p=0.001
Cherry (2007), ID:	Total = 60; control group = 30 (group of interest)	Dental: Ultrasonic scaling.	Bacteraemia	Prevalence of bacteraemia:

Study reference (including study design)	Study population	Procedures	Outcomes	Effect estimates (including analysis used)
1075 RCT	[the other 30 patients had povidone–iodine wash prophylaxis]. Adults: Mean age: 43.9 years old (SD: 20.8) Gender: 7 males; 23 females		10 ml of blood was sampled as a baseline measurement immediately following rinsing with either NaCl or POV–I and before scaling commenced, to ensure the absence of a pre-existing bacteraemia. 10 ml of blood was sampled 30 s after scaling was commenced and a further 10 ml of blood was sampled at the completion of 2 min of scaling.	Baseline = 0/30 (0%); 30s = 4/30 (13%); 2 min = 9/30 (30%), p=0.001 Overall, a positive bacteraemia of oral origin was found in 33% of the patients in the group.
Morozumi (2010), ID: 381 RCT	Total = 30; Control group = 10 (group of interest) Adults: Gender: 8 males; 2 females Mean age: 55.4 years old (SD:9.3)	Dental: Scaling and root planing	Bacteraemia At baseline, peripheral blood and subgingival plague were collected. The second sample of peripheral blood was taken 6 min after the initiation of SRP.	Prevalence of bacteraemia: Baseline = 0/10 (0%); 6 min = 9/10 (90%), p<0.05
Pineiro (2010), ID: 395 RCT	Total = 50; control group = 30 (group of interest) [the other 20 patients had chlorhexidine prophylaxis]. Adults: Mean age: 55 years old (SD: 13.5) Gender: 8 males; 22 females	Dental: Dental implant placement	Bacteraemia A peripheral venous blood sample (10 ml) was collected from each patient before the start of the surgical procedure to determine the prevalence of bacteraemia before intervention (baseline). Further peripheral blood samples (10 ml) were taken 30 s after insertion of the last implant and at 15 min after the completion of suturing of the muco-periosteal flap.	Prevalence of bacteraemia: Baseline = 1/30 (3.3%); 30 s = 2/30 (6.6%); 15 min = 1/30 (3.3%), p>0.05
Yagci	Total = 29	Dental:	Bacteraemia	Prevalence of bacteraemia:

Study reference (including study design)	Study population	Procedures	Outcomes	Effect estimates (including analysis used)
(2013), ID: 112 Before-and after study	Adults and children: Gender: 22 female, 7 male Mean age: 18.2 years old (SD: 3.4, range, 14.7-24.3)	Orthodontic stripping	All blood samples were collected from the patients under sterile conditions at 2 time points: before and soon after stripping.	Baseline = 0/29 (0%); Post stripping = 1/29 (3.4%) [*Streptococcus sanguis*], p=0.312
Sonbol (2009), ID: 545 RCT	Total = 205 (at randomisation) Children: Gender: 102 boys; 103 girls Mean age: 10.8 years old (SD: 3.67), range 4.00–17.5 years old. 43 were withdrawn with final total number of 162 children.	Dental: Rubber dam and clamp: N=41 Fast drill: N=40 Slow drill: N=40 Matrix band and wedge: N=41	Bacteraemia Blood samples of 6 ml pre-procedure and then another 6 ml 30 s after the procedure were drawn.	Prevalence of bacteraemia: Rubber dam and clamp: Baseline = 12/41 (29%); post-procedure = 22/41 (54%); p=0.01 Fast drill: Baseline = 6/40 (15%); post-procedure = 9/40 (22%); p=0.5 Slow drill: Baseline = 4/40 (10%); post-procedure = 9/40 (22%); p=0.2 Matrix band and wedge: Baseline = 13/41 (32%); post-procedure = 27/41 (66%); p=0.001 Intensity of bacteraemia (detectable ≥0.33 CFU/ml): Anaerobic: Rubber dam and clamp: Baseline = 7/41 (17%); post-procedure = 17/41 (41%); p=0.005 Fast drill: Baseline = 4/40 (10%); post-procedure = 7/40 (18%); p=0.6 Slow drill: Baseline = 2/40 (5%); post-procedure = 9/40 (23%); p=0.02 Matrix band and wedge: Baseline = 9/40 (23%); post-procedure = 18/40 (45%); p=0.002 Aerobic:

Study reference (including study design)	Study population	Procedures	Outcomes	Effect estimates (including analysis used)
				Rubber dam and clamp: Baseline = 6/41 (15%); post-procedure = 16/41 (39%); p=0.001 Fast drill: Baseline = 4/40 (10%); post-procedure = 5/40 (13%); p=0.4 Slow drill: Baseline = 2/40 (5%); post-procedure = 1/40 (3%); p=1.0 Matrix band and wedge: 6/40 (15%); post-procedure = 21/40 (53%); p=0.0001
Zhang (2013), ID: 155 Before-and-after study	Total = 30 Adults: Gender: 12 males and 18 females Mean age: 47 years old (SD: 9.5)	Dental: Scaling and root planning (SRP)	Bacteraemia A 20 ml blood sample was obtained as a baseline at the beginning of prior to SRP. Another 20 ml of blood was sampled at 5 min after the initiation of SRP, and at 30 s and 10 min after the completion of SRP.	Prevalence of bacteraemia: Baseline VSB = 0/30 (0%); 5 min after initiation = 6/30 (20%); 30 s post = 2/30 (6.7%); 10min post = 0/30 (0%), p=N/A Magnitude of bacteraemia (mean CFU/ml): VSB: 5 min after initiation = 0.4 (SD: 0.2); 30 s post = 0.3 (SD: 0.1); 10min post = 0.0, p=N/A
Lucas (2002), ID: 9668 RCT	Total = 142 Children: Mean age 13.5yrs (range 9.2 to 17.9), n = 64 males, n = 78 females	Dental: Upper alginate impression (n=39); Separator (n=42); Fit/placement of band (n=25); Archwire adjustment (n=36)	Bacteraemia Blood samples: baseline sample and 30 second sample taken after the orthodontic procedure.	Prevalence of bacteraemia: Upper alginate impression: Baseline = 9/39 (23%); post-procedure = 12/39 (31%), p>0.05 Separator: Baseline = 12/42 (27%); post-procedure = 15/42 (36%), p>0.05 Fit/placement of band: Baseline = 9/25 (36%); post-procedure = 11/25 (44%), p>0.05 Archwire adjustment: Baseline = 12/36 (23%); post-procedure = 7/36 (31%), p>0.05 Intensity of bacteraemia (mean and SD cfu per ml of blood):

Study reference (including study design)	Study population	Procedures	Outcomes	Effect estimates (including analysis used)
				Upper alginate impression: Baseline = 0.2 (0.7); post-procedure = 0.3 (0.6), p>0.05 Separator: Baseline = 0.9 (0.2); post-procedure = 2.2 (9.1), p<0.02 Fit/placement of band: Baseline = 0.1 (0.2); post-procedure = 0.3 (0.6), p>0.05 Archwire adjustment: Baseline = 0.2 (0.7); post-procedure = 0.04 (0.1), p>0.05
Roberts (2000) ID: 460 RCT	Total = 257 Children: n = 141 male, n = 116 female, mean age 9yrs 1mth (range 2yrs to 19yrs 6mths)	Dental: Rubber dam placement (n=51); Matrix band & wedge (n=56); Slow drill (n=49); Fast drill (n=47); Baseline (no procedure) (n=54)	Bacteraemia Blood samples: before procedure, 30 s after procedure.	Prevalence of bacteraemia: Baseline n = 5/54 (9.3%); rubber dam placement n = 16/51 (31.4%); slow drill n=6/49 (12.2%); fast drill n = 2/47 (4.3%; matrix band and wedge n = 18/56 (32.1%) - baseline vs. rubber dam placement (p<0.005) - baseline vs. matrix band & wedge (p<0.003) - baseline vs. fast drill (p>0.05) - baseline vs. slow drill (p>0.05)
Roberts (2006) ID: 2375 RCT	Total = 500 Children: Mean age of the children was 7.6yrs (range 3.4 to 18.9) Children were allocated to one of the time groups in random permuted blocks; 10sec, 30sec,	Dental: Dental extraction	Bacteraemia Blood samples were taken from children according to their randomised time group.	Intensity of bacteraemia (median CFU/6ml sample): 10sec: before extraction median 2.9 (range 0 to 46); after extraction median 9.8 (range 0 to 149), p=0.001 30sec: before extraction median 0.5 (range 0 to 4); after extraction median 2.6 (range 0 to 17), p=0.001 1min: before extraction median 0.4 (range 0 to 4); after extraction median 16.4 (range 0 to 247), p=0.003

Study reference (including study design)	Study population	Procedures	Outcomes	Effect estimates (including analysis used)
	1min, 2min, 4min, 7.5min, 15min, 30min, 45min, 1hr.			2min: before extraction median 1.2 (range 0 to 23); after extraction median 8.1 (range 0 to 162), p=0.009 4min: before extraction median 0.4 (range 0 to 4); after extraction median 1.7 (range 0 to 15), p=0.002 7.5min: before extraction median 0.4 (range 0 to 4); after extraction median 1.2 (range 0 to 14), p=0.002 15min: before extraction median 1.7 (range 0 to 53); after extraction median 1.9 (range 0 to 33), p>0.05 30min: before extraction median 0.3 (range 0 to 6); after extraction median 0.6 (range 0 to 8), not determined 45min: before extraction median 0.7 (range 0 to 3); after extraction median 2.4 (range 0 to 46), p>0.05 1hr: before extraction median 1.0 (range 0 to 28); after extraction median 2.1 (range 0 to 49), p>0.05 The intensity was significantly greater at the post-extraction time than at the pre-extraction time up to and including 7.5min; however by 15min and beyond, the difference was not significant. The odds of having a positive culture were significantly greater in the post-extraction time than in the pre-extraction time (OR>1) at each time point up to an including a post-procedure time of 7.5min but not beyond this time

Study reference (including study design)	Study population	Procedures	Outcomes	Effect estimates (including analysis used)
Roberts (1998) ID: 2440 RCT	Total = 143 Children: Mean age = 8.7 years old	Dental: Local anaesthetic injections: Buccal infiltration (n=32); Modified intraligamental (n=32); Conventional intraligamental (n=29); Baseline (no procedures) (n=50)	Bacteraemia Blood samples: taken 30sec after injection	Prevalence of bacteraemia: Baseline = 4/50 (8.0%; 0.5 to 15.5% 95% CI) Buccal infiltration = 5/32 (15.6%; 2.8 to 28.5%, 95% CI) Modified intraligamental = 16/32 (50.0%; 29.2 to 64.5% 95% CI) Conventional intraligamental = 28/29 (96.6%; 75.2 to 99.2%, 95% CI) - baseline vs. modified intraligamental (p<0.0001) - baseline vs. conventional intraligamental (p<0.0001) - baseline vs. buccal infiltration (p>0.05)
Tomas (2007) ID: 27 RCT	Total = 106 (Control group = 53, group of interest) Adults and children: Male = 29(55%); female = 24(45%), mean age 26.1±12.3yrs (range 8 to 52 years).	Dental: Dental extractions	Bacteraemia Blood samples: baseline (after nasotracheal intubation and before local anaesthetic injection), 30sec after final dental extraction, 15min and 1hr after finishing the surgical procedure.	Prevalence of bacteraemia: Baseline = 5/53 (9.4%); 30 s = 51/53 (96.2%), 15min = 34/53 (64.2%), 1hr = 11/53 (20%), p=0.103
Sharif-Kashani (2010), ID: 368 Before-and-after	Total = 85 Adults: Gender: 69 males (81%); 16 females (19%) Mean age: 57 years old (SD: 28); range: 34-90	Upper and lower respiratory tract: Flexible fiberoptic bronchoscopy (FB)	Bacteraemia Three aerobic and anaerobic cultures for venous blood and lavage fluid were drawn just prior, immediately following and 20 min after bronchoscopy.	Prevalence and duration of bacteraemia: Baseline: 0/85 (0%); Immediately after FB: 7/85 (8%); 20 min after FB: 1/85 (1%), p=0.317

Study reference (including study design)	Study population	Procedures	Outcomes	Effect estimates (including analysis used)
study	years old			
El Batrawy (2014), ID: 776 Before-and-after study	Total = 45 Overall mean range: 8 to 65 years old. Adults: gender: 29 males; 7 females (total = 36) Adults mean age: 48 years old (SD: 13.75) Children: gender: 4 males; 5 females (total = 9) Children mean age: 12.3 years old (SD: 2.8)	Upper and lower respiratory tract: Bronchoscopy (rigid or flexible).	Bacteraemia Blood sampling: three 10 mL blood samples were taken from the anti-cubical fossa one immediately before and two after bronchoscopy 10 min apart under complete aseptic conditions.	Prevalence of bacteraemia: Baseline = 0/45; 10 min after = 0/45; 20 min after = 0/45, p=N/A
Saayman (2009), ID: 505 Before-and-after study	Total = 118; Non-antibiotics group = 57 (group of interest) Adults: Overall gender: 43 females and 75 males (subgroup not available) Overall age range: 19–88 years of age (median 61) (subgroup not available)	Upper and lower respiratory tract: Single-stage percutaneous dilatational tracheostomy.	Bacteraemia Peripheral venous blood cultures were performed using full aseptic conditions immediately prior to the procedure (pre-tracheostomy). A second set of peripheral venous blood cultures were taken immediately after securing the tracheostomy tube (post-tracheostomy).	Prevalence of bacteraemia: Baseline = 0/57 (0%); post PDT = 5/57 (8.7%), p=0.022
Yokoyama (2014), ID: 74	Total number = 42; control group = 21 (group of interest)	Upper and lower GI tract: Oesophagectomy.	Bacteraemia Blood samples (1ml) were collected	Prevalence of bacteraemia: Baseline = 5/21 (24%); post-operative day 1 =

Study reference (including study design)	Study population	Procedures	Outcomes	Effect estimates (including analysis used)
RCT	Adults: Gender: 18 males; 8 females Mean age: 66 years old (range: 25 to 77 years old)		into a test tube on the morning of the operation after induction of anaesthesia and just before laparotomy (baseline), and on post-operative day 1.	12/21 (57%), p=0.027
Ho (1991), ID: 829 Before-and-after study	Total = 72 (n = 126 endoscopies) Adults: Age ranged from 28 to 78 years; male = 58; female = 14.	Upper and lower GI tract: Emergency endoscopy; emergency EVS; elective EVS.	Bacteraemia Blood samples taken before endoscopy, at 5min and 30min after the procedure.	Prevalence of bacteraemia: Emergency endoscopy group blood cultures: Baseline = 0/37 (0%); 5 min = 2/37 (5%); 30 min = 3/37 (8%), p=0.076 Elective EVS sclerotherapy: Baseline = 3/33 (9%); 5 min = 1/33 (3%); 30 min = 4/33 (12%), p=0.689 Emergency EVS sclerotherapy; Baseline = 7/56 (13%); 5 min = 5/56 (9%); 30 min = 5/56 (9%), p=0.541
Melendez (1991), ID: 9109 Before-and-after study	Total = 140 Adults: Mean age 53±15 years (range 19 to 84 years), male = 69; female = 71	Upper and lower GI tract: Transoesophageal echocardiography (TOE)	Bacteraemia Blood samples: immediately before the procedure, within 5mins after termination of the procedure, 1hr after the procedure.	Prevalence of bacteraemia: Baseline = 4/140 (2.9%); 5 min = 2/140 (1.4%); 1 hour = 2/140 (1.4%), p=0.406
Roudaut (1993), ID: 3797 Before-	Total = 82 n = 44 (group I) n = 38 (group II) Adults:	Upper and lower GI tract: Transoesophageal echocardiography	Bacteraemia Blood samples: • Group I blood cultures taken before procedure, immediately	Prevalence of bacteraemia: Group I: Baseline = 0/44 (0%); immediately after = 1/44 (2.3%); 15 min after = 0/44 (0%), p=N/A Group II: Baseline = 0/38 (0%); 10 min into the

Study reference (including study design)	Study population	Procedures	Outcomes	Effect estimates (including analysis used)
and-after study	Mean age = 59 years (SD: 13); male = 46; female = 36.		after the procedure, 15min after procedure. • Group II blood cultures taken before procedure, during procedure (10min after the first attempt to introduce the endoscope), immediately after procedure.	procedure = 1/38 (2.6%); immediately after = 0/38 (0%), p=N/A
Shyu (1992), ID: 3820 Before-and-after study	Total = 132 Adults: Male = 66; female = 66; mean age = 44.6 years (range from 17 to 73 years)	Upper and lower GI tract: Transoesophageal echocardiography	Bacteraemia Blood samples: 30 to 60mins before the procedure, immediately after, 180 to 240mins after the procedure.	Prevalence of bacteraemia: Baseline (pre-): 3/270 (1.1%); immediately after = 0/270 (0%); 180 to 240 min after = 1/270 (0.4%), p=0.317
Yildirim (2003), ID: 238 Before-and-after study	Total = 64 Group I = 33 Group II = 31 Adults: Male = 28; female = 36; age ranged from 3 to 35 years old.	Upper and lower respiratory tract: Tonsillectomy	Bacteraemia Group I: Blood samples: pre-operative (after intubation), early post-operative (within 2mins after tonsillectomy) and post-operative (60mins after tonsillectomy). Group II: Blood samples: pre-operative (after intubation), post-operative (15 and 60mins after tonsillectomy).	Prevalence of bacteraemia: Group I: Baseline = 0/33 (0%); 2 min = 9/33 (27.3%); 60 min = 0/33 (0%), p=N/A Group II: Baseline = 0/31 (0%); 15 min = 2/31 (6.5%); 60 min = 0/31 (0%), p=N/A
Zuccaro (1998), ID: 5981 Cohort	Total = 103 Adults: Male = 73; female = 30	Upper and lower GI tract: Esophageal stricture dilation	Bacteraemia Blood samples: pre-procedure, 5, 20 and 30mins after the procedure	Prevalence of bacteraemia (viridans streptococcus): Baseline (before) = 0/103 (0%); 1 min = 19/81 (23%); 5 min = 16/96 (17%); 20-30 min = 3/63 (5%)
Min (2008),	Total = 40 (conventional	Upper and lower	Bacteraemia	Prevalence of bacteraemia:

Study reference (including study design)	Study population	Procedures	Outcomes	Effect estimates (including analysis used)
ID: 617 Before-and-after study	EMR = 30; EMR-P = 3; ESD = 7) Adults: Gender: 28 males; 12 females Median age of 60.0 years old (range 44 to 80 years old)	GI tract: Endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD)	Blood cultures were obtained immediately before, 5 minutes after, and 30 minutes after the procedure.	Baseline = 0/40 (0%); 5 min = 0/40 (0%); 30 min = 1/40 (2.5%), p=0.312
Chun (2012), ID: 238 Before-and-after study	Total = 64 Adults: Gender: 35 males; 29 females Mean age: 68.8 years old (SD: 10.8)	Upper and lower GI tract: Colorectal stent placement.	Bacteraemia The first set of blood sample was taken immediately before the procedure, and the second set was taken 30 min after colorectal stent insertion.	Prevalence of bacteraemia: Baseline = 0/64 (0%); 30 min = 4/64 (6%), p=0.042
Weickert (2006), ID: 42 Before-and-after study	Total = 100 patients n = 50 (convention laparoscopy); n = 50 (mini-laparoscopy) Adults: Mean age = 53.5 years (range 19 to 81 years),; male = 59; female = 41	Upper and lower GI tract: Conventional laparoscopy and mimi-laparoscopy	Bacteraemia Blood samples: immediately before laproscopy and within 5mins after the procedure.	Prevalence of bacteraemia: Baseline (before): 0/100 (0%); 5 min after = 4/100 (4%), p=0.043
Kullman (1992), ID: 10028 Before-and-after	Total = 180 patients (n = 194 examinations) Diagnostic ERCP n = 115 participants (n = 126 procedures) Therapeutic ERCP n =	Upper and lower GI tract: Diagnostic ERCP Therapeutic ERCP	Bacteraemia Blood samples: before the examination, 5min after cannulation and at 5 and 15 min after the end of examination.	Prevalence of bacteraemia: Diagnostic ERCP: Baseline (before) = 1/126 (0.8%); during = 10/126 (7.9%); after 5 min =12/126 (9.5%); after 15 min = 14/126 (11.1%), p<0.001

Study reference (including study design)	Study population	Procedures	Outcomes	Effect estimates (including analysis used)
study	65 participants (n = 68 procedures) Adults: Median age 66 years (range 26–92 years); female = 104; male = 76			Therapeutic ERCP: Baseline (before) = 0/68 (0%); during = 10/68 (14.7%); after 5 min =10/68 (14.7%); after 15 min = 13/68 (19.1), p<0.001
London (1986), ID: 952 Before-and-after study	Total = 50 (204 blood samples) Adults: Mean age 58.8 years (range 22 to 80 years); male = 24; female = 26	Upper and lower GI tract: Colonoscopy	Bacteraemia Blood sample: before insertion (baseline); 5 min after insertion; 5 min after removal.	Prevalence of bacteraemia: Baseline = 3/50 (6%); 10 min of insert = 1/50 (2%); 24 min of insert = 1/50 (2%); 42 min of insert = 1/50 (2%); 5 min after removal = 0/50 (0%), p=0.078.

1 **Dental procedures**

2 **Table 6: Summary table: dental procedures - number of having positive blood samples before and after procedure**

Study	Type of procedure (N)	Baseline (pre-procedure)	Time points post procedure/duration (surrogate)						P-value[4]	Quality
Tuna (2012)[5]	Third molar extraction (N=10)	**5/10 (50%)**		1 min 4/10 (40%)		15 min 3/10 (30%)			P=0.810	HRB
Lockhart (2008)[5]	Tooth extraction (N=89)	**0/89 (0%)**		1.5 min 38/84 (45%)	5 min 42/84 (50%)	20 min 8/83 (10%)	40 min 4/83 (5%)	60 min 4/82 (5%)	***P=0.03***	LRB
Tomas (2007)[1]	Tooth extraction (N=53)	**5/53 (9.4%)**	30 s 51/53 (96%)			15 min 34/53 (64%)		60 min 11/53 (20%)	P=0.103	HRB
Assaf (2007)[6]	Ultrasonic scaling (N=22)	**0/22 (0%)**			3 min 15/22				***P<0.05***	LRB

					(68%)					
Assaf (2007)[6]	Ultrasonic scaling with diode lasers (N=22)	**0/22 (0%)**			3 min 8/22 (36%)				***P=0.001***	LRB
Cherry (2007)[5]	Ultrasonic scaling (N=30)	**0/30 (0%)**	30 s 4/30 (13%)	2 min 9/30 (30%)					***P=0.001***	HRB
Morozumi (2010)[5]	Scaling & root planning (N=10)	**0/10 (0%)**			6 min 9/10 (90%)				***P<0.05***	HRB
Zhang (2013)[6]	Scaling & root planning (N=30)	**0/30 (0%)**	30 s 2/30 (6.7%)			10 min 0/30 (0%)			N/A	HRB
Pineiro (2010)[5]	Implant placement (N=30)	**1/30 (3.3%)**	30 s 2/30 (6.6%)			15 min 1/30 (3.3%)			P>0.05	HRB
Yagci (2013)[6]	Orthodontic stripping (N=29)	**0/29 (0%)**	Post[3] 1/29 (3.4%)						P=0.312	HRB
Sonbol (2009)[2,5]	Rubber dam & clamp (N=41)	**12/41 (29%)**	30 s 22/41 (54%)						***P=0.01***	HRB
Roberts (2000)[1,2,5]	Rubber dam & clamp (N=54)	**5/54 (9.3%)**	30 s 16/51 (31%)						***P<0.005***	HRB
Sonbol (2009) [2,5]	Fast drill (N=40)	**6/40 (15%)**	30 s 9/40 (22%)						P=0.5	HRB
Roberts (2000)[1,2,5]	Fast drill (N=54)	**5/54 (9.3%)**	30 s 6/49 (12%)						P>0.05	HRB
Sonbol (2009)[2,5]	Slow drill (N=40)	**4/40 (10%)**	30 s 9/40 (22%)						P=0.2	HRB
Roberts (2000)[1,2,5]	Slow drill (N=54)	**5/54 (9.3%)**	30 s 2/47 (4%)						p>0.05	HRB
Sonbol (2009)[2,5]	Matrix band & wedge (N=41)	**13/41 (32%)**	30 s 27/41 (66%)						***p=0.001***	HRB
Roberts (2000)[1,2,5]	Matrix band & wedge (N=54)	**5/54 (9.3%)**	30 s 18/56 (32%)						***P<0.003***	HRB
Lucas	Upper alginate	**9/39 (23%)**	30 s						P=0.441	HRB

(2002)[1,2,5]	impression (N=39)		12/39 (31%)							
Lucas (2002)[1,2,5]	Separator (N=42)	**12/42 (27%)**	30 s 15/42 (36%)						P=0.483	HRB
Lucas (2002)[1,2,5]	Fit/placement of band (N=25)	**9/25 (36%)**	30 s 11/25 (44%)						P=0.562	HRB
Lucas (2002)[1,2,5]	Archwire adjustment (N=36)	**12/36 (23%)**	30 s 7/36 (31%)						P=0.180	HRB
Roberts (1998)[1,2,5]	AJ: buccal infiltration (N=50)	**4/50 (8%)**	30 s 5/32 (16%)						p>0.05	HRB
Roberts (1998)[1,2,5]	AJ: modified intraligamental (N=50)	**4/50 (8%)**	30 s 16/32 (50%)						***P<0.0001***	HRB
Roberts (1998)[1,2,5]	AJ:conventional intraligamental (N=50)	**4/50 (8%)**	30 s 28/29 (97%)						***P<0.0001***	HRB

AJ = Anaesthetic injection NRB = no risk of bias; LRB = low risk of bias; HRB = high risk of bias
[1] from CG64
[2] children
[3] only stated post-procedure, no timeframe
[4] p-value comparing baseline and last time point, from various non-parametric tests
[5] RCT (data from the control arm)
[6] Within-subjects before-and-after study

Intensity of bacteraemia

Table 7: Summary table: dental procedures - intensity of bacteraemia

Mean CFU/ml							**Quality**
Duvall (2013)[8]	Third molar extraction (N=10)	Pre- procedure 0.00	1.5 min[1] 1.26	1.5 min[2] 1.90	10 min[3] 0.45	***p=0.031***	HRB
Zhang (2013)[9]	Scaling & root planning (N=30)	Pre- procedure 0.00	5 min after initiation 0.4	30 s 0.3	10 min 0.0	N/A	HRB
Lucas (2002)[6,7,8]	Upper alginate impression (N=39)	Pre- procedure 0.2	30 s 0.3			p>0.05	HRB
Lucas (2002)[6,7,8]	Separator (N=42)	Pre- procedure 0.9	30 s 2.2			***p<0.05***	HRB

Lucas (2002)[6,7,8]	Fit/placement of band (N=25)	Pre- procedure 0.1	30 s 0.3			p>0.05	HRB
Lucas (2002)[6,7,8]	Archwire adjustment (N=36)	Pre- procedure 0.2	30 s 0.04			p>0.05	HRB
Detectable ≥0.33 CFU/ml							**Quality**
Sonbol (2009)[7,8]	Rubber dam & clamp (N=41)	Pre- procedure 7/41 (17%)[4] 6/41 (15%)[5]	30 s 17/41 (41%)[4] 16/41 (39%)[5]			***P=0.005***[4] ***P=0.001***[5]	HRB
Sonbol (2009)[7,8]	Fast drill (N=40)	Pre- procedure 4/40 (10%)[4] 4/40 (10%)[5]	30 s 7/40 (18%)[4] 5/40 (13%)[5]			P=0.6[4] P=0.4[5]	HRB
Sonbol (2009)[7,8]	Slow drill (N=40)	Pre- procedure 2/40 (5%)[4] 2/40 (5%)[5]	30 s 9/40 (23%)[4] 1/40 (3%)[5]			***P=0.02***[4] P=1.0[5]	HRB
Sonbol (2009)[7,8]	Matrix band & wedge (N=40)	Pre- procedure 9/40 (23%)[4] 6/40 (15%)[5]	30 s 18/40 (45%)[4] 21/40 (53%)[5]			***P=0.002***[4] ***P=0.0001***[5]	LRB
Median CFU/6ml							**Quality**
Roberts (2006)[6,7,8]	Tooth extraction (N=500)	10 s before extraction = 2.9 (range 0 to 46); after extraction = 9.8 (range 0 to 149), ***p=0.001*** 30 s before extraction = 0.5 (range 0 to 4); after extraction = 2.6 (range 0 to 17), ***p=0.001*** 1 min before extraction = 0.4 (range 0 to 4); after extraction = 16.4 (range 0 to 247), ***p=0.003*** 2 min before extraction = 1.2 (range 0 to 23); after extraction = 8.1 (range 0 to 162), ***p=0.009*** 4 min before extraction = 0.4 (range 0 to 4); after extraction = 1.7 (range 0 to 15), ***p=0.002*** 7.5 min before extraction = 0.4 (range 0 to 4); after extraction = 1.2 (range 0 to 14), ***p=0.002*** 15 min before extraction = 1.7 (range 0 to 53); after extraction = 1.9 (range 0 to 33), p>0.05 30 min before extraction = 0.3 (range 0 to 6); after extraction = 0.6 (range 0 to 8), p>0.05 45 min before extraction = 0.7 (range 0 to 3); after extraction = 2.4 (range 0 to 46), p>0.05 1hr before extraction = 1.0 (range 0 to 28); after extraction = 2.1 (range 0 to 49), p>0.05					HRB

LRB = low risk of bias; HBR = high risk of bias
[1] 1.5 min following initiation of the mucogingival flap #32
[2] 1.5 min following initiation of the mucogingival flap #17
[3] 10 min following initiation of the mucogingival flap #17
[4] Anaerobic
[5] Aerobic
[6] from CG64

[7] *children*
[8] *RCT (data from the control arm)*
[9] *Within-subjects before-and-after study*

Upper and lower respiratory tract procedures

Table 8: Summary table: upper and lower respiratory tract procedures - number of having positive blood samples before and after procedure

Study	Type of procedure (N)	Baseline (pre-procedure)	Time points post procedure/duration (surrogate)				P-value[2]	Quality
Sharif- Kashani (2010)[3]	Bronchoscopy (N=85)	**0/85 (0%)**	Immediate-post 7/85 (8%)		20 min 1/85 (1%)		P=0.317	HRB
El-Batrawy (2014)[3]	Bronchoscopy (N=45)	**0/45 (0%)**		10 min 0/45 (0%)	20 min 0/45 (0%)		N/A	HRB
Saayman (2009)[3]	Tracheostomy (N=57)	**0/57 (0%)**	Immediate-post 5/57 (8.7%)				***P=0.022***	HRB
Yildirim (2003)[1,3,4]	Tonsillectomy (N=33)	**0/33 (0%)**		2 min 9/33 (27.3%)		60 min 0/33 (0%)	N/A	HRB
Yildirim (2003)[1,3,4]	Tonsillectomy (N=31)	**0/31 (0%)**		15 min 2/31 (6.5%)		60 min 0/31 (0%)	N/A	HRB

NRB = no risk of bias; LRB = low risk of bias; HRB = high risk of bias
[1] *from CG64*
[2] *p-value comparing baseline and last time point, from various non-parametric tests*
[3] *Within-subjects before-and-after study*
[4] *Yildirim (2003): mixed adults and children population.*

Upper and lower GI tract procedures

Table 9: Summary table: upper and lower GI tract procedures - number of having positive blood samples before and after procedure

Study	Type of procedure (N)	Baseline (pre-procedure)	Time points post procedure/duration (surrogate)				P-value[2]	Quality
Min (2008)[3]	Endoscopic sub/mucosal resection/dissection	**0/40 (0%)**		5 min 0/40 (0%)		30 min 1/40 (2.5%)	P=0.312	HRB

	(N=40)							
Chun (2012)[3]	Colorectal stent placement (N=64)	**0/64 (0%)**				30 min 4/64 (6%)	***P=0.042***	HRB
Weickert (2006)[1,3]	Laparoscopy/mimi-laparoscopy (N=100)	**0/100 (0%)**		5 min 4/100 (4%)			***P=0.043***	HRB
Kullman (1992)[1,3]	Diagnostic ERCP (N=126)	**1/126 (0.8%)**	During 10/126 (7.9%)	5 min 12/126 (9.5%)	15 min 14/126 (11%)		***P<0.001***	HRB
Kullman (1992)[1,3]	Therapeutic ERCP (N=68)	**0/68 (0%)**	During 10/68 (15%)	5 min 10/68 (15%)	15 min 13/68 (19%)		***P<0.001***	HRB
London (1986)[1,3]	Colonoscopy (N=50)	**3/50 (6%)**	10 min of insert 1/50 (2%)	24 min of insert 1/50 (2%)	42 min of insert 1/50 (2%)	5 min after removal 0/50 (0%)	P=0.078	HRB
Yokoyama (2014)[5]	Oesophagectomy (N=21)	**5/21 (24%)**				24 hrs 12/21 (57%)	***P=0.027***	HRB
Ho (1991)[1,3]	Emergency endoscopy (N=37)	**0/37 (0%)**		5 min 2/37 (5%)	30 min 3/37 (8%)		P=0.076	HRB
Ho (1991)[1,3]	Elective EVS (N=33)	**3/33 (9%)**		5 min 1/33 (3%)	30 min 4/33 (12%)		P=0.689	HRB
Ho (1991)[1,3]	Emergency EVS (N=56)	**7/56 (13%)**		5 min 5/56 (9%)	30 min 5/56 (9%)		P=0.541	HRB
Melendez (1991)[1,3]	Transesophageal echocardiography (N=140)	**4/140 (3%)**		5 min 2/140 (1.4%)		1 hr 2/140 (2.4%)	P=0.406	HRB
Roudaut (1993)[1,3]	Transesophageal echocardiography (N=44)	**0/44 (0%)**	Immediate-post 1/44 (2.3%)	15 min 0/44 (0%)			N/A	HRB
Roudaut (1993)[1,3]	Transesophageal echocardiography (N=38)	**0/38 (0%)**	10 min during 1/38 (2.6%)	Immediate-post 0/38 (0%)			N/A	HRB
Shyu (1992)[1,3]	Transesophageal echocardiography (N=270)	**3/270 (1%)**	Immediate-post 0/270 (0%)			3-4 hrs 1/270 (0.4%)	P=0.317	HRB
Zuccaro (1998)[1,4]	Oesophageal stricture (N=103)	**0/103 (0%)**	1 min 19/81 (23%)	5 min 16/96 (17%)	20-30 min 3/63 (5%)		***P=0.025***	HRB

EVS = oesophageal variceal sclerotherapy; NRB = no risk of bias; LRB = low risk of bias; HRB = high risk of bias
[1] from CG64
[2] p-value comparing baseline and last time point, from various non-parametric tests.
[3] Within-subjects before-and-after study
[4] cohort study
[5] RCT (data from the control arm)

Genitourinary tract procedures

No study identified met the inclusion criteria

2.4.31 Clinical evidence statements

Dental procedures - Number of having positive blood samples before and after procedure

Adults:

5 RCTs (data from the control arm) and 2 before-and-after studies (N = range from 10 to 89) with various degrees of risk of bias showed inconsistent evidence on the associations between different recent dental procedures (extraction, scaling and root planning, implant placement and orthodontic stripping) and bacteraemia in adults.

Conversely, 1 RCT (data from the control arm) and 1 before-and-after study (N = range from 22 to 30) with various degrees of risk of bias suggested that there were statistical significant associations between ultrasonic scaling and bacteraemia in adults. However, the time frame for post procedure bacteraemia was relative short and only p-values were reported for these 2 studies.

Children:

4 RCTs (data from the control arm) (N = range from 10 to 89) with high risk of bias showed inconsistent and inconclusive evidence on the associations between different recent dental procedures (fast and slow drill, alginate impression, separator, fit of band, archwire adjustment buccal infiltration and intraligamental) and bacteraemia in children.

Conversely, 3 RCTs (data from the control arm) (N = range from 10 to 50) with high risk of bias suggested that there were statistical significant associations between rubber dam and clamp, matrix band and wedge, intraligamentary injection, and bacteraemia in children. However, the time frame for post procedure bacteraemia was relative short (30 seconds post-procedure) and only p-values were reported for these 2 studies.

Dental procedures - Intensity of bacteraemia

3 RCTs (data from the control arm) and 1 before-and-after study (N = range from 10 to 500) with high risk of bias showed inconsistent and inconclusive evidence on the associations between different recent dental procedures and intensity of bacteraemia in adults and children, depending on which measurements that were used in the studies (mean CFU/ml, detectable ≥0.33 CFU/ml, median CFU/6ml).

Dental procedures - Duration of bacteraemia following a procedure

No included studies reported this particular outcome.

Upper and lower respiratory tract procedures - Number of having positive blood samples before and after procedure

3 before-and-after studies with high risk of bias (N = range from 31 to 85) suggested that there were no statistical significant associations between various upper and lower respiratory tract procedures (bronchoscopy and tonsillectomy) and bacteraemia in adults and children.

Conversely, 1 before-and-after study (N = 57) suggested that there were significant associations between tracheostomy and bacteraemia in adults. However, the time frame for post procedure bacteraemia was relative short (immediately post-procedure) and only p-value was reported for this study.

Upper and lower respiratory tract procedures - Intensity of bacteraemia

No included studies reported this particular outcome.

Upper and lower respiratory tract procedures - Duration of bacteraemia following a procedure

No included studies reported this particular outcome.

Upper and lower GI tract procedures - Number of having positive blood samples before and after procedure

6 before-and-after studies with high risk of bias (N = range from 33 to 270) suggested that there were no statistical significant associations between endoscopic sub/mucosal resection/dissection, colonoscopy, emergency endoscopy, elective or emergency EVS, transesophageal echocardiography and bacteraemia in adults.

Conversely, 1 RCT (data from the control arm), 1 cohort study and 3 before-and-after studies with high risk of bias (N = range from 21 to 126) suggested that there were associations between colorectal stent placement, laparoscopy/mimi- laparoscopy, diagnostic ERCP, therapeutic ERCP, oesophagectomy, oesophageal stricture and bacteraemia in adults. However, the time frame for post procedure bacteraemia was relative short and only p-values were reported for these studies.

Upper and lower GI tract procedures - Intensity of bacteraemia

No included studies reported this particular outcome.

Upper and lower GI tract procedures - Duration of bacteraemia following a procedure

No included studies reported this particular outcome.

Genitourinary tract procedures

No study identified met the inclusion criteria.

2.4.42 Evidence to recommendations

	Committee discussions
Relative value of different outcomes	The Committee discussed and agreed that the critical outcome for this review question was to establish whether there is a clear relationship between specific interventional procedures and bacteraemia in the general population. Therefore, the only critical outcome is the measurement of such association and the precision and certainty for these measurements reported in the included studies.
Quality of evidence	The Committee discussed the utility of the EPOC checklist to assess the quality of evidence for this particular review question. It was acknowledged and agreed that the 7 criteria in the EPOC checklist were not comprehensive nor detailed enough to fully assess the complex methodology used in the included studies for this particular question, for example, how bacteraemia was measured, the different methods for blood samples collection, different methods for culturing and incubation, the issues of contamination and others. Therefore, the Committee has a degree of uncertainty around the quality of evidence based on the EPOC checklist. The Committee further discussed the evidence base and commented that: • The participants of 43% of the included studies (13/30) were already bacteraemic before the interventional procedure (positive blood samples pre-procedure) which is considered to be a major confounder • The follow-up time points for post-procedure blood samples were very short (with most studies less than 60 min), and therefore it is difficult to establish the actual duration of bacteraemia. • The sample sizes of the included studies were very small. • It is very difficult to establish the association between procedures and

	Committee discussions
	bacteraemia because where multiple time points of blood samples were obtained, it was not clear whether the number of positive bacteraemia at different time points were from the same or different participants in the study. • Only p-values from various non-parametric tests were reported, with high uncertainty on precision of the effect estimates. • In most studies on dental procedures, there was also no information on the oral health of the participants. This could potentially be a confounder that participants with poor oral health and hygiene were possibly at higher risk of bacteraemia than those with good oral hygiene. Overall, the Committee agreed that the evidence was of poor quality, and the evidence does not contribute much into the investigation of the hypothesis: *'people at risk --> undertaking interventional procedures --> bacteraemia --> the development of IE'*.
Trade-off between benefits and harms	As the aim of this review question is to investigate the relationship between interventional procedures and bacteraemia (to explore the pathogenesis of IE to inform the model structure of the health economic evaluation [please sections for question 6]), the discussion of trade-off between benefits and harms was not relevant for this question.
Trade-off between net health benefits and resource use	There is no impact on resource use related to this review question per se. Section 2.6.4 contains a systematic review of economic evaluations that investigate the cost-effectiveness of antibiotic prophylaxis.
Other considerations	For dental and non-dental procedures assessed in this review question, the Committee felt that there was some evidence that suggested some dental procedures could be associated with bacteraemia, however, there was still uncertainty for other interventional procedures. The Committee agreed that current evidence is inconclusive to draw a firm conclusion that bacteraemia that could be associated with some interventional procedures in adults and children would definitively contribute to the development of IE.

1
2

2.5 Review question 5

What levels of bacteraemia are associated with everyday activities (toothbrushing/chewing/urination/defecation)?

2.5.1 Clinical evidence review

Everyday activities such as toothbrushing, are believed to introduce similar levels of bacteraemia compared to dental procedures such as an extraction. Therefore, to evaluate which groups may need antibiotic prophylaxis, the aim of this review is to identify what levels of bacteraemia are associated everyday activities.

An update search using the original search strategy was conducted (see appendix D) which identified 299 articles. The titles and abstracts were screened and 17 studies were identified as potentially relevant. Full-text versions of these articles were obtained and reviewed against the criteria specified in the review protocol (appendix C). Of these, 14 were excluded as they did not meet the criteria. Three new studies met the criteria and were included with an additional 3 studies from the original guideline; therefore a total of 6 included studies for the update.

A review flowchart is provided in appendix E, and the excluded studies (with reasons for exclusion) are shown in appendix F.

2.5.2 Methods

Summary of review protocols

- The population included adults and children undergoing everyday activities irrespective of whether they have an underlying cardiac condition or not. No subgroups were identified for this question.
- For the above population, the incidence/level/duration of bacteraemia after an everyday activity was compared to that before or during the activity.
- The topic experts identified the following outcomes of interest for this clinical prediction review:
  - bacteraemia levels/intensity/bacterial counts per unit volume at one or more time points following the everyday activity (definition of intensity may vary by study)
  - duration of bacteraemia following an everyday activity
  - number/incidence/odds of having positive blood samples before and after procedure/everyday activity

Risk of bias

- The quality of individual studies was assessed using the checklist for prognostic studies by Hayden et al., 2006 (Developing NICE guidelines - the Manual, 2014). This checklist addresses 6 main areas including study participation, study attrition, prognostic factor measurement, outcome measurement, confounding measurement and account and finally the analysis used in the study. Each individual study was assessed against this criteria and an overall quality rating was assigned using the following thresholds:
  - all 6 criteria on checklist met: no risk of bias
  - at least 4 out of 6 criteria met: low risk of bias
  - anything else: high risk of bias

Statistical analysis

- Meta-analyses were not conducted due to the variation in population and outcome measures from study to study.
- Where appropriate, summary measures such as mean differences or odds ratios (with 95% confidence intervals) were calculated using Review Manager 5.
- All findings are based on statistical significance.

Overall summary of evidence

6 studies were included for this review of which 5 were RCTs and one study was a prospective pre- and post- test design without a control group. 3 studies were from the UK and 3 studies from the USA. Sample size ranged from 30 to 735. The populations included subjects referred for dental treatment under general anaesthesia in 4 studies, patients presenting to urgent care service with the need for extraction of at least 1 erupted tooth in one study and mechanically ventilated subjects from the surgical trauma, medical respiratory and neuroscience intensive care units in one study. 4 studies were performed in children/adolescents and 2 studies in adults of varying age. All studies examined bacteraemia levels associated with toothbrushing (various regimens).

For a summary of included studies please see table 10 (for the full evidence tables please see appendix G).

Table 10: Summary of included studies

<table>
<tr><th>Study reference (including study design)</th><th>Study population</th><th>Predictors (or risk factors)</th><th>Outcomes and effect estimates</th><th>Overall quality</th></tr>
<tr><td>Lucas et al., 2008
(RCT)</td><td>Children and adolescents having dental treatment (extractions only) under general anaesthesia</td><td><u>Toothbrushing</u>
1. Manual Oral B 30: n=32
2. Braun electric (rotary movement): n=35
3. Sonicare (oscillating movement): n=33
4. Dental handpiece and rubber cup: n=41</td><td>1. Intensity of bacteraemia
<table>
<tr><th colspan="6">a) Aerobic intensity of detectable bacteraemia (cfu/ml blood)</th></tr>
<tr><td rowspan="2">Type of toothbrush</td><td colspan="2">Baseline</td><td colspan="2">30 seconds after toothbrushing</td><td>Summary measure</td></tr>
<tr><td>Mean</td><td>SD</td><td>Mean</td><td>SD</td><td>Mean difference (95%CI)[1]</td></tr>
<tr><td>Oral B 30 (n=32)</td><td>0.05</td><td>0.21</td><td>0.39</td><td>1.34</td><td>0.34 (-0.13 to 0.84)</td></tr>
<tr><td>Braun electric (n=35)</td><td>0.05</td><td>0.11</td><td>0.28</td><td>1.15</td><td>0.23 (-0.15 to 0.61)</td></tr>
<tr><td>Sonicare electric (n=33)</td><td>0.02</td><td>0.06</td><td>0.51</td><td>2.35</td><td>0.49 (-0.31 to 1.29)</td></tr>
<tr><td>Dental handpiece and rubber cap (n=41)</td><td>0.02</td><td>0.07</td><td>1.00</td><td>3.10</td><td>0.98 (0.03 to 1.93)</td></tr>
</table>
<table>
<tr><th colspan="6">b) Anaerobic intensity of detectable bacteraemia (cfu/ml blood)</th></tr>
<tr><td rowspan="2">Type of toothbrush</td><td colspan="2">Baseline</td><td colspan="2">30 seconds after toothbrushing</td><td>Summary measure</td></tr>
<tr><td>Mean</td><td>SD</td><td>Mean</td><td>SD</td><td>Mean difference (95%CI)[1]</td></tr>
<tr><td>Oral B 30 (n=32)</td><td>0.01</td><td>0.04</td><td>0.46</td><td>1.8</td><td>0.45 (-0.17 to 1.07)</td></tr>
<tr><td>Braun electric (n=35)</td><td>0.02</td><td>0.07</td><td>0.11</td><td>0.43</td><td>0.09 (-0.05 to 0.23)</td></tr>
<tr><td>Sonicare electric (n=33)</td><td>0.04</td><td>0.10</td><td>0.79</td><td>3.68</td><td>0.75 (-0.51 to 2.01)</td></tr>
<tr><td>Dental handpiece and rubber cap (n=41)</td><td>0.008</td><td>0.04</td><td>0.94</td><td>2.87</td><td>0.93 (0.05 to 1.81)</td></tr>
</table>
2. Prevalence of bacteraemia in each group, n (%) of positive blood cultures</td><td>Low risk of bias[2]</td></tr>
</table>

<table>
<tr><th>Study reference (including study design)</th><th>Study population</th><th>Predictors (or risk factors)</th><th>Outcomes and effect estimates</th><th>Overall quality</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>Type of toothbrush</td><td>Baseline, n (%)</td><td>30 seconds after brushing for 1 minute, n (%)</td><td>Summary measure, OR (95% CI) [1]</td></tr>
<tr><td>Oral B 30 (n=32)</td><td>7 (22%)</td><td>6 (19%)</td><td>0.82 (0.24 to 2.79)</td></tr>
<tr><td>Braun electric (n=35)</td><td>9 (26%)</td><td>12 (34%)</td><td>1.51 (0.54 to 4.22)</td></tr>
<tr><td>Sonicare electric(n=33)</td><td>9 (27%)</td><td>11 (33%)</td><td>1.33 (0.46 to 3.83)</td></tr>
<tr><td>Dental handpiece and rubber cap (n=41)</td><td>6 (15%)</td><td>15 (37%)</td><td>3.37 (1.15 to 9.85)</td></tr>
</table>
</td><td></td></tr>
<tr><td>Lockhart et al., 2008 (RCT)</td><td>Patients presenting to urgent care service with the need for extraction of at least 1 erupted tooth</td><td>1. Toothbrushing (n=98)
2. Extraction-amoxicillin (n=96)
3. Extraction placebo (n=96)</td><td>
1. Magnitude of bacteraemia – all analysed samples were below the detection threshold of 10^4 CFU per millilitre of blood

2. Duration of bacteraemia at different time points
<table>
<tr><th colspan="3">a) overall duration of bacteraemia</th></tr>
<tr><td></td><td>Number of subjects (%) bacteraemic at 40 minutes after activity/procedure</td><td>Number of subjects (%) bacteraemic at 60 minutes after activity/procedure</td></tr>
<tr><td>Toothbrushing group</td><td>-</td><td>9 (9)</td></tr>
<tr><td>Extraction-amoxicillin group</td><td>2 (2)</td><td>-</td></tr>
<tr><td>Extraction-placebo group</td><td>-</td><td>2 (2)</td></tr>
</table>
<table>
<tr><th colspan="2">b) duration of bacteraemia from endocarditis-related bacterial species</th></tr>
<tr><td></td><td>Number of subjects (%) bacteraemic at 60 minutes after activity/procedure</td></tr>
<tr><td>Toothbrushing group</td><td>2 (2)</td></tr>
<tr><td>Extraction-amoxicillin group</td><td>-</td></tr>
</table>
</td><td>Low risk of bias[3]</td></tr>
</table>

Study reference (including study design)	Study population	Predictors (or risk factors)	Outcomes and effect estimates	Overall quality

Extraction-placebo group	5 (5)

3. Number/incidence/odds of having positive blood samples before and after everyday activity – reported in study as a) overall incidence of bacteraemia at any of the 6 draws b) overall incidence of bacteraemia at the time of the procedures and c) incidence of bacteraemia from endocarditis related bacterial species

a) overall incidence of bacteraemia* at any of the 6 draws	
Toothbrushing group	32%
Extraction-amoxicillin group	56%
Extraction-placebo group	80%
x^2	p<0.0001

b) overall incidence of bacteraemia* at the time of the procedures	
Toothbrushing group	28%
Extraction-amoxicillin group	56%
Extraction-placebo group	79%
x^2	Not reported

*'All baseline blood cultures were negative with the exception of 3 instances, likely from skin contamination eg: Staphylococcus epidermis'

c) cumulative incidence of bacteraemia from endocarditis related bacterial species from all 6 blood draws**	
Toothbrushing group	23%
Extraction-amoxicillin group	33%
Extraction-placebo group	60%
X^2	p<0.0001

d) incidence of positive cultures from endocarditis related bacterial species in the first 5 minutes of activity/procedure*****	
Toothbrushing group	19%
Extraction-amoxicillin group	33%

<table>
<tr><th>Study reference (including study design)</th><th>Study population</th><th>Predictors (or risk factors)</th><th>Outcomes and effect estimates</th><th>Overall quality</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>Extraction-placebo group</td><td>58%</td></tr>
<tr><td>X^2</td><td>p=not reported</td></tr>
</table>
<table>
<tr><th colspan="2">e) incidence of positive cultures** from endocarditis related bacterial species at 20 minutes***</th></tr>
<tr><td>Toothbrushing group</td><td>1%</td></tr>
<tr><td>Extraction-amoxicillin group</td><td>1%</td></tr>
<tr><td>Extraction-placebo group</td><td>10%</td></tr>
<tr><td>X^2</td><td>p=0.001</td></tr>
</table>
**All baseline blood cultures were negative, with the exception of one patients (with 2 species) in the brushing group
***The pattern observed at 20 minutes persisted to 40 minutes (numbers not reported)
</td><td></td></tr>
<tr><td>Jones et al., 2010
(Prospective pre- and post-test design without a control group)</td><td>Mechanically ventilated subjects from the surgical trauma, medical respiratory and neuroscience intensive care units</td><td>Toothbrushing</td><td>1. Incidence of transient bacteraemia by positive blood cultures before and after toothbrushing

None of the subjects had evidence of transient bacteraemia before or after toothbrushing.</td><td>Low risk of bias[4]</td></tr>
<tr><td>Lucas et al., 2000 [included in CG64, 2008]
(RCT)</td><td>Children referred for dental treatment under general anaesthetic</td><td>1. Toothbrushing: n= 52
2. Professional cleaning with a rubber cup: n= 53
3. Scaling: n=50</td><td>1. Incidence of bacteraemia (positive blood cultures)
There was NS difference in the number of positive blood samples in the groups studies [toothbrushing – 20/52 (39%), dental flossing (data from De Leo et al., 1974) – 6/7 (86%), dental polishing – 13/53 (25%), dental scaling – 20/50 (40%), dental extractions (data from Roberts et al., 1998b) – 17/44 (39%)]. p=0.305 (excluding dental flossing), p=0.305 (excluding dental flossing and extractions)

Intensity of bacteraemia
There was NS difference in the intensity of bacteraemia (colony forming units per millilitre of blood, mean (SD), range) in any of the 3 cleaning groups [toothbrushing – 32.2 (231), 0 to 1666, dental</td><td>Low risk of bias[5]</td></tr>
</table>

Study reference (including study design)	Study population	Predictors (or risk factors)	Outcomes and effect estimates	Overall quality
			flossing – no data, dental polishing – 15.9 (83.5), 0 to 557, dental scaling – 2.2 (13.2), 0 to 93, dental extractions (from Roberts et al., 1998) – 0.23 (0.8), 0 to 4]	
Bhanji et al., 2002 [included in CG64, 2008] (RCT)	Children receiving dental care under general anaesthesia	Toothbrushing 1. Sonicare electric toothbrushing: n= 25 2. Manual toothbrushing: n=25	**1. Incidence of positive blood cultures after* brushing, n (%, 95%CI)** Manual group (n=24): 11/24 (46, 26 to 66) Sonicare group (n=23): 18/23 (78, 62 to 95) p=0.022 *3 patients had positive blood cultures before toothbrushing and were excluded	Low risk of bias[6]
Roberts et al., 1997 [included in CG64, 2008] (RCT)	Children referred for dental treatment under general anaesthetic	Toothbrushing Various other predictors (see opposite)	**Positive blood cultures, n/N (%):** - baseline n = 5/53 (9.4%) - dental examination n = 9/53 (17.0%) - toothbrushing n = 20/52 (38.5%) - polishing teeth n = 13/53 (24.5%) - scaling teeth n = 20/50 (40.0%) - intraligamental injection n = 28/29 (96.6%) - nasotracheal tube n = 3/31 (9.7%) - rubber dam placement n = 15/51 (29.4%) - slow drill n = 6/47 (12.8%) - fast drill n = 2/47 (4.3%) - matrix band placement n = 18/56 (32.1%) - single extraction n = 17/44 (38.7%) - multiple extractions n = 30/59 (50.9%) - mucoperiosteal flap n = 20/51 (39.2%) - cardiac patients n = 6/59 (10.2%) **Comparison of proportions compared to baseline (95% CI):** - dental examination -5.3 to 20.49% - toothbrushing 12.8 to 45.4% - polishing teeth 0.7 to 29.4% - scaling teeth 14.0 to 47.2% - intraligamental injection 76.9 to 97.3% - nasotracheal tube -6.5 to 13.2%	Low risk of bias[7]

Study reference (including study design)	Study population	Predictors (or risk factors)	Outcomes and effect estimates	Overall quality
			- rubber dam placement 4.8 to 35.1% - slow drill -8.9 to 15.6% - fast drill -5.2 to 4.8% - matrix band placement 7.4 to 38.0% - single extraction 12.5 to 45.9% - multiple extractions 24.2 to 58.6% - mucoperiosteal flap 13.4 to 46.2% NS; dental examination, nasotracheal tube, rubber dam placement, slow drill, fast drill,	

[1] *Calculated by NICE technical team based on data reported in the article*
[2] *Study met 4/6 criteria on prognostic studies checklist. Limitations included: 1. period of recruitment not reported 2. sample size calculation not reported 3. details of toothbrushing intervention not reported 4. highly selected population undergoing dental treatment*
[3] *Study met 5/6 criteria on prognostic studies checklist. Limitations included: 1. Unclear if blood samples processed immediately 2. reporting of data in graphical form without accompanying numbers 3. highly selected population undergoing dental treatment*
[4] *Study met 4/6 criteria on prognostic studies checklist. Limitations included: 1. Study dates not reported 2. No comparison group so not possible to determine relative levels of bacteraemia associated with different activities as opposed to just toothbrushing 3. No sample size calculation 4. Subjects also given Biotene mouthwash which could contain active ingredients and therefore have reduced bacteraemia levels.*
[5] *Study met 5/6 criteria on prognostic studies checklist. Limitations included: sample size calculation not reported, intervention not well described (eg: whether standardised procedures were used and for how long intervention was carried out), highly selected population undergoing dental treatment*
[6] *Study met 5/6 criteria on prognostic studies checklist. Limitations included: 1. baseline characteristics (eg: gender, mean age etc) not reported*
[7] *Highly selected population undergoing dental treatment*

2.5.31 Clinical evidence statements

2 Levels of bacteraemia associated with toothbrushing

3 Six studies examined levels of bacteraemia associated with various types of toothbrushing.
4 Although all studies were at low risk of bias, the overall finding was inconsistent across
5 studies given the wide range of toothbrushing interventions examined and comparators
6 within individual studies. The majority of studies were also conducted in a highly selected
7 population with pre-existing dental disease. A narrative summary of each study follows.

8 One RCT including 141 children and adolescents found that there was no significant
9 difference in the intensity of bacteraemia (aerobic or anaerobic) 30 seconds after
10 toothbrushing compared to baseline for subjects brushing with Oral B 30, Braun electric
11 [rotary movement] or Sonicare [oscillating movement] but a slightly higher intensity of
12 bacteraemia following brushing with the dental handpeice and rubber cap. The same study
13 found no difference in the prevalence of bacteraemia compared to baseline following the first
14 three types of toothbrushing but a greater prevalence (3 times more) 30 seconds after
15 brushing with the dental handpeice. The evidence was at low risk of bias however, the
16 uncertainty around these effect estimates were high.

17 A second RCT with 290 adults found that the overall incidence of bacteraemia at any of the 6
18 blood draws was significantly lower in the toothbrushing group (32%) compared to the dental
19 extraction groups (extraction-amoxicillin group – 56%, extraction-placebo group – 80%;
20 $p<0.0001$). The cumulative incidence of bacteraemia from endocarditis related bacterial
21 species from all 6 blood draws was also significantly lower in the toothbrushing group
22 compared to the extraction-amoxicillin and extraction-placebo groups (23%, 33% and 60%
23 respectively; $p<0.0001$). Furthermore, the incidence of positive blood cultures from
24 endocarditis related bacteria species at 20 minutes was significantly lower in the
25 toothbrushing and extraction-amoxicillin group compared to the extraction-placebo group
26 (1%, 1% and 10% respectively; $p=0.01$). The same study examined the magnitude of
27 bacteraemia and found that all analysed samples were below the detection threshold of 10^4
28 CFU per millilitre of blood set in the study.

29 One other study, which was a prospective pre-and post-test design including 30 adults that
30 found none of the subjects, had evidence of transient bacteraemia by positive blood cultures
31 before or after toothbrushing.

32 In a further RCT including 155 children, toothbrushing was found to have no significant
33 difference in the prevalence and intensity of bacteraemia when compared with other cleaning
34 methods, professional cleaning and scaling.

35 One RCT considered a comparison of transient bacteraemia between brushing with a
36 conventional toothbrush and with an electric toothbrush. Toothbrushing was associated with
37 positive blood cultures in 46% of manual toothbrush users and in 78% of those using the
38 electric toothbrush ($p = 0.022$).

39 In the final RCT including 735 children, the incidence of positive blood cultures was
40 significantly greater following toothbrushing (38.5%) compared to the baseline value of 9.4%.
41 This was alongside other non-everyday activities such as, polishing teeth, scaling teeth,
42 intraligamental injection, rubber dam placement, matrix band placement, single extraction,
43 multiple extractions and mucoperiosteal flap. The evidence was at no risk of bias.

44 No evidence relating to other everyday activities of interest to this question (chewing,
45 urination and defecation) were identified.

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2.5.41 Evidence to recommendations

	Committee discussions
Relative value of different outcomes	The Committee discussed and agreed that the critical outcome for this review question was to establish whether there is a clear relationship between specific everyday activities and bacteraemia (including the incidence, duration and level of bacteraemia) in the general population. Therefore, the only critical outcome is the measurement of such association and the precision and certainty for these measurements reported in the included studies.
Quality of evidence	The Committee discussed the utility of the Hayden checklist to assess the quality of evidence for this particular review question. It was acknowledged and agreed that the 6 criteria in the Hayden checklist were not comprehensive nor detailed enough to fully assess the complex methodology used in the included studies for this particular question, for example, how bacteraemia was measured, the different methods for blood sample collection, different methods for culturing and incubation and also the issues of contamination. Therefore, the Committee were uncertain about the quality of evidence based on the Hayden checklist. The Committee further discussed the evidence and commented that: • The participants of 83% of the included studies (5/6) were a highly selected population with pre-existing dental disease. Therefore, the applicability of findings from these studies to the general population was questionable. • The participants of 50% of the included studies (3/6) were already bacteraemic before the everyday activity (positive blood samples pre-procedure), indicating that transient bacteraemias occur spontaneously • The sample sizes of the included studies were very small. • Only p-values from various non-parametric tests were reported, with high uncertainty on precision of the effect estimates. The committee further commented that although the study by Lockhart et al, 2008 provides an interesting finding into the idea that the incidence of bacteraemia following toothbrushing and extraction with amoxicillin is similar; the study did not provide an insight into the relative magnitudes of bacteraemia associated with the different activities. The committee highlighted that the Hayden checklist was not comprehensive enough to fully assess these issues. Overall, the Committee agreed that the evidence was of poor quality and largely undertaken in a highly selected population with pre-existing dental disease. The applicability of the evidence to the general population was therefore inadequate and the evidence does not contribute much into the investigation of whether everyday activities, such as toothbrushing, lead to similar levels of bacteraemia as dental procedures, such as extraction. The committee in addition noted the lack of evidence for other activities including chewing, urination and defecation.
Trade-off between benefits and harms	As the aim of this review question is to investigate the relationship between everyday activities and bacteraemia (to explore the pathogenesis of IE to inform the model structure of the health economic evaluation [please see sections for question 6], the discussion of trade-off between benefits and harms was not relevant for this question.
Trade-off between net health benefits and resource use	There is no impact on resource use related to this review question per se. Section 2.6.4 contains a systematic review of economic evaluations that investigate the cost-effectiveness of antibiotic prophylaxis.
Other	The Committee felt that the studies have provided inconclusive evidence on

	Committee discussions
considerations	the association between everyday activities and bacteraemia, given the type of toothbrushing and comparators within studies varied – some studies compared different types of toothbrushing with each other, whereas others compared toothbrushing with dental procedures which seemed to fit more closely with the aim of this review question. Furthermore, the committee noted that in some studies, subjects were bacteraemic at baseline before the everyday activity indicating that bacteraemias occur spontaneously.

1

2.6 Review question 6a

Does antibiotic prophylaxis in those at risk of developing IE reduce the incidence of IE when given before a defined Interventional Procedure?

2.6.1 Clinical evidence review

Since 1955, antibiotic prophylaxis that aims to prevent endocarditis has been used in at-risk patients. The rationale for prophylaxis against IE is that endocarditis usually follows bacteraemia, certain interventional procedures cause bacteraemia with organisms that can cause endocarditis and these bacteria are usually sensitive to antibiotics; therefore, antibiotics should be given to patients with predisposing heart conditions before procedures that may cause bacteraemia. The aim of this review is to assess whether antibiotic prophylaxis in those at risk of IE and undergoing interventional procedures reduces the risk of IE.

An update search using the original search strategy was conducted (see appendix D) which identified 1341 articles (across questions 6a and 7a). The titles and abstracts were screened and 45 articles were identified as potentially relevant. Full-text versions of these articles were obtained and reviewed against the criteria specified in the review protocol (appendix C). None of these met the criteria for this review and all were excluded. An additional 3 studies from CG64 were included. Therefore a total of 3 included studies for the update.

A review flowchart is provided in appendix E, and the excluded studies (with reasons for exclusion) are shown in appendix F.

2.6.2 Methods

Summary of review protocols

- The population included:
  - adults and children with known underlying structural cardiac defects undergoing interventional procedures
- No subgroups (other than adults and children) were identified for this question.
- The intervention of interest was antibiotic prophylaxis (any) compared against no prophylaxis (including placebo).
- The topic experts outlined the following outcomes:
  - incidence/odds of developing IE in those receiving prophylaxis compared to those not receiving prophylaxis and incidence of adverse effects including anaphylaxis
- The studies did not report data on all these outcomes and in some situations synonymous outcomes are presented.
- GRADE methodology was used to assess the quality of evidence as follows:
- **Risk of bias:**
  - as only observational studies from the original guideline were included in this review, risk of bias for each individual study was assessed using the methodology checklist from Developing NICE guidelines - the Manual 2014.
- **Indirectness:**
  - details from the PICOs in the review protocol(s) (see appendix C) were used to assess the directness of the included studies.
- **Inconsistency**
  - given the variation in populations across studies (including the underlying cardiac condition, regimen of antibiotic subjects received as well as the variation in

interventional procedures subjects underwent), meta-analysis of the data was not appropriate for this question.

- **Imprecision**
  - a routine search of the COMET (Core Outcome Measures in Effectiveness Trials) Initiative database was conducted to identify any relevant thresholds for defining the clinical minimal important difference (MIDs). No information was identified in the COMET database. Information about specific MIDs used to assess imprecision were also not available from the original guideline CG64. Therefore, the following thresholds were used, as per the GRADE working group recommendations: for continuous outcomes, the standard MID of 0.5 standard deviation change and for dichotomous outcomes, RRR or RRI of 25%: 0.75 or 1.25.
- **Overall quality**
  - as only observational studies studies were identified for this review, the quality rating began at 'low' and was further downgraded for potential sources of bias.
- **Statistical analysis**
  - meta-analyses were not conducted due to the variation in population and outcome measures (as explained above) from study to study.
  - where appropriate, summary measures such as mean differences or odds ratios (with 95% confidence intervals) were calculated using Review Manager 5.
- **Description of included studies**
  - Two case-control studies and one retrospective cohort study were identified for this review. One study was from Germany , one from France and one from the Netherlands. The first study examined antibiotic prophylaxis in adults with prosthetic heart valves undergoing various interventional procedures including dental, urological, oropharyngeal and gynaecological procedures. The second study examined antibiotic prophylaxis in adults with underlying valvular disease (prosthetic or native valve) who had undergone a dental procedure. The remaining studies examined antibiotic prophylaxis in children and adults with known cardiac disease (native valve and cardiovascular anomalies) largely undergoing dental procedures. Cases of infective endocarditis and antibiotic use were most commonly identified by interviewing of subjects, and reviewing of medical records.

For a summary of included studies please see table 11 (for the full evidence tables and full GRADE profiles please see appendices G and H).

Table 11: Summary of included studies

Study reference (including study design)	Study population	Intervention & comparator	Outcomes reported
Horskotte, 1987 (Retrospective cohort)	Subjects with prosthetic heart valves who underwent various interventional procedures including dental, urological, oropharyngeal and gynaecological procedures with (N=287) or without (N=390) antibiotics	Antibiotic prophylaxis vs no prophylaxis (various regimens)	- Incidence of prosthetic valve endocarditis
Lacassin, 1995 (Case-control)	171 cases of IE and controls without IE interviewed about procedures and antibiotic use over the previous 3 months	Antibiotic prophylaxis vs no prophylaxis (various regimens)	- Incidence of infective endocarditis
Van der Meer, 1992 (Case-control)	Cases were patients with known cardiac disease in whom endocarditis developed within 180 days of a medical or dental procedure for which prophylaxis was indicated (N=48). Controls were patients with the same cardiac status in whom endocarditis did not develop within 180 days of a similar procedure (N=200)	Antibiotic prophylaxis vs no prophylaxis (various regimens)	- Incidence of infective endocarditis

2.6.31 Clinical evidence statement

Antibiotic prophylaxis for infective endocarditis (grade table 154) - Incidence of IE

Very low quality evidence from two case-control studies and one retrospective cohort study including subjects with various underlying cardiac diseases were all inconclusive in the incidence of prosthetic valve endocarditis/infective endocarditis in those who received antibiotics compared to those who did not before undergoing an interventional procedure. The procedures included dental, urological, oropharyngeal and gynaecological procedures in the first study, dental in the second study and largely dental procedures in the third study. None of the studies reported on adverse events of prophylaxis.

2.6.40 Health Economics

2.6.4.11 Methods

The Committee is required to make decisions based on the best available evidence of both clinical and cost effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits rather than the total implementation cost. Evidence on cost effectiveness related to the key clinical issues being addressed in the guideline update was sought.

A systematic literature search was undertaken to identify health economic evidence within published literature relevant to prophylaxis against infective endocarditis. The evidence was identified by conducting a broad search in the NHS Economic Evaluation Database (NHS EED), the Health Technology Assessment Database (HTA) and the Health Economic Evaluations Database (HEED) from 2007 (date of the last systematic review conducted for the previous version of the guideline) to 2014. The search also included Medline and Embase databases using an economic filter. Studies published in languages other than English were not reviewed. The search was conducted on 20 November 2014. The health economic search strategy is detailed in appendix I.

The health economist also sought out relevant studies identified by the surveillance review, Standing Committee members, or Topic experts.

2.6.4.1.128 Inclusion and Exclusion criteria

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost-utility, cost-effectiveness, cost-benefit and cost-consequence analyses) and comparative costing studies that address the review question in the relevant population were considered potentially includable as economic evidence.

Studies that only reported burden of disease or cost of illness were excluded. Literature reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available, then other less relevant studies may not have been included. Where selective exclusions occurred on this basis, this is noted in the excluded economic studies table (appendix K).

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist contained in *Appendix H* of *Developing NICE Guidelines: the manual 2014*.

2.6.4.1.21 Economic evidence profile

The economic evidence profile summarises cost-effectiveness estimates. It shows an assessment of the applicability and methodological quality for each economic evaluation, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from *Appendix H* of *Developing NICE Guidelines: the manual, 2014*. It also shows the incremental cost, incremental effect and incremental cost-effectiveness ratio for the base case analysis in the evaluation, as well as information about the assessment of uncertainty.

Table 12: Explanation of fields used in the economic evidence profile

Item	Description
Study	This field is used to reference the study and provide basic details on the included interventions and country of origin.
Applicability	Applicability refers to the relevance of the study to specific review questions and the NICE reference case. Attributes considered include population, interventions, healthcare system, perspective, health effects and discounting. The applicability of the study is rated as: • Directly applicable – the study meets all applicability criteria or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness. • Partially applicable – the study fails to meet one or more applicability criteria and this could change the conclusions about cost effectiveness. • Not applicable – the study fails to meet one or more of the applicability criteria and this is likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review.
Limitations	This field provides an assessment of the methodological quality of the study. Attributes assessed include the relevance of the model's structure to the review question, timeframe, outcomes, costs, parameter sources, incremental analysis, uncertainty analysis and conflicts of interest. The methodological quality of the evaluation is rated as having: • Minor limitations – the study meets all quality criteria or fails to meet one or more quality criteria, but this is unlikely to change the conclusions about cost effectiveness. • Potentially serious limitations – the study fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness • Very serious limitations – the study fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review.
Other comments	This field contains particular issues that should be considered when interpreting the study, such as model structure and timeframe.
Incremental cost	The difference between the mean cost associated with one strategy and the mean cost of a comparator strategy.
Incremental effect	The difference between the mean health effect associated with the intervention and the mean health effect associated with the comparator. This is usually represented by quality-adjusted life years (QALYs) in accordance with the NICE reference case.
Incremental cost effectiveness ratio (ICER)	The incremental cost divided by the incremental effect which results in the cost per quality-adjusted life year gained (or lost). Negative ICERs are not reported as they could represent very different conclusions: either a decrease in cost with an increase in health effects; or an increase in cost with a decrease in health effects. For this reason, the word 'dominates' is used to represent an intervention that is associated with decreased costs and increased health effects compared to the comparator, and the word 'dominated' is used to represent an intervention that is associated with an increase in costs and decreased health effects.

Item	Description
Uncertainty	A summary of the extent of uncertainty about the ICER. This can include the results of deterministic or probabilistic sensitivity analysis or stochastic analyses or trial data.

2.6.4.1.31 Cost-effectiveness criteria

NICE's report Social value judgements: principles for the development of NICE guidance sets out the principles that GDGs should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- the intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- the intervention cost less than £20,000 per QALY gained compared with the next best strategy.

If the Committee recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'Recommendations and link to evidence' section of the relevant chapter, with reference to issues regarding the plausibility of the estimate or to the factors set out in *Social value judgements: principles for the development of NICE guidance.*

2.6.4.27 Results of economic literature review

The search retrieved 998 articles. The titles and abstracts were screened for possible inclusion and 8 articles were selected for further examination of the full text version. An additional 5 articles from the 2008 review for this guideline were also considered for inclusion along with the original economic evaluation conducted for the 2008 guideline. An economic evaluation that was not published at the time of the literature review conducted by The University of Sheffield was also included giving a total of 15 full-text economic evaluations that were considered. Four studies were selected for inclusion in the present update including the 2008 NICE model and the 2015 Sheffield model.

A review flowchart is provided in appendix J, and the excluded studies (with reasons for exclusion) are shown in appendix K.

Summaries of the included studies are provided as economic evidence profiles in table 13 for dental procedures (3 studies) and table 14 for non-dental procedures (1 study). The full economic evidence tables are provided in appendix L.

2.6.4.31 Economic evidence statement – dental procedures

Three economic evaluations were included in the literature review of economic evidence on antibiotic prophylaxis prior to dental procedures. All three studies were cost-utility analyses using a combined decision tree and Markov model structure.

A 2005 cost-utility analysis from the United States (Agha et al.) found that antibiotic prophylaxis was not cost effective for people with moderate risk of developing endocarditis. Cephalexin, clarithromycin and clindamycin were found to be cost effective for people at high risk of developing endocarditis. This study was partially applicable and downgraded due to the following departures from the NICE reference case: the use of costs based on the United States healthcare system, utility weights based on the Quality of Wellbeing measure and the adoption of a societal perspective for costs. It had potentially serious methodological limitations due to key parameters based on limited evidence, some utility weights that were based on estimates, and probabilistic sensitivity analysis was not conducted.

Original modelling conducted by NICE for the 2008 NICE guideline (CG64) found that antibiotic prophylaxis was not cost effective for people with a moderate risk of developing infective endocarditis and may be cost effective for people with a high risk of developing infective endocarditis depending on other assumptions, such as antibiotic efficacy and risk of fatal anaphylaxis due to antibiotics. This study was directly applicable as it was based on the NICE reference case for economic evaluations. It had minor methodological limitations: the key parameters relating to the risk of developing infective endocarditis following a dental procedure and efficacy of antibiotic prophylaxis to reduce this risk was based on limited evidence; and probabilistic sensitivity analysis was not conducted.

A team at the University of Sheffield conducted an economic analysis independetly of the guideline update and kindly provided the initial results of this analysis to the Committee (Franklin et al.). This was an adaption of the 2008 NICE model. A presentation was provided by one of the co-authors of the analysis along with a report containing the full details of the analysis. The full details of this analysis cannot be disclosed in the present document because it has not yet been published and is considered academic in confidence. The findings of this analysis in the final published version may differ to what is reported in this update. Please refer to Appendix P for an abstract of this analysis. The base case analysis found that antibiotic prophylaxis using amoxicillin prior to dental procedures was not cost effective with an incremental cost-effectiveness ratio of £30,967 per QALY. The base case analysis found that antibiotic prophylaxis using clindamycin prior to dental procedures resulted in higher costs and reduced health effects compared with no prophylaxis, mainly due to the risk of of death with clindamycin, usually due to *Clostridium difficile* infection. The base case assumed that the entire increase in the incidence of infective endocarditis between 2007 and 2012 was due to no prophylaxis. An alternative scenario that accounted for the increase in infective endocarditis that was already occurring prior to 2007 in a straight line manner (as per the results reported by Dayer et al. (2014)) found that the ICER for amoxicillin increased to £211,705 per QALY for a 10 year time horizon and £52,763 per QALY for a 50 year time horizon. Clindamycin was dominated by no prophylaxis under either scenario. The results of the study were highly sensitive to the risk of developing infective endocarditis following a dental procedure, the efficacy of antibiotic prophylaxis to reduce this risk, the cost of amoxicillin and clindamycin and the rate of fatal adverse events. Variation of these key parameters resulted in incremental cost-effectiveness ratios for antibiotic prophylaxis compared with no prophylaxis ranging from highly cost effective to highly cost ineffective and dominated (more costly and a reduction in health benefits). The incremental cost-effectiveness ratio increased to £53,000 per QALY using less optimistic estimates of prophylactic efficacy. Both amoxicillin and clindamycin are more cost effective if the baseline risk is higher. Using a baseline risk that may represent people with a prosthetic heart valve resulted in incremental cost-effectiveness ratios of £6,487 and £13,182 for amoxicillin and clindamycin respectively. When the price of amoxicillin was doubled from £2.28 to £4.56 the incremental cost-effectiveness ratio doubled to £65,815 per QALY. The study was directly applicable because it complied with the NICE reference case for economic evaluations. It had minor methodological limitations, mainly due to the limited evidence on the risk of developing infective endocarditis following a dental procedure and the efficacy of amoxicillin and clindamycin in reducing that risk.

2.6.4.4 Economic evidence statement – non-dental procedures

A 2004 cost-utility analysis from the United States found that antibiotic prophylaxis for febrile children who have cardiac lesions and undergo urinary catheterisation in the emergency department was not cost effective. This study was partially applicable with minor limitations.

Table 13: Economic evidence profile – dental procedures

Study	Applicability	Limitations	Other comments	Incremental			Uncertainty
				Cost	Effect	ICER	
Agha et al. 2005 7 pre-dental antibiotic prophylaxis regimens vs. no prophylaxis United States	Partially applicable[1,2,3,4]	Potentially serious limitations[5,6,7]	Decision tree for short term effects and side effects combined with a Markov model to model long term consequences and survival	Not reported	Incremental QALYs gained per 10 million patients 1. Oral amoxicillin: -3303 2. Oral clarithromycin: +1125 3. Oral clindamycin: +1118 4. Oral cephalexin: +827 5. Intravenous or intramuscular ampicillin: -3030 6. Intravenous or intramuscular cefazolin: +827 7. Intravenous clindamycin: +1118	All ICERs are compared with no prophylaxis and per QALY.[8] 1. Oral amoxicillin: dominated 2. Oral clarithromycin: $88007 2003 US dollars or £76155 2015 UK pounds 3. Oral clindamycin: $101142 2003 US dollars or £87522 2015 UK pounds 4. Oral cephalexin: $99373 2003 US dollars or £85991 2015 UK pounds 5. Intravenous or intramuscular ampicillin: dominated 6. Intravenous or intramuscular cefazolin: $199430 2003 US dollars or £172574 2015 UK pounds 7. Intravenous clindamycin: $411093 2003 US dollars or £355733 2015 UK pounds	No probabilistic sensitivity analysis conducted. A range of one way sensitivity analyses were conducted showing cost-effectiveness is sensitive to a number of input parameters. Please refer to the appendix for a summary of these analyses.
NICE 2008 8 pre-dental antibiotic prophylaxis regimens vs. no prophylaxis United	Directly applicable	Minor limitations[9,10]	Decision tree for short term effects combined with a Markov model to model long term conseque	1. Oral amoxicillin: £26 2. Oral clindamycin: £160 3. Intravenous amoxicillin then oral amoxicillin: £53 4. Oral amoxicillin	1. Oral amoxicillin: 0.00001 2. Oral clindamycin: 0.00001 3. Intravenous amoxicillin then oral amoxicillin: 0.00001 4. Oral amoxicillin	1. Oral amoxicillin: £248,912 2. Oral clindamycin: £1,513,095 3. Intravenous amoxicillin then oral amoxicillin: £498,047 4. Oral amoxicillin before and oral amoxicillin after: £499,175 5. Amoxicillin plus	No probabilistic sensitivity analysis conducted. A series of one-way sensitivity analyses were conducted. Notable findings include: • The risk of developing IE had to be at least 16 per million procedures for the ICER to reduce to £20,000 per QALY.

Study	Applicability	Limitations	Other	Incremental			Uncertainty
Kingdom			nces	before and oral amoxicillin after: £53 5. Amoxicillin plus gentamicin then oral amoxicillin: £5193 6. Intravenous vancomycin then intravenous gentamicin: £796 7. Intravenous teicoplanin plus gentamicin: £1612 8. Intravenous clindamycin then oral or intravenous clindamycin: £389	before and oral amoxicillin after: 0.00001 5. Amoxicillin plus gentamicin: 0.00001 6. Intravenous vancomycin then intravenous gentamicin: 0.00001 7. Intravenous teicoplanin plus gentamicin: 0.00001 8. Intravenous clindamycin then oral or intravenous clindamycin: 0.00001	gentamicin: £49,005,022 6. Intravenous vancomycin then intravenous gentamicin: £7,514,982 7. Intravenous teicoplanin plus gentamicin: £15,212,810 8. Intravenous clindamycin then oral or intravenous clindamycin: £3,668,040	• When the estimated costs and potential benefits of future prophylaxis are included in the analysis, this threshold rises to 48 per million. • When the efficacy of prophylaxis was varied between 25% to 75%, the ICER for strategy 1 was £503,448 and £164,069 per QALY respectively, and the ICER for strategy 2 was £3,031,864 and £1,006,853 respectively.
Franklin et al. (the 2015 Sheffield model) [11]	Directly applicable	Minor limitations [12]	Adaption of the 2008 NICE model	1. Amoxicillin: £2 2. Clindamycin: £1	1. Amoxicillin: 0.00001 2. Clindamycin: 0.00001	1. Amoxicillin: £30,967 per QALY 2. Clindamycin: dominated	The results of the study were highly sensitive to the risk of developing infective endocarditis following a dental procedure, the efficacy of antibiotic prophylaxis to reduce this risk, the cost of amoxicillin and clindamycin and the rate of fatal adverse events.

Acronyms
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year
[1] *The analysis was based on the United States healthcare system.*
[2] *A societal perspective was adopted for both cost and health consequences.*
[3] *The discount rate used in the base case was 3% rather than 3.5%.*
[4] *Utilities used to calculate quality-adjusted life years were based on the Quality of Well-being index of a United States population, rather than the EQ-5D with United Kingdom general population preferences, estimates, and a combination of both.*
[5] *Many of the key parameters driving the model are based on poor and conflicting evidence from literature sources.*

[6] *Estimates of resource use include productivity losses due to the societal perspective.*
[7] *Probabilistic sensitivity analysis was not conducted.*
[8] *All ICERs converted to 2015 UK pounds by using the Campbell and Cochrane Economics Methods Group EPPI Cost Converter available at http://www.c-cemg.org/, accessed 21-22 January 2015*
[9] *No probabilistic sensitivity analysis*
[10] *No reasonable evidence was identified to support the assumptions that individual dental procedures can lead directly to the development of infective endocarditis or that antibiotic prophylaxis reduces that risk.*
[11] *This analysis was not published at the time of writing. Please refer to Appendix P for further details and an abstract provided by the authors.*
[12] *Limited evidence to support that individual dental procedures can lead directly to the development of infective endocarditis or that antibiotic prophylaxis can reduce that risk.*

Table 14: Economic evidence profile – non-dental procedures

Study	Applicability	Limitations	Other comments	Incremental			Uncertainty
				Cost	Effect	ICER	
Caviness et al. 2004 Amoxicillin or vancomycin vs. no prophylaxis for febrile children who have cardiac lesions and undergo urinary catheterisation in the emergency department United States	Partially applicable [1,2,3,4]	Minor limitations [5,6,7,8,9]	Decision tree with most parameters taken from the literature	Amoxicillin US$495.30 (2000) Vancomycin US$666.16 (2000)	Amoxicillin -0.00045 QALYs Vancomycin 0.00005 QALYs	Amoxicillin Dominated Vancomycin US$13323200/QALY (2000) or £12213677/QALY (2015) [10]	When all antibiotic-related deaths due to amoxicillin were excluded, the ICER was US$9,875,800 (2000) or £9053368 (2015). When the prevalence of urinary tract infections is increased to 100% (from 3.9%), the ICER for amoxicillin was $311507 and $427966 for vancomycin. The conclusions were robust to all other sensitivity analyses. Probabilistic sensitivity analysis not conducted.

Acronyms
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year
[1] *Study based on the US healthcare system*
[2] *Societal perspective taken for costs*
[3] *Discount rate of 3% used*
[4] *Years of Healthy Life Measure used for utilities to derive quality adjusted life years*
[5] *Decision tree used for model structure whereas a Markov model may have been more appropriate to model long term consequences*
[6] *Parameters used for effectiveness were based on the limited evidence available in the literature*
[7] *Full range of sensitivity analyses not reported*
[8] *Probabilistic sensitivity analysis not done*
[9] *No conflicts declaration provided*
[10] *ICERs converted to 2015 UK pounds by using the Campbell and Cochrane Economics Methods Group EPPI Cost Converter available at http://www.c-cemg.org/, accessed 21-22 January 2015*

2.6.51 Evidence to recommendations

	Committee discussions
Relative value of different outcomes	The Committee discussed and agreed that the critical outcome for this review question was to establish whether there is a clear relationship between antibiotic prophylaxis and the incidence of IE in people undergoing interventional procedures who have pre-existing cardiac conditions. Therefore, the critical outcome is the measurement of such association and the precision and certainty for these measurements reported in the included studies. In addition, the committee included adverse events including anaphylaxis as an outcome as this was an important factor for consideration if treatment with antibiotics was found to be clinically effective. In order for prophylaxis to be effective, a suitable regimen that gives a balance between side effects from prophylaxis and development of the disease would need to be considered.
Quality of evidence	The committee noted the very limited evidence identified for this question, in particular the retrospective nature of all 3 included studies and lack of RCTs in this area. The committee noted the need for RCTs to assess the efficacy of antibiotic prophylaxis for IE, however they indicated that it would be very challenging to conduct such a trial given the rare nature of the condition and therefore the difficulty in recruiting sufficient numbers of participants. The committee further discussed the limited evidence and noted that: • The methodology used by all three studies was poor with high risk of bias and uncertain study designs • The retrospective nature of all 3 studies meant that the studies were reliant on the participant's memory for data regarding interventional procedures undergone and antibiotic use; in some studies, there was no indication that this data was verified in any way • Power calculation was not reported in 67% of studies (2/3) and it was therefore unclear whether the inconclusive findings observed in individual studies was due to lack of power • A wide variation in antibiotic regimen was used across the studies • All 3 included studies did not address adverse events of antibiotics prophylaxis Overall, the committee concluded that there is insufficient evidence to recommend prophylactic use of antibiotics in those at risk of IE undergoing interventional procedures. The lack of evidence has led to the use of post-procedure bacteraemia as a surrogate outcome measure for IE in some studies of antibiotic effectiveness (see section 2.41).
Trade-off between benefits and harms	All 3 studies included in this question were inconclusive as to whether antibiotics prophylaxis prevents the development of IE. The committee noted the lack of data on side effects including anaphylaxis from antibiotic prophylaxis and therefore the difficulty in establishing a balance between potential side effects and benefit of prophylaxis, if any. Furthermore, the occurrence of other effects of antibiotic usage including the risk of antibiotic resistance was noted but not covered by the evidence identified for this question. The committee highlighted that resistance is thought to be increasing in streptococci and other pathogens but is largely dependent on the patient group and therefore difficult to quantify. The committee concluded that in the absence of clear evidence on efficacy, overuse of antibiotics should be avoided to prevent community resistance.
Trade-off between net health benefits and resource use	Three studies were included in the literature review of economic evaluations examining the cost effectiveness of antibiotic prophylaxis against infective endocarditis prior to dental procedures.

	Committee discussions
	The results of all three models were highly sensitive to the risk of developing infective endocarditis following a procedure and the efficacy of antibiotic prophylaxis to reduce that risk. The Committee noted there was limited evidence to quantify either of these parameters. Regarding the risk of developing infective endocarditis following a dental procedure, the Committee were of the opinion that, if such a risk existed, it was less than 93 per million, the figure used in all three models to represent patients at a high risk of developing infective endocarditis, such as those with prosthetic valves. The Committee were unable to establish whether or not prophylaxis was effective. The 2015 Sheffield model was highly sensitive to the price of amoxicillin and clindamycin. Some Committee members noted that lower prices may be likely to occur in practice, particularly if capsules were used rather than oral suspension powder. The price of oral suspension powder was used in the base case analysis and this is more expensive than amoxicillin capsules. In other words, the lower price of amoxicillin capsules would make antibiotic prophylaxis more likely to be cost effective. A lay member confirmed that capsules are preferred to oral suspension powder from a patient perspective. However, the Committee were of the opinion that the lack of evidence supporting the efficacy of antibiotic prophylaxis outweighed the results of these scenarios. The Committee expressed some reservations about the methods used to estimate the efficacy of antibiotic prophylaxis in the 2015 Sheffield model where it was assumed that at least a proportion of the increase in incidence of infective indocarditis since the 2008 NICE guideline CG64 was attributable to the reduction in use of antibiotic prophylaxis. Also, the base case analysis did not account for the general upward trend of the incidence of infective endocarditis. The topic experts advised there were a number of confounding circumstances and events that could have contributed to the increase in incidence of infective endocarditis: • Increasing survivors and survival times specifically of people with congenital heart disease; • The severe sepsis campaign was extending into Europe at around this time with emphasis on blood culture sampling – improved case ascertainment would result as many diagnoses are made following positive blood cultures; • Increased prevalence of those at risk within the population, such as people with prosthetic valves, implantable cardiac devices and dialysis patients; • Increase in the number of older people with an inherent increase in degenerative valvular disease; • Enhanced efforts to make coding of hospital activity more accurate; • Some patients may have finished treatment as a day case rather than as an inpatient and this may have been coded multiple times for a single episode of infective endocarditis; • Improved ability to establish the diagnosis with better cardiac imaging and increased awareness; • Increased use of cardiac imaging in patients with S. Aureus bacteraemia; • The change in remuneration of general dental practitioners in 2006.

	Committee discussions
	• Migration may have increased the prevalence of people with previous rheumatic fever. • Echocardiograms are now required following a positive blood culture for staphylococci. So although absolute numbers of positive staphylococcal cultrues is falling, the increased surveillance may pick up additional cases. The Committee considered the novel data regarding adverse drug reactions from antibiotics that were included in the model. The Committee noted that this data could be subject to case ascertainment bias as it relies on accurate reporting of all adverse reactions. That is, there could be more fatal and non-fatal reactions than reflected by this data. The underreporting of adverse reactions would have the effect of overestimating the cost effectiveness of antibiotic prophylaxis. The Committee discussed whether it would be possible to conduct economic modelling to establish the cost effectiveness of antibiotic prophylaxis for high risk groups only. Based on the evidence presented in the clinical systematic reviews, the Committee determined that it would be difficult to define the population that would be considered high risk and then establish what the risk of developing infective endocarditis was for that population. Some Committee members were of the opinion that the 2008 NICE guideline had decreased cost and improved patient experience in dental clinics. For example, antibiotic prophylaxis may have been contraindicated for some patients due to already being on an antibiotic regimen – prior to the 2008 guideline this would have resulted in the dental procedure being deferred to another time. One study was included in the literature review of economic evidence on the cost effectiveness of antibiotic prophylaxis prior to non-dental procedures. This 2004 cost-utility analysis from the United States found that antibiotic prophylaxis for febrile children who have cardiac lesions and undergo urinary catheterisation in the emergency department was not cost effective. Overall, the Committee were of the opinion that antibiotic prophylaxis was unlikely to be cost effective. The Committee also considered that none of the economic models to date have attempted to include the impacts of antibiotic resistance. The negative health and cost consequences of antibiotic resistance would make antibiotic prophylaxis less cost effective.
Other considerations	For dental and non-dental procedures assessed in this review question, the Committee felt that the studies have provided inconclusive evidence on the association between antibiotic prophylaxis and incidence of IE. The Committee agreed that the current evidence is insufficient to support the hypothesis that antibiotic prophylaxis in those undergoing interventional procedures prevents the development of IE and therefore did not change the existing recommendation indicating that antibiotic prophylaxis against IE is not recommended. Patient view of the use of antibiotics for IE: the lay member discussed with the committee the reluctance of patients with long history of antibiotic use in undergoing a sudden change (i.e. discontinuing antibiotic prophylaxis) in a well-established practice. On the other hand, it was noted that new

	Committee discussions
	patients may be more likely to accept this practice of no antibiotics before undergoing an interventional procedure. The issue of conflicting information being provided by cardiologists, dental practitioners and hygienists was raised as a potential significant problem and it was thought that the health care professional missed the finer detail of the guideline around patient choice. The committee therefore discussed the importance of clear and consistent information for patients and families and also that a balanced view of the lack of evidence indicating effectiveness of prophylaxis for IE as well as any potential harms of prophylaxis should be fully explained to the person considering treatment. This will in turn allow the patient to make an informed decision about continuing/discontinuing prophylaxis. The committee further highlighted that antibiotics is only one strategy for the prevention of IE. Many other strategies for reducing the risk of IE eg: dental hygiene measures to maintain good oral health that has not been covered by the scope of this guideline. In relation to this, the committee also noted that a new dental contract was introduced in 2006 for general dental practitioners. One consequence of the contract was that it changed the incentives for dentists to provide professional cleaning and education to patients. In summary, given the lack of evidence relating to the use of antibiotics for IE, the committee decided to make a research recommendation in this area highlighting the need for a trial (see section 2.6.5). The committee concluded that the reasons for the increased incidence of IE (including within the low risk population, which is not covered by the scope of this guideline) indicated by the study (Dayer et al. 2014) that triggered this update are still unknown. The committee noted that the conclusion from the (Dayer et al. 2015) study is based on the assumption that there are 2 linear trends before and after 2008. This linear assumption has been tested by sensitivity analyses (the critique of this study, see section 2.1.2) and the sensitivity analyses suggested that if different assumptions are used, the results are likely to be different. As the evidence base has not changed significantly since 2008, together with the uncertainty of the Dayer (2015) study, the Committee overall felt that the original guideline recommendation should remain. Although, 1 lay member has expressed her concerns and disagreed with the Committee. As found by the epidemiological review (see section 1.1.1), the committee noted that interestingly, the incidence of IE continues to increase also in the US and European studies, where more conservative antibiotic prophylaxis guidelines are in place compared to the UK. As the authors of these studies postulated, this may be due to the aging population with multi-morbidity, increase of degenerative valves, increase of haemodialysis and so on; these areas were outside of the scope for this update.

2.6.62 Research recommendations

Does antibiotic prophylaxis in those at risk of developing IE reduce the incidence of IE when given before a defined interventional procedure?

Why is this important?

There is a gap in the evidence about the effectiveness of antibiotic prophylaxis in reducing the incidence of IE in those at risk of developing IE. The current evidence includes very limited data from observational studies indicating inconclusive findings. Therefore the

Committee decided that there was insufficient evidence to make a recommendation about the use of antibiotic prophylaxis and also a lack of data on side effects from antibiotic prophylaxis. The committee agreed that the need for this piece of research should be supported. More evidence is needed to enable a recommendation to be made on the use of antibiotics in those at risk of developing IE. The study should be a randomised controlled trial with long term follow-up comparing antibiotics with no antibiotic prophylaxis in adults and children with underlying structural cardiac defects undergoing interventional procedures. Outcomes should include the incidence/odds of developing IE in those receiving prophylaxis compared to those not and also the incidence of adverse effects including anaphylaxis.

1 **Table 15: Criteria for selecting high-priority research recommendations**

PICO	**Population:** adults and children with known underlying structural cardiac defects undergoing interventional procedures **Intervention:** antibiotic prophylaxis (any) **Comparison:** no antibiotic prophylaxis (including placebo) **Outcomes:** Incidence/odds of developing IE in those receiving prophylaxis compared to those not Adverse events including anaphylaxis
Current evidence base	The current evidence base consists of 3 observational studies of antibiotics compared to no prophylaxis. The population of these studies is composed of adults with valvular disease (prosthetic or native) undergoing various interventional procedures. One study included children and adults however a subgroup analysis by age was not reported. The Committee considered that they were currently unable to make a recommendation on the use of antibiotics in those at risk of IE, as the limited evidence base was inconclusive as to whether antibiotics reduces the incidence of IE. The committee also noted the lack of data on side effects including anaphylaxis from antibiotic prophylaxis and therefore the difficulty in establishing a balance between potential side effects and the benefit of prophylaxis.
Study design	RCT
Other comments	The RCT will need to have sufficient length of follow up to prospectively identify cases of IE.

2

3

4

2.71 Review question 7a

Does antibiotic prophylaxis given to those undergoing Interventional Procedures reduce the level and duration of bacteraemia?

2.7.14 Clinical evidence review

The aim of this review is to assess whether antibiotic prophylaxis in those undergoing interventional procedures reduces the level and duration of bacteraemia

The same update search as described in section 2.33 for question 6a was used for this question. Five new studies met the criteria and were included with an additional 14 studies from the original guideline; therefore a total of 19 included studies for the update.

A review flowchart is provided in appendix E, and the excluded studies (with reasons for exclusion) are shown in appendix F.

2.7.22 Methods

Summary of review protocols

- The population included:
  - adults and children undergoing interventional procedures (both dental and non-dental) irrespective of whether they have an underlying cardiac condition
- No subgroups (other than adults and children) were identified for this question.
- The intervention of interest was antibiotic prophylaxis (any) compared against no prophylaxis (including placebo).
- The topic experts outlined the following outcomes:
  - bacteraemia levels/intensity at one or more time points following prophylaxis versus before prophylaxis, duration of bacteraemia following prophylaxis versus before and number/incidence/odds of positive blood samples following prophylaxis versus before
- The studies did not report data on all these outcomes and in some situations synonymous outcomes are presented.
- GRADE methodology was used to assess the quality of evidence as follows:
- **Risk of bias:**
  - For RCTs included in this review, criteria suggested by the GRADE methodology (http://www.gradeworkinggroup.org/) were used for assessing risk of bias. For observational studies, risk of bias for each individual study was assessed using the methodology checklist from Developing NICE guidelines - the Manual 2014.
- **Indirectness:**
  - details from the PICOs in the review protocol(s) (see appendix C) were used to assess the directness of the included studies.
- **Inconsistency**
  - given the variation in populations across studies (including the regimen of antibiotic subjects received as well as the variation in interventional procedures the subjects underwent), meta-analysis of the data was not appropriate for this question. The age of the subjects and time point at which the incidence of bacteraemia was assessed post-procedure also varied from study to study; in some studies it was unclear whether the same subjects were bacteraemic at different time points therefore pooling this data could have led to double counting of subjects and thereby affected the accuracy of the results.
- **Imprecision**

- a routine search of the COMET (Core Outcome Measures in Effectiveness Trials) Initiative database was conducted to identify any relevant thresholds for defining the clinical minimal important difference (MIDs). No information was identified in the COMET database. Information about specific MIDs used to assess imprecision were also not available from the original guideline CG64. Therefore, the following thresholds were used, as per the GRADE working group recommendations: for continuous outcomes, the standard MID of 0.5 standard deviation change and for dichotomous outcomes, RRR or RRI of 25%: 0.75 or 1.25.

- **Overall quality**
  - The quality rating for RCTs began at high and for observational studies, quality rating began at low.
- **Statistical analysis**
  - meta-analyses were not conducted due to the variation in population and outcome measures (as explained above) from study to study.
  - where appropriate, summary measures such as mean differences or odds ratios (with 95% confidence intervals) were calculated using Review Manager 5.
- **Description of included studies**
  - 19 studies were included in this review: 16 RCTs,1 meta-analysis, 1 systematic review and prospective cohort study. Six studies were from the UK, three from USA, two from Sweden, two from Spain, one from South Africa , one from Japan, one from Australia and one from Germany. The meta-analysis and systematic review included studies from various counties.
  - sample size ranged from 20 to 1394 subjects in the systematic review of RCTs.
  - 12 studies examined antibiotic prophylaxis in those undergoing dental procedures; 2 of these were in children. One study examined antibiotic prophylaxis in children undergoing respiratory procedures. A further three studies looked at antibiotic prophylaxis in adults undergoing genito-urinary procedures and the remaining three studies examined antibiotics for adults undergoing gastrointestinal procedures. All studies examined the efficacy of antibiotics of different regimens compared to no antibiotic or placebo.
  - Bacteraemia was assessed at various time points following the interventional procedure. 7 studies reported the incidence of bacteraemia at baseline however the defintions of baseline varied and ranged from before prophylaxis to before procedure and after intubation and eight did not. 2 studies excluded subjects with positive blood cultures at baseline before the procedure. The remaining study did not report incidence of bacteraemia before prophylaxis separately but combined this with the incidence at any of the blood draws taken.

For a summary of included studies please see tables 13 to 16 (for the full evidence tables and full GRADE profiles please see appendices F and G).

Table 16: Summary of included studies: antibiotics for bacteraemia in those undergoing dental procedures

Study reference (including study design)	Study population	Intervention & comparator	Outcomes reported
Maharaj, 2012 (RCT)	N=80 for each comparison, adult black patients ≥18 years attending dental clinic for extraction of one tooth	3g amoxicillin or 600mg clindamycin given orally 1 hour prior to extraction vs no prophylaxis prior to extraction	- Incidence of bacteraemia after extraction
Duvall, 2013 (RCT)	N=20, adults ≥18 presenting to the surgical centre, oral surgery clinic for third molar extractions	2g amoxicillin* capsule and a placebo rinse** vs placebo rinse and placebo capsule *taken orally 1 hour prior to procedure **taken immediately before sedation medication administration; 15ml of the rinse for one minute and expectorated	- Bacteraemia levels/intensity - Incidence of bacteraemia
Diz, 2006 (RCT) [included in CG64]	N=109 for amoxicillin, 107 for clindamycin, 111 for moxifloxacin comparison, subjects >18 years who for behavioural reasons (autism, learning disabilities, phobias, etc) underwent dental extraction	2g amoxicillin or 600mg clindamycin or 400mg moxifloxacin taken orally 1 to 2 hours before anaesthesia induction vs no prophylaxis	- Incidence of bacteraemia
Hall, 1993 (RCT) [included in CG64]	N=40 per comparison, otherwise healthy adults aged 23 to 74 referred to the department of oral surgery for dental extraction	2g penicillin V plus 4 tablets of amoxicillin placebo or 4 750mg amoxicillin tablets plus 2 tablets of penicillin V placebo vs 2 tablets of penicillin V placebo and 4 tablets of amoxicillin placebo all taken 1 hr before extraction	- Incidence of bacteraemia - Bacteraemia levels/intensity (only medians without accompanying summary measures)
Roberts, 1987 (RCT) [included in CG64]	N=94, children under 16 years requiring admission for extensive conservative dental work as well as the extraction of at least 1 tooth.	Oral amoxicillin 50mg/kg 2 hours before scheduled time for surgery vs no prophylaxis	- Incidence of bacteraemia
Hall, 1996 (RCT)	N=39, adults undergoing dental extraction	Two 0.5g Cefaclor tablets taken 1 hour prior to extraction vs two tablets	- Bacteraemia levels/intensity (reported as % reduction)

Study reference (including study design)	Study population	Intervention & comparator	Outcomes reported
[included in CG64]		of placebo 1 hour prior to extraction	- Incidence of bacteraemia
Shanson, 1985 (RCT) [included in CG64]	N=82, adults aged 18 to 78 years undergoing dental extractions in the outpatient department	1.5g erythromycin stearate orally 1 hour before extraction vs matched placebo	- Incidence of bacteraemia - Side effects
Wahlmann, 1999 (RCT) [included in CG64]	N=59, adults with multiple tooth extraction in preparation for radiotherapy for oral cancer	1.5g IV cefuroxime 10 minutes before multiple tooth extraction vs 0.9%NaCl placebo	- Incidence of bacteraemia
Lockhart, 2004 (RCT) [included in CG64]	N=100, children who required dental extraction in the operating room setting because of behaviour, young age and/or the scope of treatment needs	Amoxicillin elixir 50mg/kg one hour before the anticipated time of intubation vs placebo	- Incidence of bacteraemia
Morozumi, 2010 (RCT)	N=20, systemically healthy subjects who possessed a minimum of 20 teeth and had geenralised moderate to severe chronic periodontitis undergoing scaling and root planning	Azithromycin 500mg once a day 3 days before quadrant scaling and root planning vs no prophylaxis	- Incidence of bacteraemia
Lockhart, 2008 (RCT)	N=192 adults presenting to urgent care service with the need for extraction of at least 1 erupted tooth	Amoxicillin prophylaxis according to AHA recommendations 1 hour before extraction vs placebo	- Incidence of bacteraemia - Bacteraemia levels/intensity
Shanson, 1978 (Prospective cohort)	N=120 adults presenting to the outpatient department for dental extraction	Penicillin V, 2g given as eight 250mg tablets (n=40) or amoxicillin, 2g given as eight 250mg capsules administered under supervision 1 hour before extraction vs no antibiotic	- Incidence of streptococcal bacteramia, anaerobic bacteramia and bacteramia due to aerobes or anaerobes

Table 17: Summary of included studies: antibiotics for bacteraemia in those undergoing respiratory procedures

Study reference (including study design)	Study population	Intervention and comparator	Outcomes reported
Sanchez-Carrion, 2006 (RCT)	N=101 children under 14 years scheduled for adenoidectomy (without tonsillectomy)	Cefazolin 30 to 40mg/kg given at induction of anaesthesia vs no prophylaxis	- Incidence of bacteraemia

Table 18: Summary of included studies: antibiotics for bacteraemia in those undergoing urogenital procedures

Study reference (including study design)	Study population	Intervention and comparator	Outcomes reported
Allan, 1985 (RCT) [included in CG64]	N=100, adults undergoing transurethral prostatectomy	2g intravenous mezlocillin about the time of induction of anaesthesia vs no prophylaxis	- Incidence of bacteraemia
Bhattacharya, 1995 (RCT) [included in CG64]	N=116 women with menorrhagia undergoing either transcervical resection or laser ablation of the endometrium	1.2g augmentin IV at the induction of anaesthesia vs no antibiotic	- Incidence of bacteraemia - Adverse events
Qiang, 2005 (Systematic review of RCTs) [included in CG64]	N= 10 trials, 1394 men undergoing transurethral prostatic resection	Anitbiotic vs placebo or no prophylaxis (various regimens)	- Incidence of bacteraemia

Table 19: Summary of included studies: antibiotics for bacteraemia in those undergoing gastrointestinal procedures

Study reference (including study design)	Study population	Intervention and comparator	Outcomes reported
Selby, 1994 (RCT) [included in CG64]	N=39, adults presenting with bleeding esophageal varices and who underwent emergency endoscopic sclerotherapy, defined as performed within 48 hours of bleeding	1g cefotaxime IV immediately before endoscopic sclerotherapy vs no antibiotic	- Incidence of bacteraemia - Adverse events
Rolando, 1993 (RCT) [included in CG64]	N=97 adults admitted for sclerotherapy for bleeding oesophageal varicies	IV imipenem/cilastatin over 20min vs IV dextrose-saline	- Incidence of bacteraemia
Harris, 1999 (Meta-analysis of 4 RCTs) [included in CG64]	N=478, adults undergoing diagnostic or therapeutic ERCP and had a variety of underlying pathologies	Antibiotic (various regimens) vs placebo	- Incidence of bacteraemia

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2.7.3.12 Antibiotic prophylaxis for bacteraemia in those undergoing dental procedures (grade 3 table 155/156)

4 Incidence of bacteraemia before and after prophylaxis

5 12 RCTs reported on incidence of bacteraemia at various time points. The overall finding
6 was inconsistent across studies; quality of the evidence ranged from moderate to very low. A
7 narrative summary of the findings is presented below; studies have been grouped by the
8 timing of outcomes using arbitrary thresholds. Where studies have examined more than one
9 time interval, the longest time point was used to decide which group the study should go into.

10 Incidence of bacteraemia up to 10 minutes post procedure

11 8 RCTs, one of which was in children (N= range from 20 to 94) ranging from moderate to
12 very low quality showed inconsistent evidence on the associations between antibiotic
13 prophylaxis and incidence of bacteraemia following various dental procedures. However the
14 time frame for post procedure blood samples were relatively short (up to 10 minutes post
15 procedure) and the incidence of bacteraemia before prophylaxis was not reported in 4
16 studies.

17 Incidence of bacteraemia up to 20 minutes post procedure

18 Low quality evidence from one RCT including 192 adults found that there may be a clinically
19 important decrease in the incidence of bacteraemia in the first 5 minutes of tooth extraction
20 and 20 minutes after in those receiving amoxicillin compared to placebo; this estimate was
21 however imprecise.

22 Incidence of bacteraemia up to 30 minutes post procedure

23 Moderate quality evidence from 1 RCT including 59 adults found that there is a clinically
24 important decrease in the incidence of bacteraemia at both 10 and 30 minutes after
25 extraction in those receiving cefuroxime compared to placebo. However, incidence of
26 bacteraemia before prophylaxis was not reported.

27 Incidence of bacteraemia up to 45 minutes post procedure

28 Low quality evidence from 1 RCT including 100 children found that there was a statistically
29 significant decrease in the incidence of bacteraemia after intubation, 15 minutes after
30 extraction and 45 minutes after extraction in those receiving amoxicillin compared to those
31 receiving placebo. Baseline blood samples performed after intubation were significantly lower
32 in the amoxicillin group. Clinical significance could not be assessed in both studies as data
33 was presented as crude percentages without accompanying confidence intervals in the
34 study.

35 Incidence of bacteraemia up to 1 hour post procedure

36 Low quality evidence from one RCT including around 110 adults found that there was a
37 statistically significant decrease in the incidence of bacteraemia at both 30 seconds and 1
38 hour after extraction in those receiving amoxicillin or moxifloxacin but not in those receiving
39 clindamycin. The incidence of bacteraemia before dental manipulation (but after intubation)
40 however was not comparable between the groups.

41 Duration of bacteraemia

42 No studies reported on this outcome.

43 Bacteraemia levels/intensity before and after prophylaxis

Very low quality evidence from one RCT including 20 adults was inconclusive in the total mean magnitude of bacteraemia (cfu/ml) in those receiving amoxicillin compared to placebo. The same study examined the mean magnitude of bacteraemia per blood draw and found there may be no clinical difference between the groups after draw 4 but the evidence for draws 2 and 3 were inconclusive.

A further study found that the magnitude of bacteraemia was reduced by 75% in 10 minute blood samples in both groups however the average count of colony forming units was not reported.

1 other study found that all analysed samples were below the detection threshold of 10^4 CFU per millilitre of blood.

Adverse events

Moderate quality evidence from 1 RCT including 82 adults showed that there is a clinically important increase in side effects including mild or transient nausea, abdominal discomfort or flatulence usually occurring within a few hours of extraction in those receiving erythromycin compared to placebo. This effect estimate was precise.

2.7.3.2 Antibiotic prophylaxis for bacteraemia in those undergoing respiratory procedures (grade table 157)

Incidence of bacteraemia before and after prophylaxis

Moderate quality evidence from 1 RCT including 101 children showed that there is a clinically important decrease in the incidence of bacteraemia 30 seconds after adenoidectomy (without tonsillectomy) in those receiving cefazolin compared to those receiving no prophylaxis. Very low quality evidence from the same study was inconclusive for difference in incidence of bacteraemia observed at 20 minutes after adenoidectomy. The incidence of bacteraemia before prophylaxis was not reported.

Duration of bacteraemia, bacteraemia levels/intensity before and after prophylaxis, adverse events

No studies reported on the above outcomes.

2.7.3.3 Antibiotic prophylaxis for bacteraemia in those undergoing gastrointestinal procedures (grade table 158)

Incidence of bacteraemia before and after prophylaxis

Very low quality evidence from two RCTs including 39 and 97 adults respectively and 1 meta-analysis of 4 RCTs including 478 adults was inconclusive in the incidence of bacteraemia (5 minutes after endoscopic sclerotherapy in the first study, 30 minutes post sclerotherapy in the second study and post endoscopic retrograde cholangiopancreatography (ERCP) in the third study) in those receiving antibiotic (various regimens) compared to no antibiotic/placebo. In the first study, all participants were negative 20 minutes after sclerotherapy in both groups and any participants who were positive before the procedure were excluded. In the second study, 2 participants (unclear from which group) were positive for bacteraemia before endoscopy and therefore excluded. In the third study, it was unclear how many of the subjects, if any, may have been bacteraemic before prophylaxis.

Duration of bacteraemia, bacteraemia levels/intensity before and after prophylaxis

No studies reported on the above outcomes.

Adverse events

Very low evidence from one RCT including 39 adults was inconclusive in the incidence of mortality observed in those receiving cefotaxime compared to no antibiotic.

2.7.3.43 Antibiotic prophylaxis for bacteraemia in those undergoing genitourinary procedures (grade table 159)

Incidence of bacteraemia before and after prophylaxis

Moderate quality evidence from 1 RCT including 100 adults and one systematic review of 10 RCTs including 1394 men found that there is a clinically important decrease in the incidence of bacteraemia after completion of transurethral prostatectomy in those receiving antibiotic compared to no prophylaxis/placebo. The incidence of bacteraemia at baseline before prophylaxis was not reported and the incidence of bacteraemia first day post-op and after removal of the catheter was non-significant in the first study.

Low quality evidence from 1 RCT including 116 women found that there may be a clinically important decrease in the incidence of bacteraemia immediately after transcervical resection or laser ablation of the endometrium in those receiving augmentin compared to no antibiotic; however this estimate was imprecise. The incidence of bacteraemia before prophylaxis was not reported.

Duration of bacteraemia, bacteraemia levels/intensity before and after prophylaxis

No studies reported on the above outcomes.

Adverse events

Low and very low quality evidence respectively from 1 RCT showed that there may be no clinical difference in the incidence of pain and inconclusive evidence for the incidence of offensive discharge within 2 weeks of endometrial ablation in those receiving augmentin compared to no antibiotic. Low quality evidence from the same study found there may be a clinically important increase in the incidence of fever within 2 weeks of endometrial ablation in those receiving augmentin compared to no antibiotic; this estimate was also imprecise.

2.7.4 Evidence to recommendations

	Committee discussions
Relative value of different outcomes	The Committee discussed and agreed that the critical outcome for this review question was to establish whether there is a clear relationship between antibiotic prophylaxis and the level and duration of bacteraemia in people undergoing interventional procedures regardless of whether they have a pre-existing cardiac condition. Bacteraemia, including the incidence, duration and intensity before and after prophylaxis were therefore considered to be the critical outcomes for the measurement of such association and furthermore, a surrogate outcome for IE as endocarditis usually follows bacteraemia. In addition, the committee included adverse events including anaphylaxis as an outcome as this was an important factor for consideration if treatment with antibiotics was found to be clinically effective.
Quality of evidence	The Committee discussed the utility of GRADE methodology to assess the quality of evidence for this particular review question. It was acknowledged the assessment of imprecision using the GRADE default MIDs were not suitable for this prophylaxis question examining bacteraemia as the outcome given that clinical significance for bacteraemia, a surrogate outcome for IE, could not be defined due to uncertainty in the level that may be significant for the development of IE. Therefore, the committee are uncertain about the clinical significance of evidence presented using GRADE methodology.

	Committee discussions
	The committee further discussed the evidence and noted that: • The majority of evidence came from those undergoing dental procedures (11/18 studies) • Power calculation was not reported in a number of studies • A wide variation in antibiotic regimen was used across the studies • There was very limited data on adverse events of antibiotic prophylaxis • The number bacteraemic before prophylaxis was not reported in 7 studies and of the studies that did report this, it was unclear whether this was number bacteraemic before prophylaxis or just before the procedure • The follow-up time points for post-procedure blood samples were very short (with most studies less than 60 minutes), making it difficult to establish the actual duration of bacteraemia • The sample sizes of the included studies were small It was difficult to establish the association between antibiotic prophylaxis and bacteraemia because where blood samples were obtained at multiple time points it was not clear whether the number positive for bacteraemia at different time points were from the same participants or not. Overall, the Committee concluded that although in some studies, antibiotic prophylaxis reduces the frequency of detection of bacteraemia post procedure, antibiotic prophylaxis does not eliminate bacteraemia following dental/non-dental procedures. The committee agreed that the evidence was of poor quality for investigation of whether antibiotic prophylaxis reduces the level and duration of bacteraemia and therefore the development of IE.
Trade-off between benefits and harms	Overall, there was inconsistent evidence across the studies with some studies indicating that antibiotic prophylaxis reduces the incidence of bacteraemia post-procedure but does not eliminate it. The committee noted the lack of data on side effects including anaphylaxis from prophylaxis and therefore the difficulty in establishing a balance between side effects and any potential benefit of prophylaxis in terms of preventing IE. Furthermore, the occurrence of other effects of antibiotic usage including the risk of antibiotic resistance was noted but not covered by the evidence identified for this question.
Trade-off between net health benefits and resource use	There is no impact on resource use related to this review question per se. Section 2.6.4 contains a systematic review of economic evaluations that investigate the cost-effectiveness of antibiotic prophylaxis.
Other considerations	This question somewhat overlapped with question 6a and therefore no further issues other than that outlined in section 2.35 were identified.

2.8 Review question 6b and 7b

Q6b) Does oral chlorhexidine prophylaxis in those at risk of developing IE reduce the risk of developing IE when given before a defined Interventional Procedure?

Q7b) Does oral chlorhexidine prophylaxis given to those undergoing Interventional Procedures reduce the level and duration of bacteraemia?

2.8.1 Clinical evidence review

Chlorhexidine is often used as an active ingredient in mouthwash designed to reduce dental plaque and oral bacteria. The aim of this review is to assess whether chlorhexidine prophylaxis reduces the incidence of IE in those at risk and also the level and duration of bacteraemia when given before an interventional procedure.

An update search using the original search strategy was conducted (see appendix D) which identified 674 articles (across question 6b and 7b). The titles and abstracts were screened and 22 articles were identified as potentially relevant. Full-text versions of these articles were obtained and reviewed against the criteria specified in the review protocol (appendix E). Of these, 18 were excluded as they did not meet the criteria. No studies were included for question 6b from both the original guideline and update search therefore a total of 0 included studies for question 6b. 4 new studies met the criteria for question 7b and were included with an additional 6 studies from the original guideline; therefore a total of 10 included studies for the update of question 7b.

A review flowchart is provided in appendix E, and the excluded studies (with reasons for exclusion) are shown in appendix F.

2.8.2 Methods

Summary of review protocols

- The population included:
  - for Q6b) adults and children with known underlying structural cardiac defects undergoing interventional procedures
  - for Q7b) children and adults undergoing interventional procedures (both dental and non-dental) irrespective of whether have an underlying cardiac condition.
- No subgroups (other than adults and children) were identified for this question.
- The intervention of interest was chlorhexidine prophylaxis (any concentration) compared against no chlorhexidine prophylaxis (including placebo).
- The topic experts outlined the following outcomes for this review question:
  - for Q6b) incidence/odds of developing IE in those receiving prophylaxis compared to those not receiving prophylaxis, incidence of adverse effects including anaphylaxis
  - for Q7b) bacteraemia levels/intensity at one or more timepoints following prophylaxis versus before prophylaxis, duration of bacteraemia following prophylaxis versus before, number/incidence/odds of having positive blood samples following prophylaxis versus before.
- The studies did not report data on all these outcomes and in some situations synonymous outcomes are presented.

GRADE methodology was used to assess the quality of evidence as follows:

Risk of bias

- As only RCTs were included, criteria suggested by the GRADE methodology (http://www.gradeworkinggroup.org/) were used for assessing risk of bias.

Indirectness

- Details from the PICOs in the review protocol(s) (see appendix C) were used to assess the directness of the included studies.

Inconsistency

- Given the variation in populations across studies (including the formulation and concentration of chlorhexidine subjects received as well as the variation in interventional procedures the subjects underwent), meta-analysis of the data was not appropriate for this question. The age of the subjects and time point at which the incidence of bacteraemia was assessed post-procedure also varied from study to study; in some studies it was unclear whether the same subjects were bacteraemic at different time points therefore pooling this data could have led to double counting of subjects and thereby affected the accuracy of the results.

Imprecision

- A routine search of the COMET (Core Outcome Measures in Effectiveness Trials) Initiative database was conducted to identify any relevant thresholds for defining the clinical minimal important difference (MIDs). No information was identified in the COMET database. Information about specific MIDs used to assess imprecision were also not available from the original guideline CG64. Therefore, the following thresholds were used, as per the GRADE working group recommendations: for continuous outcomes, the standard MID of 0.5 standard deviation change and for dichotomous outcomes, RRR or RRI of 25%: 0.75 or 1.25.

Statistical analysis

- Meta-analyses were not conducted due to the variation in population and outcome measures (as explained above) from study to study.
- Where appropriate, summary measures such as mean differences or odds ratios (with 95% confidence intervals) were calculated using Review Manager 5.

Overall summary of evidence

10 RCTs were included in this review 1 study was from the UK, 3 from the USA, 2 from Spain, 1 from South Africa, 1 from Turkey, 1 from Finland and 1 from Germnay. Sample size ranged from 22 to 106 subjects.

All studies included subjects undergoing some form of dental treatment such as molar extraction, placement of dental implants or intraligamental injection. 3 studies included adolescents and adults however a subgroup analyses by age was not presented. All other studies were performed in adults.

All studies used chlorhexidine as a mouth rinse however the formulation and concentrations varied with 6 studies using 0.2% chlorhexidine; 2 studies 0.12% chlorhexidine; one study 0.5% chlorhexidine; and the remaining study 1% chlorhexidine. Of the 10 RCTs, 6 compared a pre-procedural chlorhexidine rinse with some form of placebo. In the remaining 4 studies, the comparator was no prophylaxis. Bacteraemia was assessed at various time points following the dental procedure. 5 studies reported the incidence of bacteraemia at baseline but the definition of baseline ranged from before prophylaxis/ before procedure or after intubation and 3 did not. 1 study excluded subjects with positive blood cultures

preoperatively. The remaining study did not report incidence of bacteraemia before prophylaxis separately but combined this with the incidence at any of the blood draws taken.

For a summary of included studies please see table 17 (for the full evidence tables and full GRADE profiles please see appendices F and G).

Table 20: Summary of included studies

Study reference (including study design)	Study population	Intervention & comparator	Outcomes reported
Maharaj, 2012 (RCT)	N=80, adult black patients ≥18 years attending the dental clinic for extraction of one tooth	10ml 0.2% chlorhexidine rinse for 1 minute (rinsing repeated one minute later) given 1 hour prior to extraction vs no prophylaxis prior to extraction	- Incidence of bacteraemia
Pineiro, 2010 (RCT)	N=50, adults ≥18 years suitable for oral rehabilitation using osseointegrated implants	10ml 0.2% chlorhexidine rinse for 1 minute given before surgery vs no prophylaxis prior to implant placement	- Incidence of bacteraemia
Duvall, 2013 (RCT)	N=20, adults ≥18 years presenting to the surgical centre, oral surgery clinic for third molar extractions	15ml 0.12% chlorhexidine rinse for 1 minute given immediately before conscious sedation medication administration + placebo capsule* vs 15ml placebo rinse for 1 minute also given before conscious sedation medication administration + placebo capsule* *placebo capsule for both groups given with a small amount of water 1 hour prior to procedure	- Bacteraemia levels/intensity - Incidence of bacteraemia
Tuna, 2012 (RCT)	N=22, adults >18 years undergoing surgical removal of impacted mandibular third molar extraction	15ml 0.2% chlorhexidine rinse for 1 minute before surgical procedure vs 0.9% NaCl (sterile saline) solution	- Incidence of bacteraemia
Brown, 1998 (RCT) [included in CG64]	N=55, adolescents/adults aged 15 to 35 requiring removal of third molar which would require at least 8 sutures	30 cubic centimetres 0.12% chlorhexidine rinse for 1 minute before extraction vs no treatment before extraction	- Incidence of bacteraemia
Jokinen, 1978 (RCT) [included in CG64]	N=76, adolescents/adults aged 16 to 75 from various departments of the hospital for a cleaning of the mouth or because of acute symptoms in the teeth or periodontal tissues indicating dental extraction	Operative field isolation and disinfection with 0.5% chlorhexidine gluconate solution vs operative field isolation with sterile cotton rolls and saliva ejector	- Incidence of bacteraemia

Study reference (including study design)	Study population	Intervention & comparator	Outcomes reported
Lockhart, 1996 [included in CG64]	N=70, adults >18 years undergoing dental extractions	10ml 0.2% chlorhexidine hydrochloride rinse for 30 seconds (rinsing repeated 1 minute later) given prior to extraction vs 10ml placebo rinse for 30 seconds (rinsing repeated 1 minute later)	- Incidence of bacteraemia
MacFarlane, 1984 (RCT) [included in CG64]	N=40, adolescents and adults aged 16 to 70 years requiring extraction of a single premolar or first or second molar tooth (extractions confined to lower teeth in order to reduce variability)	10ml 1% chlorhexidine rinse for 2 minutes before extraction vs 10ml normal saline	- Incidence of bacteraemia
Rahn, 1995 (RCT) [included in CG64]	N=80, adults aged 22 to 77 undergoing dental treatment involving either intraligamental injection or molar extraction	0.2% chlorhexidine solution for 2 minutes vs sterile water	- Incidence of bacteraemia
Tomas, 2007 (RCT) [included in CG64]	N=106, adults with mental and behavioural disabilities undergoing dental extractions	0.2% digluconate chlorhexidine solution for 30 seconds before dental manipulation vs no prophylaxis	- Incidence of bacteraemia

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2.8.3.12 0.12% chlorhexidine (grade table 160 and 161)

3 Incidence of bacteraemia before and after prophylaxis

4 Very low quality evidence from two RCTs including 20 adults in the first and 55
5 adolescents/adults in the second was inconclusive in the incidence of bacteraemia (in at
6 least one of the four blood draws taken (including before prophylaxis) up to 10 minutes
7 following initiation of the mucogingival flap in the first study and 90 seconds after intraoral
8 suture removal in the second study) in subjects receiving chlorhexidine compared to
9 placebo/no prophylaxis before third molar extraction. Pre-treatment blood samples in the
10 second study were all negative.

11 Duration of bacteraemia

12 No studies examining 0.12% chlorhexidine reported on this outcome.

13 Bacteraemia levels/intensity before and after prophylaxis

14 Very low quality evidence from one RCT including 20 adults was inconclusive in the total
15 mean magnitude of bacteraemia (cfu/ml) in those receiving chlorhexidine prophylaxis
16 compared to those receiving placebo before third molar extractions. The same study found
17 that there may be a clinically important decrease in the magnitude of bacteraemia at blood
18 draw 4, no difference at blood draw 1 and inconclusive evidence at blood draw 2 and 3.

19 Adverse events

20 No studies examining 0.12% chlorhexidine reported on this outcome.

2.8.3.21 0.2% chlorhexidine (grade table 162)

22 Incidence of bacteraemia before and after prophylaxis

23 Six RCTs reported on incidence of bacteraemia at various time points. The overall finding
24 was inconsistent across studies; quality of the evidence ranged from moderate to very low. A
25 narrative summary of the findings is presented below; studies have been grouped by the
26 timing of outcomes using arbitrary thresholds. Where studies have examined more than one
27 time interval, the longest time point was used to decide which group the study should go into.

28 Incidence of bacteraemia up to 15 minutes post procedure

29 Very low quality evidence from 4 RCTs including 80, 50, 22 and 80 adults respectively was
30 inconclusive in the incidence of bacteraemia (3 minutes following tooth extraction in the first
31 study, at both 30 seconds and 15 minutes following dental implant placement in the second
32 study, at both 1 minute and 15 minutes following extraction in the third study and upto 6
33 minutes post dental treatment (intraligamental injection or extraction of molar) in the fourth
34 study) in those receiving chlorhexidine compared to no prophylaxis/placebo. The incidence of
35 bacteraemia at before prophylaxis was not reported for either group in the first study. The
36 incidence of bacteraemia before the procedure was lower but not significantly lower in the
37 chlorhexidine group of the second study but it was unclear if this was incidence before
38 prophylaxis. In the third study, subjects with positive preoperative blood cultures were
39 excluded and in the fourth study, all samples were negative.

40 Moderate quality evidence from one other RCT including 70 subjects showed no clinically
41 important difference in the incidence of bacteraemia at 1 or 3 minutes postextraction in those
42 receiving chlorhexidine prophylaxis compared to those receiving a placebo rinse; this effect
43 estimate was precise. The incidence of bacteraemia before prophylaxis was not reported.

Incidence of bacteraemia up to 1 hour post procedure

Low quality evidence from the final RCT including 106 adults showed there may be no clinically important difference in the incidence of bacteraemia at 30 seconds postextraction and there may be a clinically important decrease at 1 hour postextraction in those receiving chlorhexidine compared to those receiving no prophylaxis. The incidence of bacteraemia at baseline before dental manipulation but after endotracheal intubation was higher in the chlorhexidine group however this was not a significant difference.

Duration of bacteraemia

No studies examining 0.2% chlorhexidine reported on duration of bacteraemia.

Bacteraemia levels/intensity before and after prophylaxis

No studies examining 0.2% chlorhexidine reported on duration of bacteraemia.

Adverse events

No studies examining 0.2% chlorhexidine reported on this outcome.

2.8.3.3 0.5% chlorhexidine (grade table 163)

Incidence of bacteraemia before and after prophylaxis

Very low quality evidence from 1 RCT including 76 adolescents/adults showed that there may be a clinically important decrease in the incidence of bacteraemia at 30 to 60 seconds post extraction; however the uncertainty was high. The incidence of bacteraemia before prophylaxis was not reported for either group.

Duration of bacteraemia

No studies examining 0.5% chlorhexidine reported on this outcome.

Bacteraemia levels/intensity before and after prophylaxis

No studies examining 0.5% chlorhexidine reported on this outcome.

Adverse events

No studies examining 0.5% chlorhexidine reported on this outcome.

2.8.3.4 1% chlorhexidine (grade table 164)

Incidence of bacteraemia before and after prophylaxis

Moderate quality evidence from 1 RCT including 40 adolescents/adults undergoing tooth extraction showed that there is a clinically important decrease in the incidence of bacteraemia at 30 seconds postextraction in those receiving chlorhexidine compared to normal saline placebo; this was a precise estimate. There were no positive blood cultures at before extraction (unclear if this is before prophylaxis) in either group.

Duration of bacteraemia

No studies examining 1% chlorhexidine reported on this outcome.

Bacteraemia levels/intensity before and after prophylaxis

No studies examining 1% chlorhexidine reported on this outcome.

Adverse events

1 No studies examining 1% chlorhexidine reported on this outcome.

2.8.42 Evidence to recommendations

	Committee discussions
Relative value of different outcomes	For question 6b, the Committee discussed and agreed that the critical outcome for this review question was to establish whether there is a clear relationship between chlorhexidine prophylaxis and the incidence of IE in people undergoing interventional procedures who have pre-existing cardiac conditions. Therefore, the critical outcome is the measurement of such an association and the precision and certainty for these measurements reported in the included studies. In addition, the committee included adverse events as an outcome as this was an important factor for consideration if treatment with chlorhexidine was found to be clinically effective. In order for prophylaxis to be effective, a suitable regimen that gives a balance between side effects from prophylaxis and development of the disease would need to be considered. For question 7b, the Committee discussed and agreed that the critical outcome for this review question was to establish whether there is a clear relationship between chlorhexidine prophylaxis and the the level and duration of bacteraemia in people undergoing interventional procedures regardless of whether they have pre-existing cardiac conditions. Bacteraemia, including the incidence, duration and intensity before and after prophylaxis were therefore considered to be the critical outcomes for the measurement of such association and furthermore, a surrogate outcome for IE as endocarditis usually follows bacteraemia. In addition, the committee included adverse events as an outcome.
Quality of evidence	The committee noted that no evidence was identified for Q6b which aimed to assess whether chlorhexidine prophylaxis reduces the incidence of IE when given before a defined interventional procedure. Furthermore, it was highlighted that oral chlorhexidine used as an oral rinse did not significantly reduce the level of bacteraemia following dental procedures. The committee further discussed the evidence base and noted that: • A power calculation was not reported in a number of studies • A wide variation of chlorhexidine concentration was used across the studies • The number of participants bacteraemic before prophylaxis was not reported in 4/10 studies and of some studies that did report this, it was unclear whether this was the number of participants bacteraemic before prophylaxis or just before the procedure • The follow-up time points for post-procedure blood samples were very short (with most studies less than 60 min), making it difficult to establish the actual duration of bacteraemia • The sample sizes of the included studies were small • It was difficult to establish the association between chlorhexidine prophylaxis and bacteraemia because where multiple time points of blood samples were obtained, it was not clear whether the number positive for bacteraemia at different time points were from the same participants or not. • All included studies gave chlorhexidine once to subjects under study – it was suggested that chlorhexidine is needed to be given over a longer period in order to be effective. As with the antibiotic question, the committee noted that the assessment of imprecision using the GRADE default MIDs were not suitable for Q7b examining bacteraemia as the outcome given that clinical significance for bacteraemia, a surrogate outcome for IE, could not be defined due to uncertainty in the level that may be significant for the development of IE.

	Committee discussions
	Therefore, the committee are uncertain about the clinical significance of the evidence presented using GRADE methodology. Overall, the Committee concluded that chlorhexidine prophylaxis did not significantly reduce the level of bacteraemia following dental procedures. The committee therefore concluded that the current recommendation indicating that oral chlorhexidine mouthwash should not be used for prophylaxis against IE should remain given that the evidence shows that it does not reduce the frequency of bacteraemia.
Trade-off between benefits and harms	Overall, the evidence suggested that oral chlorhexidine does not significantly reduce the level of bacteraema following dental procedures. The committee noted the lack of data on chlorhexidine prophylaxis to reduce incidence of IE and further noted that data on side effects from prophylaxis was lacking, however no major side effects are believed to exist.
Trade-off between net health benefits and resource use	Cost savings are available to the NHS by not administering ineffective medicines.
Other considerations	There were no further issues highlighted by the committee.

1

3 References

3.1 Overview of epidemiology

Bor DH, Woolhandler S, Nardin R et al. (2013) Infective endocarditis in the U.S., 1998-2009: a nationwide study. PLoS ONE [Electronic Resource] 8: e60033.

Correa de Sa DD, Tleyjeh IM, Anavekar NS et al. (2010) Epidemiological trends of infective endocarditis: a population-based study in Olmsted County, Minnesota.[Erratum appears in Mayo Clin Proc. 2010 Aug;85(8):772]. Mayo Clinic Proceedings 85: 422-6.

Dayer MJ, Jones S, Prendergast B et al. (2014) Incidence of infective endocarditis in England, 2000–13: a secular trend, interrupted time-series analysis. Lancet: DOI: http://dx.doi.org/10.1016/S0140-6736(14)62007-9

Fedeli U, Schievano E, Buonfrate D et al. (2011) Increasing incidence and mortality of infective endocarditis: a population-based study through a record-linkage system. BMC Infectious Diseases 11: 48.

Federspiel JJ, Stearns SC, Peppercorn AF et al. (2012) Increasing US rates of endocarditis with Staphylococcus aureus: 1999-2008. Archives of Internal Medicine 172: 363-5.

Lee CH, Tsai WC, Liu PY et al. (2007) Epidemiologic features of infective endocarditis in Taiwanese adults involving native valves. American Journal of Cardiology 100: 1282-5.

Pant S, Patel NJ, Deshmukh A et al. (2015) Trends in Infective Endocarditis Incidence, Microbiology, and Valve Replacement in the United States From 2000 to 2011. Journal of the American College of Cardiology 65(19): 2070-6.

Pasquali SK, He X, Mohamad Z et al. (2012) Trends in endocarditis hospitalizations at US children's hospitals: impact of the 2007 American Heart Association Antibiotic Prophylaxis Guidelines. American Heart Journal 163: 894-9.

Ternhag A, Cederstrom A, Torner A et al. (2013) A nationwide cohort study of mortality risk and long-term prognosis in infective endocarditis in Sweden. PLoS ONE [Electronic Resource] 8: e67519.

3.2 Review question 1a and 1b

Alagna L, Park L, Nicholson B et al. (2014) Repeat endocarditis: analysis of risk factors based on the International collaboration of Endocarditis – Prospective Cohort Study. Clinical Microbiology and Infection. 20: 566-575.

Ammar W, El Aroussi W, El Mahy A et al. (2013) Case-Control study of potential culprit procedures for infective endocarditis in an Egyptian tertiary care centre. The Egyptian Heart Journal. 65, 153-157

Clemens JD, Horwitz RI, Jaffe CC, et al. (1982) A controlled evaluation of the risk of bacterial endocarditis in persons with mitral-valve prolapse. N Engl J Med 307: 776–81.

Hickey AJ, MacMahon SW, Wilcken DE, et al. (1985) Mitral valve prolapse and bacterial endocarditis: when is antibiotic prophylaxis necessary? American Heart Journal 109: 431–35.

Richet H, Casalta JP, Thuny F et al (2008). Development and assessment of a new early scoring system using non-specific clinical signs and biological results to identify children and adult patients with a high probability of infective endocarditis on admission. Journal of Antimicrobial Chemotherapy; 62:1434-1440.

Rushani D, Kaufman J, Ionescu-Ittu R. et al. (2013) Infective Endocarditis in Children with congenital heart disease. Cumulative incidence and predictors. Circulation. 128:1412-1419.

Strom BL, Abrutyn E, Berlin J et al (1998) Dental and cardiac risk factors for infective endocarditis: a population-based case-control study. Ann Int Med;129:761-9.

3.35 Review question 2

Aksoy O, Sexton D, Wang A et al (2007). Early surgery in patients with infective endocarditis: A propensity score analysis. Clinical Infectious diseases; 44:364-72.

Alagna L, Park L, Nicholson B et al (2014) Repeat endocarditis: analysis of risk factors based on the International collaboration of Endocarditis – Prospective Cohort Study. Clinical Microbiology and Infection. 20: 566-575.

Alonso-valle H, farinas-Alvarez C, Garcia-Palomo J. et al. (2010). Clinical course and predictors of death in prosthetic valve endocarditis over a 20-year period. The Journal of Thoracic and Cardiovascular Surgery. 139:4887-893

Bannay A, Hoen B, Duval X et al. (2011) The impact of valve surgery on short- and long-term mortality in left-sided infective endocarditis: do differences in methodological approaches explain previous conflicting results? European Heart Journal; 32, 2003-2015.

Da Costa M, Wollmann DR, Campos A et al. (2007) Risk index for death by infective endocarditis: a multivariate logistic model. Brazilian Journal of Cardiovascular Surgery. 22(2):192-200.

Delahaye F, Alla F, Beguinot I et al. (2007) In-hospital mortality of infective endocarditis: Prognostic factors and evaluation over an 8-year period. Scandinavian Journal of Infectious Diseases. 39:849-857.

Erbay AR, Erbay A, Canga A et al. (2010). Risk Factors for In-Hospital Mortality in Infective Endocarditis: Five years' Experience at a Tertiary Care Hospital in Turkey. Journal Heart Valve Disease; 19:2:216-224.

Fernandez Guerrero M, Goyenechea A, Verdejo C et al. (2007). Enterococcal endocarditis on native and prosthetic valves. A review of clinical and prognostic factors with emphasis on hospital-acquired infections as a major determinant of outcome. Medicine. 86:6:363-377

Fernandez Guerrero M, Alvarez B, Manzarbeitia F et al (2010) Left-sided Endocarditis caused by staphylococcus aureus. A comparison of clinical and prognostic factors of patients with native and prosthetic valve endocarditis. Infectious Diseases in Clinical Practice; 18:308-312.

Galvez-Acebal J, Rodriquez-Bano J, Martinez-Marcos F et al (2010). Prognostic factors in left-sided endocarditis: results from the Andalusian multicentre cohort. BMC Infectious diseases. 10:17.

Lin YT, Hsieh K, Chen, YS et al (2013) Infective endocarditis in children without underlying heart disease. Journal of Microbiology, Immunology and Infection. 46, 121-128.

Murakami T, Niwa K, Yoshinaga M et al (2012) Factors associated with surgery for active endocarditis in congenital heart disease. International Journal of Cardiology 157; 59-62.

Murdoch D, Corey G, Hoen B et al (2009). Clinical presentation, etiology, and outcome of Infective endocarditis in the 21st century. Archives of Internal Medicine; 169:5:463-473

San Roman J, Lopez J, Vilacosta I et al. (2007) Prognostic Stratification of patients with left sided endocarditis determined at admission. The American Journal of Medicine; 120, 369.e1-369.e7.

Smith MJ, So RR, Engel AM. (2007) Clinical predictors of mortality from infective endocarditis. International journal of Surgery. 5, 31-34.

Ternhag A, Cederstrom A, Torner A et al. (2013) A nationwide cohort study of mortality risk and long-term prognosis in infective endocarditis in Sweden. 8, 7, e67519.

Thuny F, Avierinos J, Tribouilloy C et al (2007) Impact of cerebrovascular complications on mortality and neurologic outcome during infective endocarditis: a prospective multicentre study. 28, 1155-1161.

Thuny F, Giorgi R, Habachi R et al. (2012) Excess mortality and morbidity in patients surviving infective endocarditis. Valvular and congenital heart disease. 164:94-101.

Tleyjeh IM, Anavekar N, Mirzoyev et al (2007) The impact of valve surgery on 6 month mortality in left-sided infective endocarditis. Circulation. 115:1721-1728.

Wang A, Athan E, Pappas PA et al. (2007) Contemporary clinical profile and outcome of prosthetic valve endocarditis 2926. JAMA: Journal of the American Medical Association 297: 1354-61

Wong CW, Porter G, Tisch J et al. (2009). Outcome and prognostic factors on 57 cases of infective endocarditis in a single centre. Journal of the New Zealand Medical Association. 122:1304:54-62.

Yoshinaga M, Niwa K, Niwa A et al. (2008) Risk factors for in-hospital mortality during infective endocarditis in patients with congenital heart disease. American Journal of Cardiology. 101:114-118.

3.4 Review question 3

Ammar W, El AW, El MA et al. (2013) Case - control study of potential culprit procedures for infective endocarditis in an Egyptian tertiary care center. Egyptian Heart Journal 65: 153-7.

Chen SJ, Liu CJ, Chao TF et al. (2013) Dental scaling and risk reduction in infective endocarditis: a nationwide population-based case-control study. The Canadian journal of cardiology 29: 429-33.

Duval X, Alla F, Hoen B et al. (2006) Estimated risk of endocarditis in adults with predisposing cardiac conditions undergoing dental procedures with or without antibiotic prophylaxis. Clinical Infectious Diseases 42: e102-e107.

Lacassin F, Hoen B, Leport C et al. (1995) Procedures associated with infective endocarditis in adults. A case control study. European Heart Journal 16: 1968-74.

Mohee AR, West R, Baig W et al. (2014) A case-control study: are urological procedures risk factors for the development of infective endocarditis? BJU international 114: 118-24.

Strom BL, Abrutyn E, Berlin JA et al. (2000) Risk factors for infective endocarditis: oral hygiene and nondental exposures. Circulation 102: 2842-8.

3.5 Review question 4

Assaf M, Yilmaz S, Kuru B et al. (2007) Effect of the diode laser on bacteremia associated with dental ultrasonic scaling: a clinical and microbiological study. Photomedicine and laser surgery 25: 250-6.

Barragan Casas JM, Hernandez Hernandez JM, Garcinuno Jimenez MA et al. (1999) Bacteremia cases by digestive system endoscopy. Revista Espanola de Enfermedades Digestivas 91: 111-6.

Cherry M, Daly CG, Mitchell D et al. (2007) Effect of rinsing with povidone-iodine on bacteraemia due to scaling: a randomized-controlled trial. Journal of clinical periodontology 34: 148-55.

Chun YJ, Yoon NR, Park JM et al. (2012) Prospective assessment of risk of bacteremia following colorectal stent placement. Digestive diseases and sciences 57: 1045-9.

Duval X, Delahaye F, Alla F et al. (2012) Temporal trends in infective endocarditis in the context of prophylaxis guideline modifications: Three successive population-based surveys. Journal of the American College of Cardiology 59: 1968-76.

El BS, Elassal G, Moustafa A et al. (2014) Bacteremia associated with bronchoscopy. Egyptian Journal of Chest Diseases and Tuberculosis 63: 701-4.

Ho H, Zuckerman MJ, Wassem C (1991) A prospective controlled study of the risk of bacteremia in emergency sclerotherapy of esophageal varices. Gastroenterology 101: 1642-8.

Kullman E, Borch K, Lindstrom E et al. (1992) Bacteremia following diagnostic and therapeutic ERCP. Gastrointestinal Endoscopy 38: 444-9.

Lockhart PB, Brennan MT, Sasser HC et al. (2008) Bacteremia associated with toothbrushing and dental extraction. Circulation 117: 3118-25.

London MT, Chapman BA, Faoagali JL et al. (1986) Colonoscopy and bacteraemia: an experience in 50 patients 952. New Zealand Medical Journal 99: 269-71.

Lucas VS, Omar J, Vieira A et al. (2002) The relationship between odontogenic bacteraemia and orthodontic treatment procedures. European Journal of Orthodontics 24: 301.

Melendez LJ, Chan KL, Cheung PK et al. (1991) Incidence of bacteremia in transesophageal echocardiography: a prospective study of 140 consecutive patients. Journal of the American College of Cardiology 18: 1650-4.

Min BH, Chang DK, Kim DU et al. (2008) Low frequency of bacteremia after an endoscopic resection for large colorectal tumors in spite of extensive submucosal exposure. Gastrointestinal endoscopy 68: 105-10.

Morozumi T, Kubota T, Abe D et al. (2010) Effects of irrigation with an antiseptic and oral administration of azithromycin on bacteremia caused by scaling and root planing. Journal of periodontology 81: 1555-63.

Pineiro A, Tomas I, Blanco J et al. (2010) Bacteraemia following dental implants' placement. Clinical oral implants research 21: 913-8.

Roberts GJ, Simmons NB, Longhurst P et al. (1998) Bacteraemia following local anaesthetic injections in children. British Dental Journal 185: 295-8.

Roberts GJ, Gardner P, Longhurst P et al. (2000) Intensity of bacteraemia associated with conservative dental procedures in children. British Dental Journal 188: 95-8.

Roberts GJ, Jaffray EC, Spratt DA et al. (2006) Duration, prevalence and intensity of bacteraemia after dental extractions in children. Heart 92: 1274-7.

Roudaut R, Lartigue MC, Texiermaugein J et al. (1993) Incidence of bacteremia or fever during transesophageal echocardiography - a prospective-study of 82 patients. European Heart Journal 14: 936-940.

Saayman AG, Findlay GP, Barnes RA et al. (2009) Bacteraemia following single-stage percutaneous dilatational tracheostomy. Intensive care medicine 35: 1970-3.

Sharif-Kashani B, Shahabi P, Behzadnia N et al. (2010) Incidence of fever and bacteriemia following flexible fiberoptic bronchoscopy: a prospective study. Acta medica Iranica 48: 385-8.

Shyu KG, Hwang JJ, Lin SC et al. (1992) Prospective study of blood culture during transesophageal echocardiography. American Heart Journal 124: 1541-4.

Sonbol H, Spratt D, Roberts GJ et al. (2009) Prevalence, intensity and identity of bacteraemia following conservative dental procedures in children. Oral microbiology and immunology 24: 177-82.

Tomas I, Alvarez M, Limeres J et al. (2007) Prevalence, duration and aetiology of bacteraemia following dental extractions. Oral Diseases 13: 56-62.

Tuna A, Delilbasi C, Arslan A et al. (2012) Do antibacterial mouthrinses affect bacteraemia in third molar surgery? A pilot study. Australian dental journal 57: 435-9.

Weickert U, Vetter S, Burkhardt U et al. (2006) Bacteremia after diagnostic conventional laparoscopy and minilaparoscopy: a prospective study in 100 patients. Journal of Clinical Gastroenterology 40: 701-4.

Yagci A, Uysal T, Demirsoy KK et al. (2013) Relationship between odontogenic bacteremia and orthodontic stripping. American journal of orthodontics and dentofacial orthopedics : official publication of the American Association of Orthodontists, its constituent societies, and the American Board of Orthodontics 144: 73-7.

Yildirim I, Okur E, Ciragil P et al. (2003) Bacteraemia during tonsillectomy. Journal of Laryngology & Otology 117: 619-23.

Yokoyama Y, Nishigaki E, Abe T et al. (2014) Randomized clinical trial of the effect of perioperative synbiotics versus no synbiotics on bacterial translocation after oesophagectomy. The British journal of surgery 101: 189-99.

Zhang W, Daly CG, Mitchell D et al. (2013) Incidence and magnitude of bacteraemia caused by flossing and by scaling and root planing. Journal of clinical periodontology 40: 41-52.

Zuccaro G Jr, Richter JE, Rice TW et al. (1998) Viridans streptococcal bacteremia after esophageal stricture dilation. Gastrointestinal Endoscopy 48: 568-73.

3.6 Review question 5

Bhanji S, Williams B, Sheller B, et al. (2002) Transient bacteremia induced by toothbrushing: a comparison of the Sonicare toothbrush with a conventional toothbrush. Pediatric Dentistry 24: 295–99.

Jones, DJ., Munro, CL., Grap, MJ., Kitten, T., Edmond, M. (2010). Oral care and bacteraemia risk in mechanically ventilated adults. Heart Lung. 39 (60): S57 –S65.

Lockhart, PB., Brennan, MT., Sasser, HC., Fox, PC., Paster, BJ., Bahrani-Mougeot, FK. (2008). Bacteremia associated with toothbrushing and dental extraction. Circulation. 117: 3118-3125.

Lucas V, Roberts GJ, Lucas V, Roberts GJ. Odontogenic bacteremia following tooth cleaning procedures in children 891. Pediatric dentistry 2000;22:96-100.

Lucas,VS., Gafan, G., Dewhurst, S., Roberts, GJ. (2008). Prevalence, intensity and nature of bacteraemia after toothbrushing. Journal of Dentistry. 36: 481-487.

Roberts GJ, Holzel HS, Sury MR, Simmons NA, Gardner P, Longhurst P. Dental bacteremia in children. SO: Pediatric cardiology 1997;18:24-7.

3.7 Review question 6a

Agha Z, Lofgren RP, VanRuiswyk JV (2005) Is antibiotic prophylaxis for bacterial endocarditis cost-effective? Medical Decision Making 25:308-320.

Caviness AC, Cantor SB, Coburn HA, Ward MA (2004) A cost-effectiveness analysis of bacterial endocarditis prophylaxis for febrile children who have cardiac lesions and undergo urinary catheterization in the emergency department. Pediatrics, 113 (5), 1291-1296.

Horstkotte D, Rosin H, Friedrichs W, Loogen F (1987) Contribution for choosing the optimal prophylaxis of bacterial endocarditis. Eur Heart J. 8: 379–81.

Lacassin F, Hoen B, Leport C, Selton-Suty C, Delahaye F, Goulet V et al. Procedures associated with infective endocarditis in adults. A case control study. European heart journal 1995;16:1968-74.

National Institute for Health and Clinical Excellence (2008) NICE clinical guideline 64 Prophylaxis against infective endocarditis: antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures.

Van der Meer JT, van Wijk W, Thompson J, Vandenbroucke JP, Valkenburg HA, Michel MF. Efficacy of antibiotic prophylaxis for prevention of native-valve endocarditis. Lancet 1992;339:135-9.

3.8 Review question 7a

Allan WR, Kumar A (1985) Prophylactic mezlocillin for transurethral prostatectomy. British Journal of Urology 57: 46–49.

Bhattacharya S, Parkin DE, Reid TM et al. (1995) A prospective randomised study of the effects of prophylactic antibiotics on the incidence of bacteraemia following hysteroscopic surgery. European Journal of Obstetrics, Gynecology & Reproductive Biology 63: 37–40

Duvall, NB., Fisher, TD., Hensley, D. (2013). The comparative efficacy of 0.12% chlorhexidine and amoxicillin to reduce the incidence and magnitude of bacteraemia during third molar extractions. Oral surgery, oral medicine and oral pathology. 115 (6): 752-763

Diz DP, Tomas C, Limeres PJ, et al. (2006) Comparative efficacies of amoxicillin, clindamycin, and moxifloxacin in prevention of bacteremia following dental extractions. Antimicrobial Agents & Chemotherapy 50: 2996–3002.

Hall G, Hedstrom SA, Heimdahl A, Nord CE. Prophylactic administration of penicillins for endocarditis does not reduce the incidence of postextraction bacteremia.[see comment]. Clinical Infectious Diseases 1993;17:188-94

Hall G, Heimdahl A, Nord CE. Effects of prophylactic administration of cefaclor on transient bacteremia after dental extraction. European journal of clinical microbiology & infectious diseases 1996; 15: 646–49

Harris A, Chan AC, Torres-Viera C et al. (1999) Meta-analysis of antibiotic prophylaxis in endoscopic retrograde cholangiopancreatography (ERCP). Endoscopy 31: 718-24

Lockhart PB, Brennan MT, Kent ML, Norton HJ, Weinrib DA. Impact of amoxicillin prophylaxis on the incidence, nature, and duration of bacteraemia in children after intubation and dental procedures. Circulation 2004;109:2878-84

Lockhart, PB., Brennan, MT., Sasser, HC., Fox, PC., Paster, BJ., Bahrani-Mougeot, FK. (2008). Bacteremia associated with toothbrushing and dental extraction. Circulation. 117: 3118-3125

Maharaj, B., Coovadia, Y., Vayej, AC. (2012). A comparative study of amoxicillin, clindamycin and chlorhexidine in the prevention of post-extraction bacteraemia. Cardiovascular journal of Africa. 23 (9): 491-494

Morozumi T, Kubota T, Abe D, Shimizu T. (2010) Effects of irrigation with an antiseptic and oral administration of azithromycin on bacteraemia caused by scaling and root planning. Journal of Periodontology 81 (11): 1555-1563

Qiang W, Jianchen W, MacDonald R et al. (2005) Antibiotic prophylaxis for transurethral prostatic resection in men with preoperative urine containing less than 100,000 bacteria per ml: a systematic review. [Review] [40 refs]. Journal of Urology 173: 1175-81

Roberts GJ, Radford P, Holt R. Prophylaxis of dental bacteraemia with oral amoxycillin in children. British Dental Journal 1987;162:179-82.

Rolando N, Gimson A, Philpott-Howard J et al. (1993) Infectious sequelae after endoscopic sclerotherapy of oesophageal varices: role of antibiotic prophylaxis. Journal of Hepatology 18: 290-4

Sanchez-Carrion, S., Prim, MP., De Diego, JI., Sastre, N., Pena-Garcia, P. (2006). Utility of prophylactic antibiotics in pediatric adenoidectomy. International journal of pediatric otorhinolaryngology. 70 (7): 1275 -1281

Selby WS, Norton ID, Pokorny CS et al. (1994) Bacteremia and bacterascites after endoscopic sclerotherapy for bleeding esophageal varices and prevention by intravenous cefotaxime: a randomized trial. Gastrointestinal Endoscopy 40: 680-4

Shanson DC, Akash S, Harris M, Tadayon M. Erythromycin stearate, 1.5 g, for the oral prophylaxis of streptococcal bacteraemia in patients undergoing dental extraction: efficacy and tolerance. Journal of Antimicrobial Chemotherapy 1985;15:83-90

Shanson DC, Cannon P, Wilks M. Amoxicillin compared with penicillin V for the prophylaxis of dental bacteremia Journal of Antimicrobial Chemotherapy 1978;4:431-436

Wahlmann U, Al Nawas B, Jutte M, Wagner W. Clinical and microbiological efficacy of single dose cefuroxime prophylaxis for dental surgical procedures. International Journal of Antimicrobial Agents 1999;12:253-6

3.9 Review question 7b

Brown AR, Papasian CJ, Shultz P, et al (1998) Bacteremia and intraoral suture removal: can an antimicrobial rinse help? Journal of the American Dental Association 129: 1455–61.

Duvall, NB., Fisher, TD., Hensley, D. (2013). The comparative efficacy of 0.12% chlorhexidine and amoxicillin to reduce the incidence and magnitude of bacteraemia during third molar extractions. Oral surgery, oral medicine and oral pathology. 115 (6): 752-763.

Jokinen MA. Prevention of postextraction bacteremia by local prophylaxis. International Journal of Oral Surgery 1978;7:450-2.

Lockhart PB. An analysis of bacteremias during dental extractions. A double-blind, placebo-controlled study of chlorhexidine. Archives of Internal Medicine 1996;156:513-20.

MacFarlane TW, Ferguson MM, Mulgrew CJ. Post-extraction bacteremia : role of antiseptics and antibiotics. Br Dent J 1984;156:179-81.

Maharaj, B., Coovadia, Y., Vayej, AC. (2012). A comparative study of amoxicillin, clindamycin and chlorhexidine in the prevention of post-extraction bacteraemia. Cardiovascular journal of Africa. 23 (9): 491-494.

Pineiro, A., Tomas, I., Blanco, J., Alvarez, M. (2010). Bacteraemia following dental implants' placement. Clinical oral implants research. 21: 913-918.

Rahn R, Schneider S, Diehl O, Schafer V, Shah PM. Preventing post-treatment bacteremia: comparing topical povidone-iodine and chlorhexidine.[see comment]. Journal of the American Dental Association 1995;126:1145-9.

Tomas I, Alvarez M, Limeres J, Tomas M, Medina J, Otero JL et al. Effect of a chlorhexidine mouthwash on the risk of postextraction bacteremia. Infection Control & Hospital Epidemiology 2007;28:577-82.

Tuna, A., Delilbasi, C., Arslan, A., Gurol, Y., Tekkanat, ZT. (2012). Do antibacterial mouthrinses affect bacteraemia in third molar surgery? A pilot study. Australian dental journal. 57: 435-439.

4 Glossary and abbreviations

Please refer to the NICE glossary.

1 Appendices

2 Appendix A: Standing Committee 3 members and NICE teams

A.1 4 Core members

Name	Role
Damien Longson (Chair)	Consultant Liaison Psychiatrist, Manchester Mental Health and Social Care Trust
Catherine Briggs	GP Principal, Bracondale Medical Centre, Stockport
John Cape	Director of Psychological Therapies Programme, University College London
Alun Davies	Professor of Vascular Surgery and Honorary Consultant Surgeon, Charing Cross & St Mary's Hospital & Imperial College NHS Trust
Alison Eastwood	Senior Research Fellow, Centre for Reviews and Dissemination, University of York
Sarah Fishburn	Lay Member
Jim Gray	Consultant Medical Microbiologist, The Birmingham Children's Hospital NHS Foundation Trust
Kath Nuttall	Director, Lancashire & South Cumbria Cancer Network (- April 2013)
Tilly Pillay	Consultant Neonatologist, Staffordshire, Shropshire and Black Country Newborn Network, Royal Wolverhampton Hospitals Trust
Nick Screaton	Radiologist, Papworth Hospital NHS Foundation Trust
Lindsay Smith	Principal in General Medical Practice, Somerset
Philippa Williams	Lay Member
Sophie Wilne	Paediatric Oncologist, Nottingham Children's Hospital

A.2 5 Topic expert Committee members

Name	Role
Richard Balmer	Paediatric Dentist, University of Leeds
Mark Dayer (Non-voting expert witness)	Consultant Cardiologist, Taunton & Somerset NHS Trust
Valentina Gallo	Epidemiologist, University of London
Alison Loescher	Dentist, University of Sheffield
Suzannah Power	Lay Member
Craig Ramsay (Non-voting expert witness)	Professor of Healthcare Assessment, University of Aberdeen
Jon Sandoe	Consultant Microbiologist, Leeds Teaching Hospital NHS Trust
Richard Watkin	Consultant Cardiologist, Good Hope Hosptial, Birmingham

A.3 6 NICE project team

Name	Role
Catharine Baden-Daintree	Editor
Mark Baker	Clinical Advisor
Christine Carson	Guideline Lead

Joy Carvill	Guideline Co-ordinator
Jessica Fielding	Public Involvement Advisor
Bhash Naidoo	Technical Lead (Health Economics)
Beth Shaw	Technical Lead
Louise Shires	Guideline Commissioning Manager

A.41 Clinical guidelines update team

Name	Role
Phil Alderson	Clinical Advisor
Emma Banks	Co-ordinator
Paul Crosland	Health Economist
Nicole Elliott	Associate Director
Sarah Glover	Information Specialist
Cheryl Hookway	Technical Analyst
Susannah Moon	Programme Manager
Rebecca Parsons	Project Manager
Nitara Prasannan	Technical Analyst
Charlotte Purves	Administrator
Toni Tan	Technical Adviser
Allan Wailoo	Professor of Health Economics and Director of NICE Decision Support Unit, University of Sheffield

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Appendix B: Declarations of interest

Standing Committee	Interest Declared	Type of Interest	Decision
Damien Longson	Family member employee of NICE.	Personal family non-specific	Declare and participate
Damien Longson	Director of Research & Innovation, Manchester Mental Health & Social Care NHS Trust.	Personal non-specific financial	Declare and participate
Catherine Briggs	Husband is a consultant anaesthetist at the University Hospital of South Manchester.	Personal family non-specific	Declare and participate
Catherine Briggs	Member of the Royal College of Surgeons, the Royal College of General Practitioners, the Faculty of Sexual and Reproductive Health and the BMA.	Personal non-specific financial	Declare and participate
John Cape	Trustee of the Anna Freud Centre, a child and family mental health charity which applies for and receives grants from the department of health and the national institute for health research.	Personal non-specific non-financial	Declare and participate
John Cape	Member of British Psychological Society & British Association for Behaviour & Cognitive Psychotherapists who seek to influence policy towards psychology & psychological therapies.	Personal non-specific non-financial	Declare and participate
John Cape	Clinical Services Lead half-day a week to Big Health, a digital health company that has one commercial product; an online CBT self-help programme for insomnia with online support	Personal non-specific financial	Declare and participate
Alun Davies	Research grant funding – commercial: Vascular Insights;	Personal non-specific financial	Declare and participate

Standing Committee	Interest Declared	Type of Interest	Decision
	Acergy Ltd; Firstkind; URGO laboratoire; Sapheon Inc (terminated 2013). All administered by Imperial College London as Sponsor and Professor Davies as CI.		
Alun Davies	Research grant funding – non-commercial: National Institute for Health Research, British Heart Foundation, Royal College of Surgeons, Circulation Foundation, European Venous Forum.	Personal non-specific financial	Declare and participate
Alun Davies	Non-commercial: Attendance at numerous national & international meetings as an invited guest to lecture where the organising groups receive funding from numerous sources including device and pharmaceutical manufacturers. Organising groups pay expenses and occasionally honoraria - the exact source of funding is often not known.	Personal non-specific financial	Declare and participate
Alison Eastwood	Member of an independent academic team at Centre for Review & Dissemination, University of York commissioned by NICE through NIHR to undertake technology assessment reviews.	Non-personal non-specific financial	Declare and participate
Sarah Fishburn	Organises workshops for physiotherapists treating pelvic girdle pain. Paid for this work.	Personal non-specific financial	Declare and participate
Sarah Fishburn	Receives payment and expenses from the Nursing and Midwifery Council as a lay panellist of the Fitness	Personal non-specific financial	Declare and participate

Standing Committee	Interest Declared	Type of Interest	Decision
	to Practise Investigating Committee.		
Sarah Fishburn	Lay reviewed with the Local Supervising Authority auditing supervision of midwives - receives payment and expenses for this work.	Personal non-specific financial	Declare and participate
Sarah Fishburn	Lay reviewer for the National Institute for Health Research; has reviewed a number of research proposals being considered for funding. Paid for carrying out these reviews.	Personal non-specific financial	Declare and participate
Sarah Fishburn	Chair of the Pelvic Partnership, a support group for women with pregnancy-related pelvic girdle pain. This is a voluntary position.	Personal non-specific financial	Declare and participate
Sarah Fishburn	Trained as a chartered physiotherapist and qualified in 1988 but have not been in clinical practice since 1997. Remains a non-practicing member of the Chartered Society of Physiotherapy.	Personal non-specific financial	Declare and participate
Sarah Fishburn	Appointed by Mott MacDonald to carry out reviews as a lay reviewer on behalf to the Nursing and Midwifery Council of Local Supervising Authorities and Universities providing courses for nurses and midwives. This is paid work.	Personal non-specific financial	Declare and participate
Jim Gray	Deputy Editor, Journal of Hospital Infection, funded by the Healthcare Infection Society (HIS pay the hospital for my time)	Personal financial non-specific	Declare and participate
Jim Gray	Co-investigator in four major trials (3 HTA-funded; 1 British Council funded. Two trials are about antibiotic prophylaxis	Non-personal financial non-specific	Declare and participate

Standing Committee	Interest Declared	Type of Interest	Decision
	on obstetrics and gynaecology to prevent pelvic infections, one is comparing different suture materials and the fourth is a diagnostic test accuracy study for use in woman in labour).		
Jim Gray	Associate Editor, International Journal of Antimicrobial Agents.	Non-personal financial non-specific	Declare and participate
Jim Gray	Associate Editor Journal of Pediatric Infectious Diseases.	Non-personal financial non-specific	Declare and participate
Jim Gray	Expert Advisor, British National Formulary for Children.	Non-personal financial non-specific	Declare and participate
Jim Gray	My Department is in receipt of an Educational Grant from Pfizer Ltd to develop improved diagnosis of invasive fungal infections in immunocompromised children	Non-personal financial non-specific	Declare and participate
Kath Nuttall	None		No action
Tilly Pillay	None		No action
Nick Screaton	Attended Thorax meeting – travel expenses paid.	Non-specific personal financial	Declare and participate
Nick Screaton	Clinical Commissioning Group stakeholder member	Non-specific personal non-financial	Declare and participate
Nick Screaton	Senior Editor British Journal of Radiology	Non-specific personal non-financial	Declare and participate
Nick Screaton	Advisory Editor Clinical Radiology	Non-specific personal non-financial	Declare and participate
Nick Screaton	Chair East of England British Institute of Radiology	Non-specific personal non-financial	Declare and participate
Nick Screaton	Director – Cambridge Clinical Imaging LTD	Non-specific personal financial	Declare and participate
Nick Screaton	British Thoracic Society Bronchiectasis Guidelines Group	Non-specific personal non-financial	Declare and participate
Nick Screaton	Specialised Imaging Clinical Commissioning Group stakeholder member	Non-specific personal non-financial	Declare and participate
Lindsay Smith	None		Declare and participate
Philippa Williams	None		Declare and

Standing Committee	Interest Declared	Type of Interest	Decision
			participate
Sophie Wilne	Recipient of NHS Innovation Challenge Award for clinical awareness campaign to reduce delays in diagnosis of brain tumours in children & young adults. Award will be used to develop the campaign.	Personal non-specific non-financial	Declare and participate
Sophie Wilne	Co-investigator for RFPB grant to undertake systematic reviews in childhood brain tumours.	Personal non-specific non-financial	Declare and participate
Sophie Wilne	Co-investigator for grant awards from charity to evaluate impact of brain tumour awareness campaign.	Personal non-specific non-financial	Declare and participate
Sophie Wilne	Funding for travel and accommodation from Novartis to attend a conference on the management of tuberous sclerosis	Personal non-specific financial	Declare and participate
Topic Expert	**Interest declared**	**Type of interest**	**Decision**
Richard Balmer	Co-author: Hollis A, Willcoxon F, Smith A, Balmer R. An investigation into dental anxiety amongst paediatric cardiology patients. International Journal of Paediatric Dentistry. Article first published online	Specific personal non-financial	Declare and participate
Richard Balmer	Committee member (representing British Society Paediatric Dentistry) on specialist advisory committee for paediatric dentistry.	Specific personal non-financial	Declare and participate
Mark Dayer (non-voting expert)	Fees and expenses paid as a member of an advisory board to RESMED (developers, manufacturers and distributors of medical equipment for sleep-disordered breathing and other respiratory disorders).	Non-specific personal financial	Declare and participate

Standing Committee	Interest Declared	Type of Interest	Decision
Mark Dayer (non-voting expert)	Fees paid by Pfizer/Bristol Myers Squibb, for presentations on the diagnosis and management of atrial fibrillation.	Non-specific personal financial	Declare and participate
Mark Dayer (non-voting expert)	Fees paid by Boehringer-Ingelheim, for presentations on the diagnosis and management of atrial fibrillation.	Non-specific personal financial	Declare and participate
Mark Dayer (non-voting expert)	Fee paid by Roche, for presentations on the diagnosis and management of heart failure.	Non-specific personal financial	Declare and participate
Mark Dayer (non-voting expert)	Expenses paid by Sorin for educational support to attend “New Horizons in Heart Failure” conference in London.	Non-specific personal financial	Declare and participate
Mark Dayer (non-voting expert)	Commercial trial sponsored by Novartis (PARAGON: heart failure) undertaken by department	Non-specific non-personal financial	Declare and participate
Mark Dayer (non-voting expert)	Commercial trial sponsored by Novartis (CANTOS: coronary artery disease) undertaken by department	Non-specific non-personal financial	Declare and participate
Mark Dayer (non-voting expert)	Commercial trial sponsored by Boehringer-Ingelheim (GLORIA AF: atrial fibrillation) undertaken by department	Non-specific non-personal financial	Declare and participate
Mark Dayer (non-voting expert)	Commercial trial sponsored by Bristol Myers Squibb (AEGEAN: atrial fibrillation) undertaken by department	Non-specific non-personal financial	Declare and participate
Mark Dayer (non-voting expert)	Commercial trial sponsored by Biotronik (MATRIX: device registry) undertaken by department	Non-specific non-personal financial	Declare and participate

Standing Committee	Interest Declared	Type of Interest	Decision
Mark Dayer (non-voting expert)	Commercial trial sponsored by Astra Zeneca (TIGRIS: coronary artery disease) undertaken by department	Non-specific non-personal financial	Declare and participate
Mark Dayer (non-voting expert)	Lead author of a publication in The Lancet that has in part led to the review of the PIE update.	Specific personal non-financial	Declare and leave prior to the recommendations being made (non-voting expert)
Suzannah Power	None		Declare and participate
Craig Ramsay (non-voting expert)	None		Declare and leave (non-voting expert)
Jon Sandoe	Registration for 24th European Congress of Clinical Microbiology and Infectious Diseases in Barcelona provided by Abbott	Specific personal financial	Declare and participate
Jon Sandoe	Accommodation/travel/ subsistence for 24th European Congress of Clinical Microbiology and Infectious Diseases in Barcelona funded by Eumedica	Specific personal financial	Declare and participate
Jon Sandoe	Honoraria paid by Astellas to a Leeds Charitable Trust Account for lecturing on the 7 point summary and implementation of AMR (antimicrobial resistance) Strategy	Non-specific non-personal financial	Declare and participate
Jon Sandoe	Advisor board: Cubicin (medication used to treat serious bacterial infections)	Specific personal Non-financial	Declare and participate
Jon Sandoe	Chairman of the British Society for Antimicrobial Chemotherapy endocarditis working party.	Non-specific personal non-financial	Declare and participate
Jon Sandoe	Member of a British Heart Valve Society valve disease working party	Non-specific personal non-financial	Declare and participate
Richard Watkin	Expenses paid to attend Medtronic sponsored EURO PCR	Non-specific personal financial	Declare and participate

Standing Committee	Interest Declared	Type of Interest	Decision
	meeting (technological advances in complex cardiovascular interventions)		
Richard Watkin	Expenses paid to attend 2015 Medtronic sponsored BCIS advanced coronary intervention meeting	Personal financial non-specific	Declare and participate
Valentina Gallo	None		Declare and participate
Alison Loescher	Professor Martin Thornhill works within the same University Department as myself. To date I have not been involved in the endocarditis research in any way.	Specific non-personal non-financial	Declare and participate

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1 Appendix C: Review protocol

C.1 2 Review questions 1a, 1b and 2

	Details
Review question 1a/1b/2	Q1a) What pre-existing cardiac conditions, in adults and children increase the risk of developing infective endocarditis (IE)? Q1b) What pre-existing cardiac conditions are not associated with increased risk of developing IE? Q2) Which pre-existing cardiac conditions are associated with relatively poorer outcomes from IE?
Background/Objectives	Patients with certain cardiac conditions are known to be at risk of developing IE. Guidelines and discussion on prophylaxis against IE start from the principle that it is possible to classify those with underlying cardiac conditions into those who are at increased risk and those whose risk is considered to be the same as, or little greater than, the general population. We therefore ought to review which underlying cardiac conditions affect a person's risk of developing IE/outcome of IE because it will influence decisions made about offering prophylaxis.
Original review questions (if relevant)	Same as above
Type of review question	Clinical prediction and risk identification review
Language	English language only
Study design	Cohort studies (prospective/retrospective), case-control and cross sectional studies
Status	Published studies (full text only) since 2008
Population	Adults and children with known underlying cardiac conditions Adults and children who have previously had IE (irrespective of whether they have a known underlying cardiac condition) *Subgroups: adults vs children (if data allows for this)
Intervention	For i.) above - prevalence of IE in those with underlying cardiac conditions For ii.) above - prevalence of cardiac conditions in those with IE
Comparator	For i.) above - prevalence of IE in those without underlying cardiac conditions For ii.) above - prevalence of cardiac conditions in those without IE
Outcomes	For all 3 review questions stated above: *Relative risks/odds ratios For Q2) poorer outcomes chosen by the TSM include: 1) mortality 2) cardiac surgery 3) stroke/systemic embolism 4) length of stay 5) recurrent attacks of IE 6) acute kidney injury
Other criteria for inclusion / exclusion of studies	For exclusion: *Single case report and qualitative studies *Case series *People at increased risk of IE who do not have underlying cardiac conditions (such as intravenous drug users)

	Details
	*Non-infective and fungal causes of IE. The guideline defines IE as bacterial endocarditis (including the HACEK group bacteria). *Rhythmic disorders
Review strategies	*A list of excluded studies will be provided following sifting of the database *Data on all included studies will be extracted into evidence tables *Where statistically possible, a meta-analytical approach will be used to give an overall summary effect *For intervention question, all critical and important outcomes from evidence will be presented in GRADE profiles (where appropriate) and further summarized in evidence statements. For epidemiology question, narrative summary with indication of quality (using checklist from Developing NICE guidelines - the Manual2014) will be used to summarise the evidence, and then further summarized in evidence statements. *Distinctions between relapse and recurrent IE to be made clear in the evidence tables *The bacteria reported in the study to be specified in the evidence tables.

C.21 Review questions 3

	Details
Review question 3	Q3) Which dental and other interventional procedures are associated with increased incidence of IE in those considered at risk of IE?
Background/Objectives	IE is a rare condition and therefore it is difficult to determine which interventional procedures may be associated with an increased incidence of IE in those with defined pre-existing cardiac conditions. It has been suggested that some interventional procedures can cause bacteraemia which in healthy people, eliminates naturally. However those with certain other conditions may be at risk of this bacteraemia leading to the development of IE. It is hence important to consider any evidence of significant postprocedure bacteraemia that may be contributing to the risk of developing IE.
Original review questions (if relevant)	Same as above
Type of review question	Clinical prediction and early identification review
Language	English language only
Study design	Cohort studies (prospective/retrospective), case-control and cross sectional studies
Status	Published studies (full text only) since 2008
Population	i.) Adults and children undergoing interventional procedures (with underlying cardiac condition); dental, upper and lower gastrointestinal tract, genitourinary tract (this includes urological, gynaecological and obstetric procedures including childbirth), upper and lower respiratory tract (includes ear nose and throat and bronchoscopy procedures). ii.) Adults and children who have previously had IE (with underlying cardiac condition) *Subgroups: adults vs children (if data allows for this)
Intervention	For i.) above: prevalence of IE in those undergoing interventional

	Details
	procedures (one or more procedures) For ii.) above: prevalence of interventional procedures in adults and children who had IE
Comparator	For i.) above: prevalence of IE in those not undergoing interventional procedures For ii.) above: prevalence of interventional procedures in those without IE
Outcomes	*Relative risks/odds ratios
Other criteria for inclusion / exclusion of studies	Criteria for exclusion: *Single case report and qualitative studies *Case series *People at increased risk of IE who do not have structural cardiac defects (such as intravenous drug users) *Non-infective and fungal causes of IE will not be considered. The guideline defines IE as bacterial endocarditis (including the HACEK group bacteria). *All other interventional procedures not listed above
Review strategies	*A list of excluded studies will be provided following sifting of the database *Although an explicit timeframe between undergoing the procedure and onset of IE could not be defined, if reported in the study, the time period needs to be noted in the evidence tables *Data on all included studies will be extracted into evidence tables *Where statistically possible, a meta-analytical approach will be used to give an overall summary effect *For intervention question, all critical and important outcomes from evidence will be presented in GRADE profiles (where appropriate) and further summarized in evidence statements. For epidemiology question, narrative summary with indication of quality (using checklist from Developing NICE guidelines - the Manual 2014) will be used to summarise the evidence, and then further summarized in evidence statements. * The bacteria reported in the study to be specified in the evidence tables.

C.51 Review question 4 and 5

	Details
Review question 4/5	Q4) What levels of bacteraemia are associated with interventional procedures, both pre and post-procedure (including consideration of what is considered significant bacteraemia)? Q5) What levels of bacteraemia are associated with everyday activities (toothbrushing/chewing/urination/defecation)?
Background/Objectives	The basis for many of the decisions which have been made regarding which procedures merit antibiotic prophylaxis is the assumption that the bacteraemia that arises following interventional procedures is a key part of the causative process in the development of IE. The aim of this review is to identify what levels of bacteraemia are associated with interventional procedures (dental and non-dental) and everyday activities.
Original review questions (if relevant)	Same as above
Type of review question	Clinical prediction

	Details
Language	English language only
Study design	RCTs, cohort studies, case-control studies and cross-sectional studies
Status	Published studies (full text only) since 2008
Population	Adults and children undergoing interventional procedures (both dental and non-dental)/everyday activities irrespective of whether they have an underlying cardiac condition
Intervention	Level/duration of bacteraemia after procedure or everyday activity, incidence/odds of having positive blood samples after procedure or activity
Comparator	Level/duration of bacteraemia at baseline/during procedure or activity, incidence/odds of having positive blood sample at baseline/during procedure or activity
Outcomes	*Bacteraemia levels/intensity/bacterial counts per unit volume at one or more timepoints following the procedure/everyday activity (definition of intensity may vary by study) *Duration of bacteraemia following a procedure/everyday activity *Number/incidence/odds of having positive blood samples before and after procedure/everyday activity For all of the above, studies may report p values comparing before procedure/activity versus after procedure/activity. 95% CIs will be calculated if possible.
Other criteria for inclusion / exclusion of studies	Criteria for inclusion: *Sequential blood sampling is needed to determine the duration of bacteraemia. You can quantify bacteria in a single blood sample. Therefore, to measure the duration of bacteraemia there must be sequential sampling and to quantify bacteraemia a test must be used that measures the number of bacteria (any test measuring numbers of bacteria can be included as there is no gold standard).
Criteria for exclusion:	*Single case report and qualitative studies *Case series *Bacteraemia means bacteria in the blood so measurement of bacteria in any other body fluid is not relevant for this question.
Review strategies	*A list of excluded studies will be provided following sifting of the database *Data on all included studies will be extracted into evidence tables *Where statistically possible, a meta-analytical approach will be used to give an overall summary effect *For intervention question, all critical and important outcomes from evidence will be presented in GRADE profiles (where appropriate) and further summarized in evidence statements. For epidemiology question, narrative summary with indication of quality (using checklist from Developing NICE guidelines - the Manual 2014) will be used to summarise the evidence, and then further summarized in evidence statements *Definitions/terminology used in the studies (bacteraemia vs sepsis vs inflammatory response) to be extracted as term bacteraemia may be used incorrectly. *Level/intensity of bacteraemia and definition of significant bacteraemia may vary in studies - any variation will be noted in evidence tables. *The method for measuring number and duration of bacteraemia (mean/median) should be extracted into the evidence tables. Also state if sequential or not.

C.6.1 Review question 6a and 7a

	Details
Review question 6a/7a	Q6a) Does antibiotic prophylaxis in those at risk of developing IE reduce the incidence of IE when given before a defined Interventional Procedure? Q7a) Does antibiotic prophylaxis given to those undergoing Interventional Procedures reduce the level and duration of bacteraemia?
Background/Objectives	Since 1955, antibiotic prophylaxis that aims to prevent endocarditis has been used in at-risk patients. The rationale for prophylaxis against IE is that endocarditis usually follows bacteraemia, certain interventional procedures cause bacteraemia with organisms that can cause endocarditis and these bacteria are usually sensitive to antibiotics; therefore, antibiotics should be given to patients with predisposing heart conditions before procedures that may cause bacteraemia. The aim of these 2 reviews is to assess whether antibiotic prophylaxis in those at risk of IE/undergoing interventional procedures reduces the risk of IE and the level and duration of bacteraemia.
Original review questions (if relevant)	Same as above
Type of review question	Intervention
Language	English language only
Study design	Systematic review of RCTs, RCTs, case-control, cohort studies
Status	Published studies (full text only) since 2008
Population	For Q6a) adults and children with known underlying structural cardiac defects undergoing interventional procedures For Q7a) adults and children undergoing interventional procedures (both dental and non-dental) irrespective of whether they have an underlying cardiac condition Subgroups: adults vs children if data allows for this
Intervention	Antibiotic prophylaxis (all types)
Comparator	No antibiotic prophylaxis or placebo (if non-active placebo)
Outcomes	For Q6a) *Incidence/odds of developing IE in those receiving prophylaxis compared to those not receiving prophylaxis, incidence of adverse effects including anaphylaxis For Q7a) *bacteraemia levels/intensity/bacterial counts per unit volume at one or more timepoints following prophylaxis versus before prophylaxis (definition of intensity may vary by study) *Duration of bacteraemia following prophylaxis versus before *Number/incidence/odds of having positive blood samples following prophylaxis versus before For all of the above, studies may report p values comparing before prophylaxis versus after prophylaxis but where possible, 95% confidence intervals will be calculated
Other criteria for inclusion / exclusion of studies	Criteria for exclusion: *Single case report and qualitative studies *Case series *People at increased risk of IE who do not have structural cardiac defects (such as intravenous drug users) *Non-infective and fungal causes of IE will not be considered. The guideline defines IE as bacterial endocarditis (including the HACEK group bacteria).
Review strategies	*A list of excluded studies will be provided following sifting of the

	Details
	database *Data on all included studies will be extracted into evidence tables *Although a specific route of administration/timing of administration for antibiotics could not be specified, it was noted that any variation in studies (in particular, the number of doses and whether prophylaxis continues after the interventional procedure) should be extracted into the evidence tables *Where statistically possible, a meta-analytical approach will be used to give an overall summary effect *All critical and important outcomes from evidence will be presented in GRADE profiles and further summarized in evidence statements

C.71 Review question 6b and 7b

	Details
Review question 6b/7b	Q6b) Does oral chlorhexidine prophylaxis in those at risk of developing IE reduce the risk of developing IE when given before a defined Interventional Procedure? Q7b) Does oral chlorhexidine prophylaxis given to those undergoing Interventional Procedures reduce the level and duration of bacteraemia?
Background/Objectives	Chlorhexidine is often used as an active ingredient in mouthwash designed to reduce dental plaque and oral bacteria. The aim of this review is to assess whether oral chlorhexidine prophylaxis in those at risk of IE reduces the risk of developing IE and the level and duration of bacteraemia when given before an interventional procedure.
Original review questions (if relevant)	Same as above
Type of review question	Intervention
Language	English language only
Study design	Systematic review of RCTs, RCTs, case-control and cohort studies
Status	Published studies (full text only) since 2008
Population	For Q6b) adults and children with known underlying structural cardiac defects undergoing interventional procedures For Q7b) adults and children undergoing interventional procedures (both dental and non-dental) irrespective of whether they have an underlying cardiac condition Subgroups: adults vs children if data allows for this
Intervention	Chlorhexidine prophylaxis (any concentration)
Comparator	No chlorhexidine prophylaxis or placebo (if non-active placebo)
Outcomes	For Q6b) *Incidence/odds of developing IE in those receiving prophylaxis compared to those not receiving prophylaxis, incidence of adverse effects including anaphylaxis For Q7b) *bacteraemia levels/intensity at one or more timepoints following prophylaxis versus before prophylaxis (definition of intensity may vary by study) *Duration of bacteraemia following prophylaxis versus before *Number/incidence/odds of having positive blood samples following prophylaxis versus before For all of the above, studies may report p values comparing before prophylaxis versus after prophylaxis
Other criteria for inclusion / exclusion of	Criteria for exclusion: *Single case report and qualitative studies

	Details
studies	*Case series *People at increased risk of IE who do not have structural cardiac conditions (such as intravenous drug users) *Non-infective and fungal causes of IE will not be considered. The guideline defines IE as bacterial endocarditis (including the HACEK group bacteria).
Review strategies	*A list of excluded studies will be provided following sifting of the database *Data on all included studies will be extracted into evidence tables *Concentration of chlorhexidine in formulation needs to be documented in evidence tables as well as any other ingredients. *Where statistically possible, a meta-analytical approach will be used to give an overall summary effect *All critical and important outcomes from evidence will be presented in GRADE profiles and further summarized in evidence statements

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Appendix D: Search strategy

Databases that were searched, together with the number of articles retrieved from each database for each question are shown in tables 20, 22, 24, 26, 28 and 30. The search strategy for each question is shown in table 21, 23, 25, 27, 29 and 31. The same strategy was translated for the other databases listed.

D.1 Overview of epidemiology

Table 21: Clinical search summary (overview of epidemiology)

Database	Date searched	Number retrieved
MEDLINE (Ovid)	12/02/2015	2845

Table 22: Clinical search terms (overview of epidemiology)

Line number	Search term	Number retrieved
	MEDLINE (Ovid)	
1	exp Endocarditis/ (23944)	23944
2	endocardit$.tw. (25238)	25238
3	1 or 2 (30535)	30535
4	incidence/ (180952)	180952
5	incidence*.tw. (498625)	498625
6	epidemiology/ (11592)	11592
7	pharmacoepidemiology/ (1285)	1285
8	epidemiol*.tw. (250400)	250400
9	epidemiology.fs. (1224547)	1224547
10	Epidemiologic Studies/ (6084)	6084
11	prevalence/ (197503)	197503
12	prevalenc*.tw. (367263)	367263
13	trends.fs. (291107)	291107
14	trend*.tw. (229895)	229895
15	or/4-14 (2195239)	2195239
16	3 and 15 (4638)	4638
17	animals/ not humans/ (3890800)	3890800
18	16 not 17 (4525)	4525
19	limit 18 to english language (3637)	3637
20	limit 19 to yr="1990 -Current" (2845)	2845

D.2 Review question 1 and 2

Table 23: Clinical search summary (review question 1 & 2)

Database	Date searched	Number retrieved
MEDLINE (Ovid)	20/11/2014	2223
MEDLINE IN PROCESS (Ovid)	20/11/2014	124
EMBASE (Ovid)	20/11/2014	3204
CDSR (Wiley)	20/11/2014	4

Database	Date searched	Number retrieved
Database of Abstracts of Reviews of Effects – DARE (Wiley)	20/11/2014	77
HTA database (Wiley)	20/11/2014	6
CENTRAL (Wiley)	20/11/2014	1

1 **Table 24: Clinical search terms (review question 1 & 2)**

Line number / Search term	Number retrieved
MEDLINE OVID 1 exp Endocarditis/ (24453) 2 endocardit$.tw. (25708) 3 1 or 2 (31159) 4 Observational Study as Topic/ (497) 5 Observational Study/ (6239) 6 Epidemiologic Studies/ (6267) 7 exp Case-Control Studies/ (710179) 8 exp Cohort Studies/ (1438148) 9 Cross-Sectional Studies/ (192723) 10 Comparative Study.pt. (1730486) 11 case control$.tw. (80639) 12 case series.tw. (35292) 13 (cohort adj (study or studies)).tw. (89735) 14 cohort analy$.tw. (3823) 15 (follow up adj (study or studies)).tw. (37500) 16 (observational adj (study or studies)).tw. (44307) 17 longitudinal.tw. (141448) 18 prospective.tw. (354362) 19 retrospective.tw. (271969) 20 cross sectional.tw. (166880) 21 or/4-20 (3436224) 22 Meta-Analysis.pt. (54493) 23 Meta-Analysis as Topic/ (14587) 24 Review.pt. (1963157) 25 exp Review Literature as Topic/ (8125) 26 (metaanaly$ or metanaly$ or (meta adj3 analy$)).tw. (64401) 27 (review$ or overview$).ti. (278689) 28 (systematic$ adj5 (review$ or overview$)).tw. (59139) 29 ((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw. (4589) 30 ((studies or trial$) adj2 (review$ or overview$)).tw. (26231) 31 (integrat$ adj3 (research or review$ or literature)).tw. (5738) 32 (pool$ adj2 (analy$ or data)).tw. (15001) 33 (handsearch$ or (hand adj3 search$)).tw. (5666) 34 (manual$ adj3 search$).tw. (3290) 35 or/22-34 (2129806) 36 animals/ not humans/ (3998169) 37 35 not 36 (1991468) 38 Randomized Controlled Trial.pt. (399610) 39 Controlled Clinical Trial.pt. (90639) 40 Clinical Trial.pt. (500856)	Please see number in the bracket at the end of each line.

Line number / Search term	Number retrieved
41 exp Clinical Trials as Topic/ (294593)	
42 Placebos/ (34004)	
43 Random Allocation/ (84070)	
44 Double-Blind Method/ (132421)	
45 Single-Blind Method/ (20589)	
46 Cross-Over Studies/ (36201)	
47 ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw. (775730)	
48 (random$ adj3 allocat$).tw. (21548)	
49 placebo$.tw. (159726)	
50 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (129984)	
51 (crossover$ or (cross adj over$)).tw. (58906)	
52 or/38-51 (1442998)	
53 animals/ not humans/ (3998169)	
54 52 not 53 (1345397)	
55 21 or 37 or 54 (5841865)	
56 3 and 55 (10268)	
57 animals/ not humans/ (3998169)	
58 56 not 57 (10049)	
59 limit 58 to english language (7904)	
60 limit 59 to ed=20070529-20141120 (2223)	
Ovid MEDLINE(R)	
1 exp Endocarditis/ (0)	
2 endocardit$.tw. (1431)	
3 1 or 2 (1431)	
4 Observational Study as Topic/ (0)	
5 Observational Study/ (9)	
6 Epidemiologic Studies/ (0)	
7 exp Case-Control Studies/ (3)	
8 exp Cohort Studies/ (6)	
9 Cross-Sectional Studies/ (0)	
10 Comparative Study.pt. (173)	
11 case control$.tw. (6943)	
12 case series.tw. (4660)	
13 (cohort adj (study or studies)).tw. (9916)	
14 cohort analy$.tw. (385)	
15 (follow up adj (study or studies)).tw. (1882)	
16 (observational adj (study or studies)).tw. (6571)	
17 longitudinal.tw. (14373)	
18 prospective.tw. (27851)	
19 retrospective.tw. (27666)	
20 cross sectional.tw. (22291)	
21 or/4-20 (101280)	
22 Meta-Analysis.pt. (45)	
23 Meta-Analysis as Topic/ (0)	
24 Review.pt. (15815)	
25 exp Review Literature as Topic/ (0)	
26 (metaanaly$ or metanaly$ or (meta adj3 analy$)).tw. (9610)	
27 (review$ or overview$).ti. (33748)	
28 (systematic$ adj5 (review$ or overview$)).tw. (10832)	

Line number / Search term		Number retrieved
29	((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw. (674)	
30	((studies or trial$) adj2 (review$ or overview$)).tw. (2965)	
31	(integrat$ adj3 (research or review$ or literature)).tw. (841)	
32	(pool$ adj2 (analy$ or data)).tw. (1597)	
33	(handsearch$ or (hand adj3 search$)).tw. (659)	
34	(manual$ adj3 search$).tw. (458)	
35	or/22-34 (59928)	
36	animals/ not humans/ (5)	
37	35 not 36 (59928)	
38	Randomized Controlled Trial.pt. (390)	
39	Controlled Clinical Trial.pt. (28)	
40	Clinical Trial.pt. (390)	
41	exp Clinical Trials as Topic/ (5)	
42	Placebos/ (0)	
43	Random Allocation/ (0)	
44	Double-Blind Method/ (2)	
45	Single-Blind Method/ (0)	
46	Cross-Over Studies/ (0)	
47	((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw. (64709)	
48	(random$ adj3 allocat$).tw. (2061)	
49	placebo$.tw. (9497)	
50	((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (7112)	
51	(crossover$ or (cross adj over$)).tw. (6246)	
52	or/38-51 (74224)	
53	animals/ not humans/ (5)	
54	52 not 53 (74224)	
55	21 or 37 or 54 (202085)	
56	3 and 55 (261)	
57	animals/ not humans/ (5)	
58	56 not 57 (261)	
59	limit 58 to english language (246)	
60	limit 59 to ed=20070529-20141120 (124)	

D.3 Review question 3

Note: review question 3 overlapped with both review question 1 and review question 4, hence, both searches for review question 1 and review question 4 have been sifted for review question 3 as well. For search strategies, please see review question 1 and review question 4.

D.4 Review question 4

Table 25: Clinical search summary (review question 4)

Database	Date searched	Number retrieved
MEDLINE (Ovid)	1/12/2014	718
MEDLINE IN PROCESS (Ovid)	1/12/2014	36
EMBASE (Ovid)	1/12/2014	605
CDSR (Wiley)	1/12/2014	52
Database of Abstracts of Reviews of Effects – DARE (Wiley)	1/12/2014	0
HTA database (Wiley)	1/12/2014	0
CENTRAL (Wiley)	1/12/2014	208

Table 26: Clinical search terms (review question 4)

Line number	Search term	Number retrieved
	MEDLINE (Ovid)	Please see number in the bracket at the end of each line.
1	exp Dentistry, Operative/ (43172)	
2	exp Dental Prophylaxis/ (6702)	
3	((dent$ or tooth$ or teeth$ or peridont$ or orthodont$) adj4 (prophyla$ or debridement)).tw. (1395)	
4	(crown adj4 length$).tw. (2643)	
5	exp Endodontics/ (23721)	
6	endodontic$.tw. (12546)	
7	Apicoectom$.tw. (436)	
8	(pulp$ adj4 cap$).tw. (1149)	
9	(pulpectom$ or pulpotom$).tw. (1063)	
10	exp Oral Surgical Procedures/ (53252)	
11	(gingivectom$ or gingivoplast$ or glossectom$).tw. (1068)	
12	mucoperio$ flap$.tw. (521)	
13	(tartar adj4 remov$).tw. (24)	
14	Sialography/ (1521)	
15	(sialograph$ or radiosialograph$).tw. (1080)	
16	(root adj4 canal adj4 (therap$ or treat$)).tw. (2619)	
17	((dent$ or oral$ or tooth$ or teeth or peridont$ or orthodont$ or root$) adj4 (restorat$ or implant$ or replant$ or reimplant$ or re-implant$ or extract$ or remov$ or scal$ or polish$ or fill$ or irrigat$ or separat$ or expos$ or bond$ or band$ or prob$ or investigat$ or rubber dam$ or wedg$ or lining$ or liner$ or planing$)).tw. (94312)	
18	((dent$ or oral$ or tooth$ or teeth$ or peridont$ or orthodont$ or root$ canal$) adj4 (surg$ or procedure$ or endoscop$ or operat$ or incis$ or excis$ or intervention$ or invasiv$ or biops$ or inject$)).tw. (42084)	
19	or/1-18 (210506)	

Line number	Search term	Number retrieved
20	exp Digestive System Surgical Procedures/ (284006)	
21	((digestive or gastro$) adj4 (surg$ or operati$)).tw. (10530)	
22	(roux-en-y or appendectom$).tw. (12144)	
23	(Bili$ adj4 (bypas$ or divers$ or surg$)).tw. (5805)	
24	(cholecystectom$ or cholecystostom$ or choledochostom$).tw. (21956)	
25	(gallbladder adj4 remov$).tw. (662)	
26	(portoenterostom$ or sphincterotom$ or sphincteroplast$ or papillotom$).tw. (6915)	
27	(colectom$ or proctocolectom$ or coloproctectom$).tw. (9909)	
28	(laparotom$ or endoscop$ or colonoscop$).tw. (184236)	
29	(duodenoscop$ or gastroscop$ or proctoscop$).tw. (6748)	
30	Cholangiopancreatograph$.tw. (6766)	
31	(ercp or esophagoscop$ or esophagogastroduodenoscop$).tw. (10077)	
32	(oesophagoscop$ or oesophagogastroduodenoscop$).tw. (598)	
33	Echocardiography, Transesophageal/ (15719)	
34	Echocardiography/ (68982)	
35	((trans?esophag$ or trans-esophag or trans-oesophag) adj4 echo$).tw. (13261)	
36	((esophag$ or oesophag$) adj4 echo$).tw. (468)	
37	(tee or toe).tw. (14555)	
38	((esophag$ or oesophag$) adj4 dilat$).tw. (2170)	
39	exp Lithotripsy/ (9116)	
40	(lithotrip$ or litholapax$ or ESWL or ESWLS).tw. (8847)	
41	(enterostom$ or cecostom$ or colostom$).tw. (7665)	
42	(duodenostom$ or ileostom$ or jejunostom$).tw. (7280)	
43	(esophagectom$ or oesophagectom$).tw. (6552)	
44	(esophagoplast$ or oesophagoplast$).tw. (783)	
45	(esophagostom$ or oesophagostom$).tw. (1252)	
46	(fundoplicat$ or nissen or billroth).tw. (7335)	
47	(gastrectom$ or gastroenterostom$ or gastrojejunostom$).tw. (19512)	
48	(Gast$ adj4 Bypass).tw. (6227)	
49	(gastroplast$ or gastrostom$ or hepatectom$ or hemorrhoidectom$).tw. (24524)	
50	((jejunoileal or jejuno-ileal or ileojejunal or intestin$) adj4 bypass).tw. (1592)	
51	((liver or hepat$ or pancrea$) adj4 (transplant$ or graft$)).tw. (56852)	
52	Pancreatectom$.tw. (6447)	
53	(pancrea$ adj4 remov$).tw. (973)	
54	(pancreaticoduodenectom$ or duodenopancreatectom$ or pancreatoduodenectom$ or pancreaticojejunostom$).tw. (6422)	
55	((periton$ or leveen) adj4 shunt$).tw. (2294)	
56	((digest$ or gastr$ or intestin$ or gi or oesophag$ or esophag$ or stomach or bowel$ or colon$ or liver or hepat$ or bili$ or duoden$ or gall$ or pancrea$ or append$ or abdom$ or anal or anus or sphinct$) adj4 (surg$ or procedure$ or operat$ or incis$ or excis$ or intervention$ or invasiv$ or biops$ or endoscop$ or sclerotherap$ or diversion$)).tw. (208685)	
57	or/20-56 (659400)	
58	exp Urogenital Surgical Procedures/ (270819)	
59	(colposcop$ or colpotom$ or culdoscop$ or endometrial ablation$).tw.	

Line number	Search term	Number retrieved
	(8043)	
60	((dilatation or vacuum) adj4 curettage).tw. (1138)	
61	(hysterectom$ or hysteroscop$ or uterine myomectom$).tw. (29793)	
62	(uter$ adj4 endoscop$).tw. (114)	
63	(ovariectom$ or oophorectom$ or salpingostom$).tw. (30264)	
64	((reproduct$ or tub$) adj4 sterili$).tw. (2380)	
65	(tub$ adj4 ligat$).tw. (2054)	
66	aldridge.tw. (54)	
67	(tub$ adj4 occlu$).tw. (1976)	
68	cooke.tw. (321)	
69	(cornual adj4 coagulat$).tw. (2)	
70	fimbriectom$.tw. (76)	
71	(irving or kroener or madlener or pomeroy).tw. (594)	
72	(tub$ adj4 (excis$ or ring$)).tw. (1197)	
73	(uchida or vasectom$ or salpingectom$).tw. (5458)	
74	(cystectom$ or cystoscop$ or cysto?tom$).tw. (17072)	
75	(kidney$ adj4 (transplant$ or graft$)).tw. (35238)	
76	(nephrectom$ or vesicotom$ or ureteroscop$).tw. (28194)	
77	(Urin$ adj4 Diver$).tw. (5004)	
78	(nephrostom$ or nephroli$).tw. (8869)	
79	(ureterostom$ or orchiectom$).tw. (5307)	
80	(Pen$ adj4 Implant$).tw. (1313)	
81	Prostatectom$.tw. (20532)	
82	Trans?uret$.tw. (13240)	
83	Trans?rect$.tw. (7494)	
84	(vasovasostom$ or castrat$ or circumci$).tw. (25193)	
85	(uret$ adj4 (catheter$ or dilatat$)).tw. (5010)	
86	exp Obstetric Surgical Procedures/ (107928)	
87	(abortion$ or embryotom$ or cerclage).tw. (48693)	
88	((obstetr$ or abdom$) adj4 deliver$).tw. (2469)	
89	C?esarean.tw. (40409)	
90	Episiotom$.tw. (1888)	
91	(Obstetr$ adj4 extract$).tw. (245)	
92	(Induc$ adj4 (labor$ or labour$)).tw. (8675)	
93	Parturition/ (3604)	
94	(parturit$ or childbirth$ or birth$).tw. (252670)	
95	(vagina$ adj4 deliver$).tw. (12130)	
96	((fet$ or cepha$) adj4 version$).tw. (562)	
97	Fetoscop$.tw. (887)	
98	Intrauterine Devices/ (7990)	
99	(Intra?uterine adj4 device$).tw. (5317)	
100	iud.tw. (6060)	
101	Vaginal Smears/ (20355)	
102	((vagina$ or cervi$ or papanicolaou) adj4 smear$).tw. (8697)	
103	((genit$ or urin$ or uro$ or uret$ or endometr$ or ovar$ or ooph$ or uter$ or bladder or vagina$ or cervi$ or gyn$ or obstet$ or prostat$ or reproduct$) adj4 (surg$ or procedure$ or operat$ or incis$ or excis$ or intervention$ or invasiv$ or biops$ or endoscop$)).tw. (106657)	
104	or/58-103 (801009)	
105	exp Pulmonary Surgical Procedures/ (57243)	
106	(pulmonary adj4 (surg* or operati*)).tw. (10089)	

Line number	Search term	Number retrieved
107	(Collapse adj4 Therap$).tw. (431)	
108	(pneumonolys$ or pneumothora$).tw. (16038)	
109	Bronchoscopy/ (20952)	
110	Bronchoscopes/ (2035)	
111	bronchoscop$.tw. (19032)	
112	thyroidectomy/ or adenoidectomy/ or laryngoplasty/ or laryngectomy/ or laryngoscopy/ or neck dissection/ or pharyngectomy/ or pharyngostomy/ or rhinoplasty/ or tonsillectomy/ or tracheostomy/ or tracheotomy/ (68513)	
113	(thyroidectom$ or adenoidectom$).tw. (15189)	
114	(laryngectom$ or laryngoscop$ or laryngoplast$).tw. (14170)	
115	neck dissect$.tw. (6297)	
116	(pharyngectom$ or pharyngostom$).tw. (411)	
117	rhinoplast$.tw. (3965)	
118	tonsillectom$.tw. (6389)	
119	tracheo?tom$.tw. (14393)	
120	(nasal adj4 pack$).tw. (806)	
121	Pneumonectomy/ (21682)	
122	Pneumonectom$.tw. (6678)	
123	(lung$ adj4 (transplant$ or graft$ or reduct$)).tw. (17321)	
124	((nasal or sinus$ or rhino$ or rhina$ or pharyn$ or laryn$ or trache$ or bronch$ or lung$ or pulmonar$ or respirat$) adj4 (surg$ or procedure$ or endoscop$ or operat$ or incis$ or excis$ or intervention$ or invasiv$ or biops$)).tw. (80249)	
125	or/105-124 (228071)	
126	19 or 57 or 104 or 125 (1814014)	
127	(bacter$ adj6 (level$ or rate$ or incidence$ or prevalence$ or duration$ or cumulat$ or transient or translocat$ or trans-locat$ or transfer$)).tw. (34586)	
128	(streptococ$ adj6 (level$ or rate$ or incidence$ or prevalence$ or duration$ or cumulat$ or transient or translocat$ or trans-locat$ or transfer$)).tw. (3730)	
129	(staphylococ$ adj6 (level$ or rate$ or incidence$ or prevalence$ or duration$ or cumulat$ or transient or translocat$ or trans-locat$ or transfer$)).tw. (4149)	
130	(enterococ$ adj6 (level$ or rate$ or incidence$ or prevalence$ or duration$ or cumulat$ or transient or translocat$ or trans-locat$ or transfer$)).tw. (1635)	
131	or/127-130 (42760)	
132	126 and 131 (4196)	
133	Observational Study as Topic/ (501)	
134	Observational Study/ (6356)	
135	Epidemiologic Studies/ (6272)	
136	exp Case-Control Studies/ (711198)	
137	exp Cohort Studies/ (1439568)	
138	Cross-Sectional Studies/ (193002)	
139	Comparative Study.pt. (1731142)	
140	case control$.tw. (80732)	
141	case series.tw. (35347)	
142	(cohort adj (study or studies)).tw. (89864)	
143	cohort analy$.tw. (3830)	
144	(follow up adj (study or studies)).tw. (37517)	
145		

Line number	Search term	Number retrieved
146	(observational adj (study or studies)).tw. (44392)	
147	longitudinal.tw. (141606)	
148	prospective.tw. (354704)	
149	retrospective.tw. (272363)	
150	cross sectional.tw. (167096)	
151	or/133-149 (3438792)	
152	Meta-Analysis.pt. (54585)	
153	Meta-Analysis as Topic/ (14595)	
154	Review.pt. (1964534)	
155	exp Review Literature as Topic/ (8135)	
156	(metaanaly$ or metanaly$ or (meta adj3 analy$)).tw. (64511)	
157	(review$ or overview$).ti. (278949)	
158	(systematic$ adj5 (review$ or overview$)).tw. (59256)	
159	((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw. (4592)	
160	((studies or trial$) adj2 (review$ or overview$)).tw. (26255)	
161	(integrat$ adj3 (research or review$ or literature)).tw. (5748)	
162	(pool$ adj2 (analy$ or data)).tw. (15021)	
163	(handsearch$ or (hand adj3 search$)).tw. (5670)	
164	(manual$ adj3 search$).tw. (3296)	
165	or/151-163 (2131312)	
166	animals/ not humans/ (4000367)	
167	164 not 165 (1992913)	
168	Randomized Controlled Trial.pt. (399960)	
169	Controlled Clinical Trial.pt. (90666)	
170	Clinical Trial.pt. (501003)	
171	exp Clinical Trials as Topic/ (294731)	
172	Placebos/ (34008)	
173	Random Allocation/ (84113)	
174	Double-Blind Method/ (132489)	
175	Single-Blind Method/ (20614)	
176	Cross-Over Studies/ (36229)	
177	((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw. (776483)	
178	(random$ adj3 allocat$).tw. (21567)	
179	placebo$.tw. (159821)	
180	((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (130057)	
181	(crossover$ or (cross adj over$)).tw. (58948)	
182	or/167-180 (1444186)	
183	animals/ not humans/ (4000367)	
184	181 not 182 (1346509)	
185	150 or 166 or 183 (5846186)	
186	132 and 184 (2358)	
187	animals/ not humans/ (4000367)	
188	185 not 186 (2265)	
189	limit 187 to english language (2018)	
	limit 188 to ed=20070831-20141201 (718)	

D.5 Review question 5

Table 27: Clinical search summary (review question 5)

Databases	Date searched	No. retrieved
MEDLINE (Ovid)	26/11/2014	201
MEDLINE IN PROCESS (Ovid)	26/11/2014	12
EMBASE (Ovid)	26/11/2014	108
CDSR (Wiley)	26/11/2014	28
Database of Abstracts of Reviews of Effects – DARE (Wiley)	26/11/2014	1
CENTRAL (Wiley)	26/11/2014	76
HTA database (Wiley)	26/11/2014	0

Table 28: Clinical search terms (review question 5)

Line number	Search terms	No retrieved
	Ovid MEDLINE	Please see brackets at end of each line for numbers. retrieved
1	Oral Hygiene/ (10647)	
2	((oral$ or dent$ or mouth$) adj4 hyg$).tw. (12867)	
3	Toothbrushing/ (6264)	
4	(toothbrush$ or tooth-brush$).tw. (4686)	
5	((tooth$ or teeth) adj4 (brush$ or clean$ or pick$)).tw. (3665)	
6	(tongue$ adj4 (brush$ or scrap$ or clean$)).tw. (182)	
7	Dental Devices, Home Care/ (1759)	
8	floss$.tw. (957)	
9	Mastication/ (8301)	
10	(masticat$ or chew$).tw. (19420)	
11	or/1-10 (47303)	
12	exp Exercise/ (127628)	
13	exercis*.tw. (195111)	
14	(physical$ adj4 (activit$ or effort$)).tw. (63019)	
15	exp Sports/ (134852)	
16	sport$.tw. (40291)	
17	(workout$ or work$ out$).tw. (8111)	
18	Physical exertion/ (53902)	
19	exertion$.tw. (14526)	
20	Physical Fitness/ (22953)	
21	fit$.tw. (191367)	
22	or/12-21 (572788)	
23	Defecation/ (5905)	
24	(defecat$ or defaecat$).tw. (6508)	
25	((void$ or pass$ or excret$ or evac$ or discharg$ or empt$ or mov$ or motion$ or open$) adj4 bowel$).tw. (3867)	

Line number	Search terms	No retrieved
26	laxation.tw. (123)	
27	((void$ or pass$ or discharg$ or excret$) adj4 (excreta or stool$ or feces or fecal or faec$)).tw. (10873)	
28	or/23-27 (23844)	
29	Urination/ (8534)	
30	(urinat$ or micturit$).tw. (8945)	
31	((void$ or pass$ or excret$ or evac$ or discharg$ or empt$) adj4 (bladder or urin$)).tw. (72741)	
32	((pass$ or mak$) adj3 water$).tw. (2128)	
33	or/29-32 (87879)	
34	11 or 22 or 28 or 33 (723634)	
35	(bacter$ adj6 (level$ or rate$ or incidence$ or prevalence$ or duration$ or cumulat$ or transient or translocat$ or trans-locat$ or transfer$)).tw. (34586)	
36	(streptococ$ adj6 (level$ or rate$ or incidence$ or prevalence$ or duration$ or cumulat$ or transient or translocat$ or trans-locat$ or transfer$)).tw. (3730)	
37	(staphylococ$ adj6 (level$ or rate$ or incidence$ or prevalence$ or duration$ or cumulat$ or transient or translocat$ or trans-locat$ or transfer$)).tw. (4149)	
38	(enterococ$ adj6 (level$ or rate$ or incidence$ or prevalence$ or duration$ or cumulat$ or transient or translocat$ or trans-locat$ or transfer$)).tw. (1635)	
39	or/35-38 (42760)	
40	34 and 39 (1346)	
41	limit 40 to english language (1212)	
42	animals/ not humans/ (4000367)	
43	41 not 42 (1022)	
44	limit 43 to ed=20070809-20141126 (447)	
45	Observational Study as Topic/ (501)	
46	Observational Study/ (6356)	
47	Epidemiologic Studies/ (6272)	
48	exp Case-Control Studies/ (711198)	
49	exp Cohort Studies/ (1439568)	
50	Cross-Sectional Studies/ (193002)	
51	Comparative Study.pt. (1731142)	
52	case control$.tw. (80732)	
53	case series.tw. (35347)	
54	(cohort adj (study or studies)).tw. (89864)	
55	cohort analy$.tw. (3830)	
56	(follow up adj (study or studies)).tw. (37517)	
57	(observational adj (study or studies)).tw. (44392)	
58	longitudinal.tw. (141606)	
59	prospective.tw. (354704)	
60	retrospective.tw. (272363)	
61	cross sectional.tw. (167096)	

Line number	Search terms	No retrieved
62	or/45-61 (3438792)	
63	Meta-Analysis.pt. (54585)	
64	Meta-Analysis as Topic/ (14595)	
65	Review.pt. (1964534)	
66	exp Review Literature as Topic/ (8135)	
67	(metaanaly$ or metanaly$ or (meta adj3 analy$)).tw. (64511)	
68	(review$ or overview$).ti. (278949)	
69	(systematic$ adj5 (review$ or overview$)).tw. (59256)	
70	((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw. (4592)	
71	((studies or trial$) adj2 (review$ or overview$)).tw. (26255)	
72	(integrat$ adj3 (research or review$ or literature)).tw. (5748)	
73	(pool$ adj2 (analy$ or data)).tw. (15021)	
74	(handsearch$ or (hand adj3 search$)).tw. (5670)	
75	(manual$ adj3 search$).tw. (3296)	
76	or/63-75 (2131312)	
77	animals/ not humans/ (4000367)	
78	76 not 77 (1992913)	
79	Randomized Controlled Trial.pt. (399960)	
80	Controlled Clinical Trial.pt. (90666)	
81	Clinical Trial.pt. (501003)	
82	exp Clinical Trials as Topic/ (294731)	
83	Placebos/ (34008)	
84	Random Allocation/ (84113)	
85	Double-Blind Method/ (132489)	
86	Single-Blind Method/ (20614)	
87	Cross-Over Studies/ (36229)	
88	((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw. (776483)	
89	(random$ adj3 allocat$).tw. (21567)	
90	placebo$.tw. (159821)	
91	((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (130057)	
92	(crossover$ or (cross adj over$)).tw. (58948)	
93	or/79-92 (1444186)	
94	animals/ not humans/ (4000367)	
95	93 not 94 (1346509)	
96	62 or 78 or 95 (5846186)	
97	44 and 96 (201)	

D.61 Review question 6a and 7a

2 **Table 29: Clinical search summary (review question 6a and 7a)**

Databases	Date searched	No. retrieved

Databases	Date searched	No. retrieved
MEDLINE (Ovid)	02/12/2014	801
MEDLINE In-Process (Ovid)	02/12/2014	55
EMBASE (Ovid)	02/12/2014	801
CDSR (Ovid, Wiley)*	02/12/2014	89
Database of Abstracts of Reviews of Effects – DARE (CRD, Ovid, Wiley)*	02/12/2014	34
CENTRAL (Ovid, Wiley)*	02/12/2014	366
HTA database (CRD, Ovid, Wiley)*	02/12/2014	6
NHS Economic Evaluation Database - NHS EED (CRD, Ovid, Wiley)*	02/12/2014	15

1 **Table 30: Clinical search terms (review question 6a and 7a)**

Line number	Search terms	Number retrieved
	Ovid MEDLINE(R)	Please see number in brackets for each line
1	exp Dentistry, Operative/ (43182)	
2	exp Dental Prophylaxis/ (6703)	
3	((dent$ or tooth$ or teeth$ or peridont$ or orthodont$) adj4 (prophyla$ or debrid$)).tw. (1413)	
4	(crown adj4 length$).tw. (2646)	
5	exp Endodontics/ (23730)	
6	endodontic$.tw. (12554)	
7	Apicoectom$.tw. (436)	
8	((pulp$ adj4 cap$).tw. (1149)	
9	(pulpectom$ or pulpotom$).tw. (1063)	
10	exp Oral Surgical Procedures/ (53293)	
11	(gingivectom$ or gingivoplast$ or glossectom$).tw. (1068)	
12	mucoperio$ flap$.tw. (522)	
13	(tartar adj4 remov$).tw. (24)	
14	Sialography/ (1521)	
15	(sialograph$ or radiosialograph$).tw. (1080)	
16	(root adj4 canal adj4 (therap$ or treat$)).tw. (2619)	
17	((dent$ or oral$ or tooth$ or teeth or peridont$ or orthodont$ or root$) adj4 (restorat$ or implant$ or replant$ or reimplant$ or re-implant$ or extract$ or remov$ or scal$ or polish$ or fill$ or irrigat$ or separat$ or expos$ or bond$ or band$ or prob$ or investigat$ or rubber dam$ or wedg$ or lining$ or liner$ or planing$)).tw. (94397)	
18	((dent$ or oral$ or tooth$ or teeth$ or peridont$ or orthodont$ or root$ canal$) adj4 (surg$ or procedure$ or endoscop$ or operat$ or incis$ or excis$ or intervention$ or invasiv$ or biops$ or inject$)).tw. (42156)	
19	or/1-18 (210674)	
20	exp Digestive System Surgical Procedures/ (284321)	
21	((digestive or gastro$) adj4 (surg$ or operati$)).tw. (10539)	
22	(roux-en-y or appendectom$).tw. (12163)	
23	(Bili$ adj4 (bypas$ or divers$ or surg$)).tw. (5812)	

Line number	Search terms	Number retrieved
24	(cholecystectom$ or cholecystostom$ or choledochostom$).tw. (21972)	
25	(gallbladder adj4 remov$).tw. (662)	
26	(portoenterostom$ or sphincterotom$ or sphincteroplast$ or papillotom$).tw. (6918)	
27	(colectom$ or proctocolectom$ or coloproctectom$).tw. (9919)	
28	(laparotom$ or endoscop$ or colonoscop$).tw. (184414)	
29	(duodenoscop$ or gastroscop$ or proctoscop$).tw. (6753)	
30	Cholangiopancreatograph$.tw. (6774)	
31	(ercp or esophagoscop$ or esophagogastroduodenoscop$).tw. (10087)	
32	(oesophagoscop$ or oesophagogastroduodenoscop$).tw. (598)	
33	Echocardiography, Transesophageal/ (15730)	
34	Echocardiography/ (69032)	
35	((trans?esophag$ or trans-esophag or trans-oesophag) adj4 echo$).tw. (13269)	
36	((esophag$ or oesophag$) adj4 echo$).tw. (468)	
37	(tee or toe).tw. (14573)	
38	((esophag$ or oesophag$) adj4 dilat$).tw. (2171)	
39	exp Lithotripsy/ (9123)	
40	(lithotrip$ or litholapax$ or ESWL or ESWLS).tw. (8854)	
41	(enterostom$ or cecostom$ or colostom$).tw. (7669)	
42	(duodenostom$ or ileostom$ or jejunostom$).tw. (7282)	
43	(esophagectom$ or oesophagectom$).tw. (6560)	
44	(esophagoplast$ or oesophagoplast$).tw. (783)	
45	(esophagostom$ or oesophagostom$).tw. (1252)	
46	(fundoplicat$ or nissen or billroth).tw. (7343)	
47	(gastrectom$ or gastroenterostom$ or gastrojejunostom$).tw. (19535)	
48	(Gast$ adj4 Bypass).tw. (6242)	
49	(gastroplast$ or gastrostom$ or hepatectom$ or hemorrhoidectom$).tw. (24548)	
50	((jejunoileal or jejuno-ileal or ileojejunal or intestin$) adj4 bypass).tw. (1592)	
51	((liver or hepat$ or pancrea$) adj4 (transplant$ or graft$)).tw. (56910)	
52	Pancreatectom$.tw. (6460)	
53	(pancrea$ adj4 remov$).tw. (977)	
54	(pancreaticoduodenectom$ or duodenopancreatectom$ or pancreatoduodenectom$ or pancreaticojejunostom$).tw. (6441)	
55	((periton$ or leveen) adj4 shunt$).tw. (2294)	
56	((digest$ or gastr$ or intestin$ or gi or oesophag$ or esophag$ or stomach or bowel$ or colon$ or liver or hepat$ or bili$ or duoden$ or gall$ or pancrea$ or append$ or abdom$ or anal or anus or sphinct$) adj4 (surg$ or procedure$ or operat$ or incis$ or excis$ or intervention$ or invasiv$ or biops$ or endoscop$ or sclerotherap$ or diversion$)).tw. (208872)	
57	or/20-56 (659975)	
58	exp Urogenital Surgical Procedures/ (271012)	

Line number	Search terms	Number retrieved
59	(colposcop$ or colpotom$ or culdoscop$ or endometrial ablation$).tw. (8050)	
60	((dilatation or vacuum) adj4 curettage).tw. (1138)	
61	(hysterectom$ or hysteroscop$ or uterine myomectom$).tw. (29808)	
62	(uter$ adj4 endoscop$).tw. (114)	
63	(ovariectom$ or oophorectom$ or salpingostom$).tw. (30281)	
64	((reproduct$ or tub$) adj4 sterili$).tw. (2380)	
65	(tub$ adj4 ligat$).tw. (2055)	
66	aldridge.tw. (54)	
67	(tub$ adj4 occlu$).tw. (1976)	
68	cooke.tw. (321)	
69	(cornual adj4 coagulat$).tw. (2)	
70	fimbriectom$.tw. (76)	
71	(irving or kroener or madlener or pomeroy).tw. (594)	
72	(tub$ adj4 (excis$ or ring$)).tw. (1198)	
73	(uchida or vasectom$ or salpingectom$).tw. (5460)	
74	(cystectom$ or cystoscop$ or cysto?tom$).tw. (17097)	
75	(kidney$ adj4 (transplant$ or graft$)).tw. (35254)	
76	(nephrectom$ or vesicotom$ or ureteroscop$).tw. (28214)	
77	(Urin$ adj4 Diver$).tw. (5008)	
78	(nephrostom$ or nephroli$).tw. (8876)	
79	(ureterostom$ or orchiectom$).tw. (5315)	
80	(Pen$ adj4 Implant$).tw. (1315)	
81	Prostatectom$.tw. (20581)	
82	Trans?uret$.tw. (13258)	
83	Trans?rect$.tw. (7510)	
84	(vasovasostom$ or castrat$ or circumci$).tw. (25216)	
85	(uret$ adj4 (catheter$ or dilatat$)).tw. (5016)	
86	exp Obstetric Surgical Procedures/ (107992)	
87	(abortion$ or embryotom$ or cerclage).tw. (48699)	
88	((obstetr$ or abdom$) adj4 deliver$).tw. (2473)	
89	C?esarean.tw. (40438)	
90	Episiotom$.tw. (1891)	
91	(Obstetr$ adj4 extract$).tw. (245)	
92	(Induc$ adj4 (labor$ or labour$)).tw. (8680)	
93	Parturition/ (3610)	
94	(parturit$ or childbirth$ or birth$).tw. (252872)	
95	(vagina$ adj4 deliver$).tw. (12148)	
96	((fet$ or cepha$) adj4 version$).tw. (562)	
97	Fetoscop$.tw. (890)	
98	Intrauterine Devices/ (7992)	
99	(Intra?uterine adj4 device$).tw. (5318)	
100	iud.tw. (6060)	
101	Vaginal Smears/ (20361)	
102	((vagina$ or cervi$ or papanicolaou) adj4 smear$).tw. (8698)	

Line number	Search terms	Number retrieved
103	((genit$ or urin$ or uro$ or uret$ or endometr$ or ovar$ or ooph$ or uter$ or bladder or vagina$ or cervi$ or gyn$ or obstet$ or prostat$ or reproduct$) adj4 (surg$ or procedure$ or operat$ or incis$ or excis$ or intervention$ or invasiv$ or biops$ or endoscop$)).tw. (106763)	
104	or/58-103 (801574)	
105	exp Pulmonary Surgical Procedures/ (57266)	
106	(pulmonary adj4 (surg* or operati*)).tw. (10095)	
107	(Collapse adj4 Therap$).tw. (431)	
108	(pneumonolys$ or pneumothora$).tw. (16053)	
109	Bronchoscopy/ (20962)	
110	Bronchoscopes/ (2036)	
111	bronchoscop$.tw. (19041)	
112	thyroidectomy/ or adenoidectomy/ or laryngoplasty/ or laryngectomy/ or laryngoscopy/ or neck dissection/ or pharyngectomy/ or pharyngostomy/ or rhinoplasty/ or tonsillectomy/ or tracheostomy/ or tracheotomy/ (68569)	
113	(thyroidectom$ or adenoidectom$).tw. (15206)	
114	(laryngectom$ or laryngoscop$ or laryngoplast$).tw. (14178)	
115	neck dissect$.tw. (6308)	
116	(pharyngectom$ or pharyngostom$).tw. (411)	
117	rhinoplast$.tw. (3971)	
118	tonsillectom$.tw. (6392)	
119	tracheo?tom$.tw. (14400)	
120	(nasal adj4 pack$).tw. (808)	
121	Pneumonectomy/ (21686)	
122	Pneumonectom$.tw. (6681)	
123	(lung$ adj4 (transplant$ or graft$ or reduct$)).tw. (17339)	
124	((nasal or sinus$ or rhino$ or rhina$ or pharyn$ or laryn$ or trache$ or bronch$ or lung$ or pulmonar$ or respirat$) adj4 (surg$ or procedure$ or endoscop$ or operat$ or incis$ or excis$ or intervention$ or invasiv$ or biops$)).tw. (80300)	
125	or/105-124 (228216)	
126	19 or 57 or 104 or 125 (1815407)	
127	exp Chemoprevention/ (13624)	
128	(chemoprevent$ or chemo-prevent$).tw. (16449)	
129	(prophyla$ or chemoprophyla$ or chemo-prophyla$).tw. (123271)	
130	exp anti-infective agents/ (1306763)	
131	exp Penicillins/ (70946)	
132	penicillin$.tw. (44607)	
133	"pen v".tw. (19)	
134	"pen g".tw. (43)	
135	(antibiot$ or anti-biot$).tw. (223952)	
136	(antibacter$ or anti-bacter$).tw. (43572)	
137	(antimycobacter$ or anti-mycobacter$).tw. (3359)	
138	bacteriocid$.tw. (518)	
139	(microbicid$ or antimicrob$ or anti-microb$).tw. (96075)	
140	(anti-infect$ or antiinfect$).tw. (4084)	

Line number	Search terms	Number retrieved
141	exp Gentamicins/ (17561)	
142	(gentam?cin$ or cidomycin$ or garam?cin$).tw. (21303)	
143	(gentacycol$ or gentavet$ or genticin$).tw. (17)	
144	Glycopeptides/ (7994)	
145	(teicoplanin$ or teichom?cin$ or targocid$).tw. (2820)	
146	exp Clindamycin/ (5013)	
147	(clindam?cin$ or dalacin c).tw. (7777)	
148	(deoxylincomycin$ or chlo?lincocin$ or cleocin$).tw. (46)	
149	exp Ceftriaxone/ (4774)	
150	(cef?triaxon$ or rocephin).tw. (7266)	
151	exp Cephalexin/ (3180)	
152	(cephalexin$ or cefalexin$).tw. (2372)	
153	(ceporex or Keflex).tw. (30)	
154	exp Azithromycin/ (3792)	
155	(az?throm?cin$ or zithromax).tw. (5100)	
156	exp Clarithromycin/ (5208)	
157	clar?throm?cin$.tw. (6670)	
158	(clarosip or klaricid).tw. (10)	
159	exp Vancomycin/ (10687)	
160	(vancom?cin$ or vancocin$).tw. (17807)	
161	exp Cefuroxime/ (1958)	
162	(cefuroxime or cephuroxime).tw. (3437)	
163	(zinacef or zinnat).tw. (49)	
164	exp Ampicillin/ (24218)	
165	(ampicillin$ or penbritin or amcill).tw. (18058)	
166	(aminobenzylpenicillin$ or aminobenzyl-penicillin$).tw. (118)	
167	(benzylpenicillin$ or benzyl-penicillin$).tw. (2350)	
168	(omnipen or pentrexyl or polycillin$ or ukapen).tw. (9)	
169	xp Amoxicillin/ (9522)	
170	(augmentin$ or amox?cillin$).tw. (21506)	
171	(co-amox$ or coamox$).tw. (473)	
172	hydroxyampicillin$.tw. (1)	
173	(actimoxi$ or amoxil$ or amoyl$).tw. (61)	
174	(clamoxyl or penamox or polymox).tw. (20)	
175	(trimox or wymox).tw. (2)	
176	exp Floxacillin/ (619)	
177	(flucloxacillin$ or floxacillin$).tw. (632)	
178	(fluorochloroxacillin or floxapen).tw. (3)	
179	exp Cefazolin/ (2437)	
180	(cefazolin$ or cephazolin$).tw. (3564)	
181	(cefamedin$ or cefamezine$ or gramaxin$).tw. (11)	
182	or/127-181 (1559034)	
183	((bacter$ or staphylococ$ or streptococ$ or enterococ$) adj5 eliminat$ or prevent$ or reduc$ or decreas$ or lower$)).tw. (37313)	
184	126 and 182 and 183 (1858)	

Line number	Search terms	Number retrieved
185	(chemoprevent$ or chemo-prevent$).ti. (4898)	
186	(chemoprophyla$ or chemo-prophyla$).ti. (1887)	
187	(antibiot$ and prophyla$).ti. (4134)	
188	(anti-biot$ and prophyla$).ti. (0)	
189	(antimicrob$ and prophyla$).ti. (806)	
190	(anti-microb$ and prophyla$).ti. (3)	
191	(antibacter$ and prophyla$).ti. (143)	
192	(anti-bacter$ and prophyla$).ti. (4)	
193	(antibiot$ and premedi$).ti. (8)	
194	(anti-biot$ and premedi$).ti. (0)	
195	(antimicrob$ and premedi$).ti. (0)	
196	(anti-microb$ and premedi$).ti. (0)	
197	(antibacter$ and premedi$).ti. (0)	
198	(anti-bacter$ and premedi$).ti. (0)	
199	(antibiot$ and prevent$).ti. (1493)	
200	(anti-biot$ and prevent$).ti. (1)	
201	antimicrob$ and prevent$).ti. (385)	
202	(anti-microb$ and prevent$).ti. (2)	
203	(antibacter$ and prevent$).ti. (109)	
204	(anti-bacter$ and prevent$).ti. (7)	
205	or/185-204 (13551)	
206	126 and 205 (2934)	
207	184 or 206 (4643)	
208	Observational Study as Topic/ (508)	
209	Observational Study/ (6505)	
210	Epidemiologic Studies/ (6277)	
211	exp Case-Control Studies/ (712372)	
212	exp Cohort Studies/ (1441303)	
213	Cross-Sectional Studies/ (193365)	
214	Comparative Study.pt. (1731817)	
215	case control$.tw. (80825)	
216	case series.tw. (35413)	
217	(cohort adj (study or studies)).tw. (90024)	
218	cohort analy$.tw. (3836)	
219	(follow up adj (study or studies)).tw. (37541)	
220	(observational adj (study or studies)).tw. (44485)	
221	longitudinal.tw. (141799)	
222	prospective.tw. (355138)	
223	retrospective.tw. (272845)	
224	cross sectional.tw. (167433)	
225	or/208-224 (3441792)	
226	Meta-Analysis.pt. (54725)	
227	Meta-Analysis as Topic/ (14604)	
228	Review.pt. (1966250)	
229	exp Review Literature as Topic/ (8137)	

Line number	Search terms	Number retrieved
230	(metaanaly$ or metanaly$ or (meta adj3 analy$)).tw. (64666)	
231	(review$ or overview$).ti. (279292)	
232	(systematic$ adj5 (review$ or overview$)).tw. (59439)	
233	((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw. (4602)	
234	((studies or trial$) adj2 (review$ or overview$)).tw. (26283)	
235	(integrat$ adj3 (research or review$ or literature)).tw. (5767)	
236	(pool$ adj2 (analy$ or data)).tw. (15049)	
237	(handsearch$ or (hand adj3 search$)).tw. (5677)	
238	(manual$ adj3 search$).tw. (3301)	
239	or/226-238 (2133166)	
240	animals/ not humans/ (4001991)	
241	239 not 240 (1994683)	
242	Randomized Controlled Trial.pt. (400332)	
243	Controlled Clinical Trial.pt. (90710)	
244	Clinical Trial.pt. (501127)	
245	exp Clinical Trials as Topic/ (294922)	
246	Placebos/ (34020)	
247	Random Allocation/ (84147)	
248	Double-Blind Method/ (132581)	
249	Single-Blind Method/ (20647)	
250	Cross-Over Studies/ (36257)	
251	((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw. (777356)	
252	(random$ adj3 allocat$).tw. (21589)	
253	placebo$.tw. (159942)	
254	((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (130155)	
255	(crossover$ or (cross adj over$)).tw. (58984)	
256	or/242-255 (1445480)	
257	animals/ not humans/ (4001991)	
258	256 not 257 (1347733)	
259	225 or 241 or 258 (5851229)	
260	207 and 259 (3052)	
261	Animals/ not Humans/ (4001991)	
262	260 not 261 (2989)	
263	limit 262 to ed=20070907-20141202 (878)	
264	limit 263 to english language (801)	

D.7 Review question 6b and 7b

Table 31: Clinical search summary (review question 6b and 7b)

Databases	Date searched	No. retrieved
MEDLINE (Ovid)	01/12/2014	389
MEDLINE In-Process (Ovid)	01/12/2014	26
EMBASE (Ovid)	01/12/2014	222
CDSR (Wiley)	01/12/2014	33

Databases	Date searched	No. retrieved
Database of Abstracts of Reviews of Effects – DARE (Wiley)	01/12/2014	9
CENTRAL (Wiley)	01/12/2014	206
HTA Database (Wiley)	01/12/2014	1

1 **Table 32: Clinical search terms (review question 6b and 7b)**

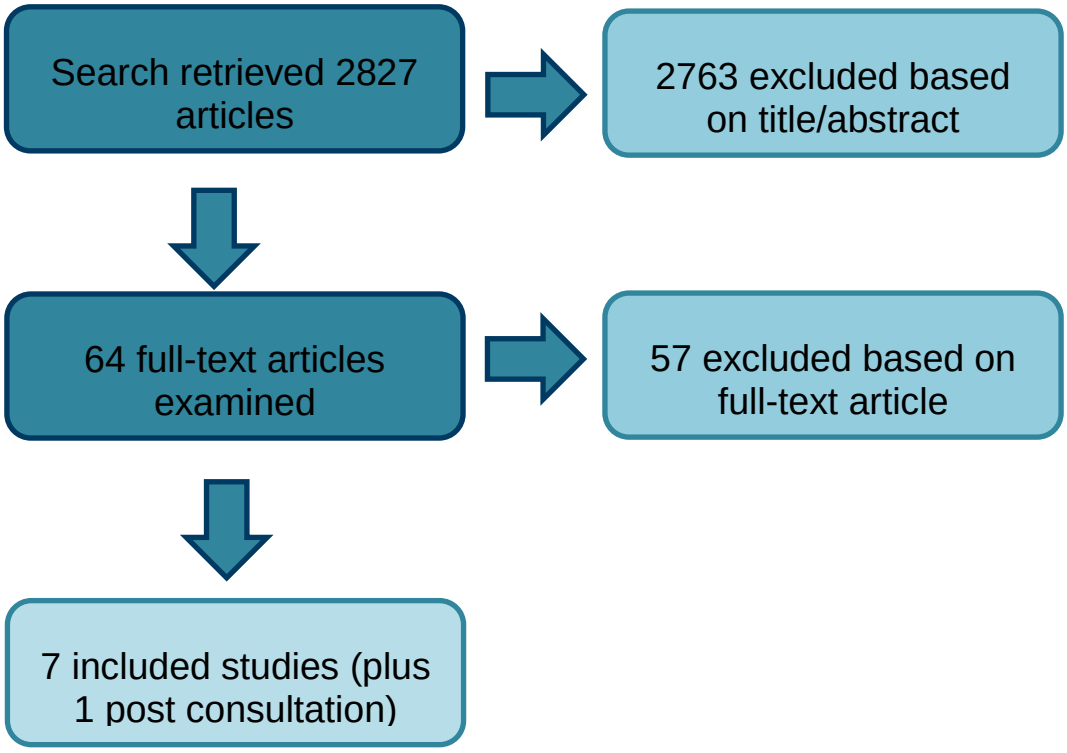
Line number	Search terms	No. retrieved
	Ovid MEDLINE	Please see number in brakcets for each line
1	exp Dentistry, Operative/ (43172)	
2	exp Dental Prophylaxis/ (6702)	
3	((dent$ or tooth$ or teeth or peridont$ or orthodont$) adj4 (prophyla$ or debrid$)).tw. (1413)	
4	(crown adj4 length$).tw. (2643)	
5	exp Endodontics/ (23721)	
6	endodontic$.tw. (12546)	
7	Apicoectom$.tw. (436)	
8	(pulp$ adj4 cap$).tw. (1149)	
9	(pulpectom$ or pulpotom$).tw. (1063)	
10	exp Oral Surgical Procedures/ (53252)	
11	(gingivectom$ or gingivoplast$ or glossectom$).tw. (1068)	
12	mucoperio$ flap$.tw. (521)	
13	(tartar adj4 remov$).tw. (24)	
14	Sialography/ (1521)	
15	(sialograph$ or radiosialograph$).tw. (1080)	
16	(root adj4 canal adj4 (therap$ or treat$)).tw. (2619)	
17	((dent$ or oral$ or tooth$ or teeth or peridont$ or orthodont$ or root$) adj4 (restorat$ or implant$ or replant$ or reimplant$ or re-implant$ or extract$ or remov$ or scal$ or polish$ or fill$ or irrigat$ or separat$ or expos$ or bond$ or band$ or prob$ or investigat$ or rubber dam$ or wedg$ or lining$ or liner$ or planing$)).tw. (94312)	
18	((dent$ or oral$ or tooth$ or teeth$ or peridont$ or orthodont$ or root$ canal$) adj4 (surg$ or procedure$ or endoscop$ or operat$ or incis$ or excis$ or intervention$ or invasiv$ or biops$ or inject$)).tw. (42084)	
19	or/1-18 (210511)	
20	Mouthwashes/ (4487)	
21	Dentifrices/ (3458)	
22	(mouthwash$ or mouth wash$ or dentifrice$ or toothpaste$).tw. (6212)	
23	Chlorobenzenes/ (2496)	
24	chlorobenzene$.tw. (1116)	
25	Biguanides/ (2822)	
26	biguanide$.tw. (2078)	
27	Chlorhexidine/ (6430)	
28	chlor?hex$.tw. (6767)	
29	(corsodyl or eludril or tubulicid).tw. (89)	

Line number	Search terms	No. retrieved
30	((cavit$ or oral or dent$ or mouth$ or endodontic$ or orthodontic$ or peridont$) adj4 (antibiot$ or anti-biot$ or antimicrob$ or anti-microb$ or anti-bacter$ or antibacter$ or anti-mycobacter$ or antimycobacter$ or bacteriocid$ or microbicid$ or anti-infect$ or antiinfect$ or anti-sept$ or antisept$ or disinfect$ or dis-infect$ or prophyla$ or chemoprophyla$ or chemo-prophyla$ or irrigant$)).tw. (11944)	
31	or/20-30 (34259)	
32	exp Bacteria/ (1106581)	
33	Bacterial Infections/ (61532)	
34	exp Bacteremia/ (22201)	
35	exp Endotoxemia/ (3565)	
36	(bacter$ or eubacter$ or endotox?emia$).tw. (583926)	
37	(enterococ$ or streptococ$ or staphylococ$).tw. (178823)	
38	or/32-37 (1378332)	
39	19 and 31 and 38 (1859)	
40	Animals/ not Humans/ (4000367)	
41	39 not 40 (1759)	
42	meta-analysis.pt. (54585)	
43	review.pt. (1964534)	
44	exp review literature/ (1968883)	
45	meta-analysis/ (54585)	
46	(metaanaly$ or metanaly$ or (meta adj2 analy$)).tw. (64437)	
47	(review$ or overview$).ti. (278949)	
48	(systematic$ adj4 (review$ or overview$)).tw. (58934)	
49	((quantitative$ or qualitative$) adj4 (review$ or overview$)).tw. (4010)	
50	((studies or trial$) adj1 (review$ or overview$)).tw. (7967)	
51	(integrat$ adj2 (research or review$ or literature)).tw. (3984)	
52	(pool$ adj1 (analy$ or data)).tw. (10184)	
53	(handsearch$ or (hand adj2 search$)).tw. (5614)	
54	(manual$ adj2 search$).tw. (3136)	
55	or/42-54 (2121198)	
56	randomized controlled trial.pt. (399960)	
57	controlled clinical trial.pt. (90666)	
58	clinical trial.pt. (501003)	
59	exp clinical trial/ (816374)	
60	placebos/ (34008)	
61	random allocation/ (84113)	
62	double-blind method/ (132489)	
63	single-blind method/ (20614)	
64	cross-over studies/ (36229)	
65	((random$ or control$ or clinical$) adj2 (trial$ or stud$)).tw. (675952)	
66	(random$ adj2 allocat$).tw. (20999)	
67	placebo$.tw. (159821)	

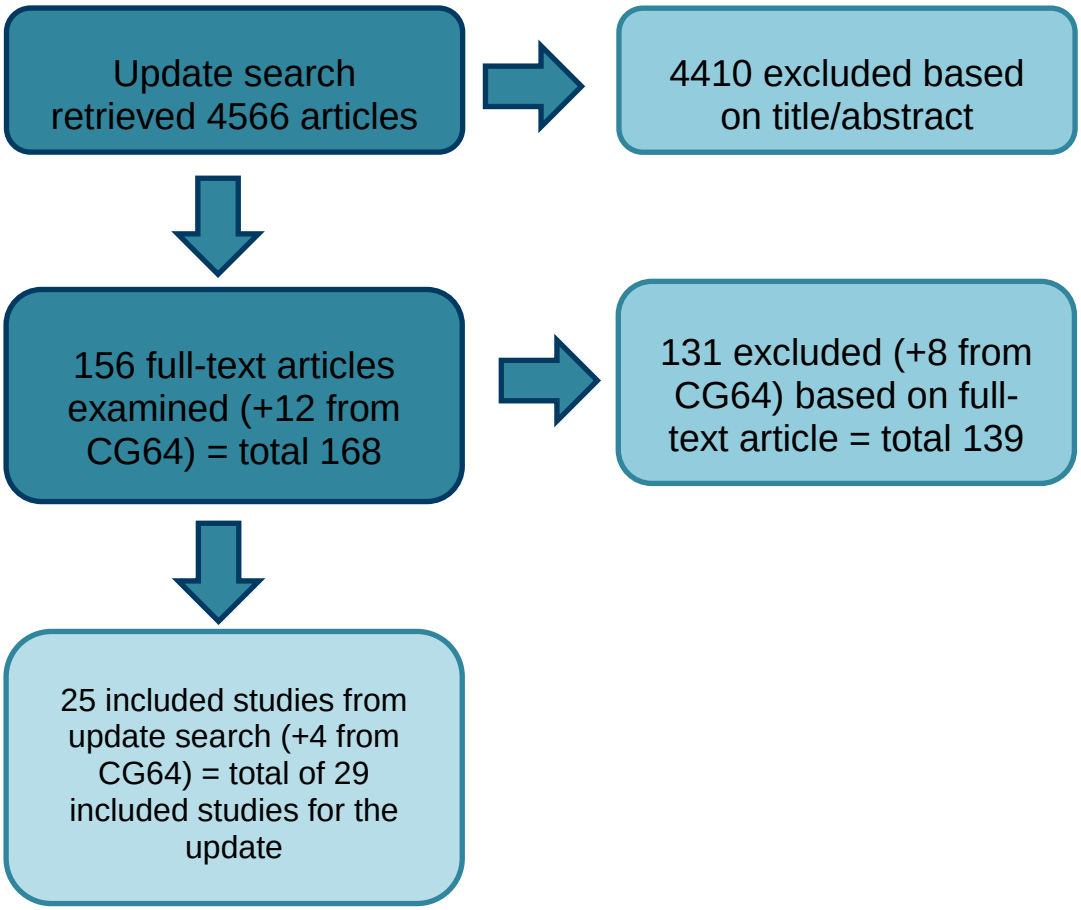
Line number	Search terms	No. retrieved
68	((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (130057)	
69	(crossover$ or (cross adj over$)).tw. (58948)	
70	or/56-69 (1376504)	
71	Epidemiologic Studies/ (6272)	
72	exp Case-Control Studies/ (711198)	
73	exp Cohort Studies/ (1439568)	
74	Cross-Sectional Studies/ (193002)	
75	Comparative Study.pt. (1731142)	
76	case control$.tw. (80732)	
77	case series.tw. (35347)	
78	(cohort adj (study or studies)).tw. (89864)	
79	cohort analy$.tw. (3830)	
80	(follow up adj (study or studies)).tw. (37517)	
81	(observational adj (study or studies)).tw. (44392)	
82	longitudinal.tw. (141606)	
83	prospective.tw. (354704)	
84	retrospective.tw. (272363)	
85	cross sectional.tw. (167096)	
86	or/71-85 (3438039)	
87	55 or 70 or 86 (5994621)	
88	Animals/ not Humans/ (4000367)	
89	87 not 88 (5345098)	
90	41 and 89 (1093)	
91	limit 90 to ed=20070904-20141201 (407)	
92	limit 91 to english language (389)	

Appendix E: Review flowchart

E.1 Overview of epidemiology

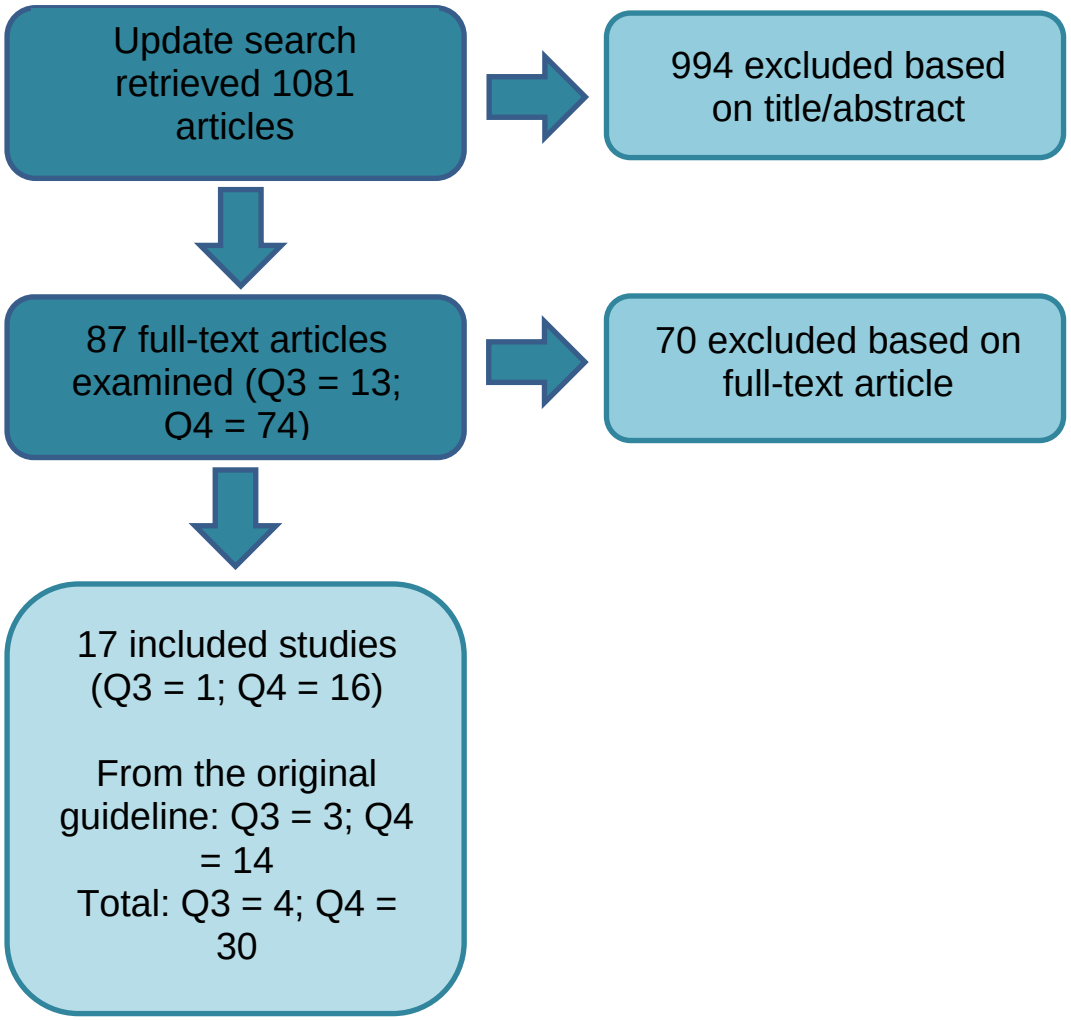


E.2 Review questions 1a 1b and 2

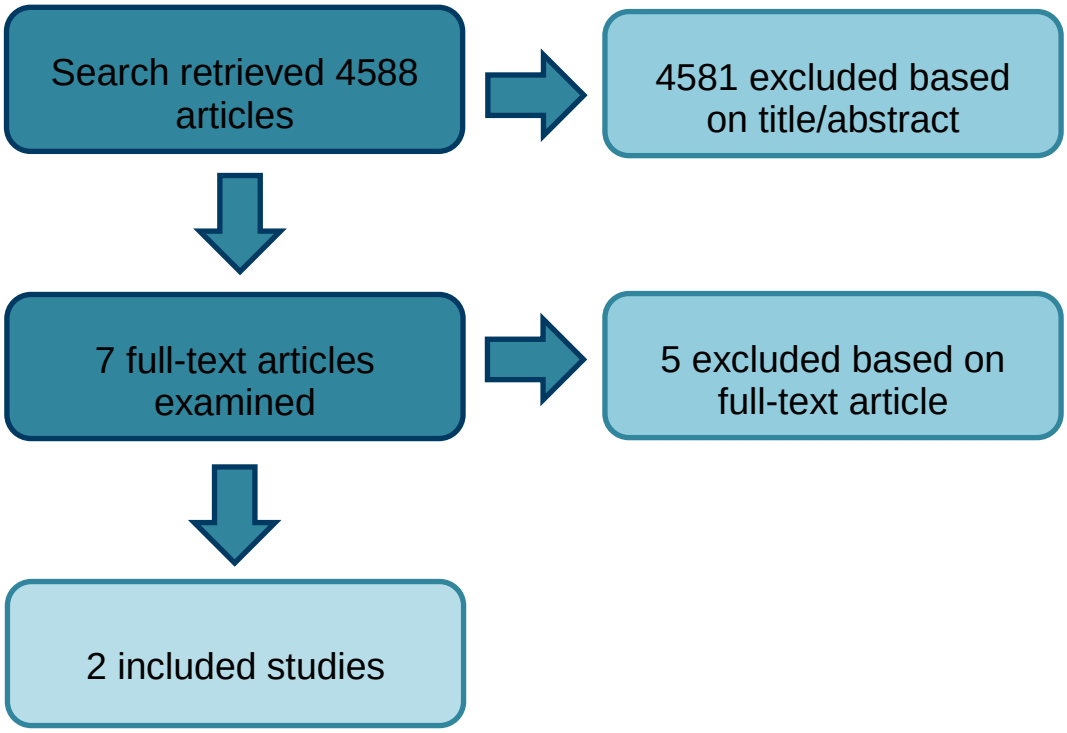


E.3 Review questions 3 and 4

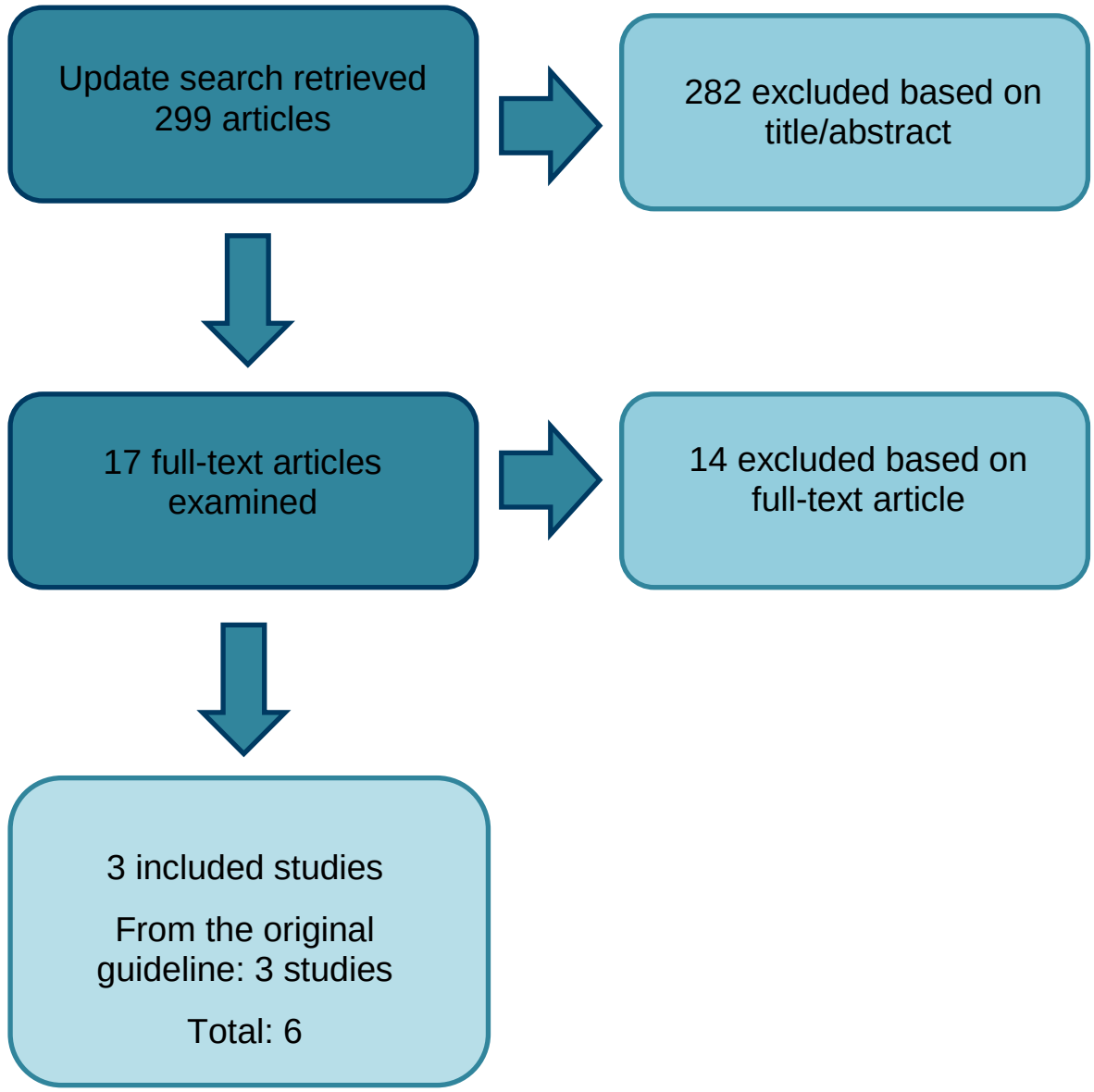
Update search for question 3 and 4 was conducted under one search



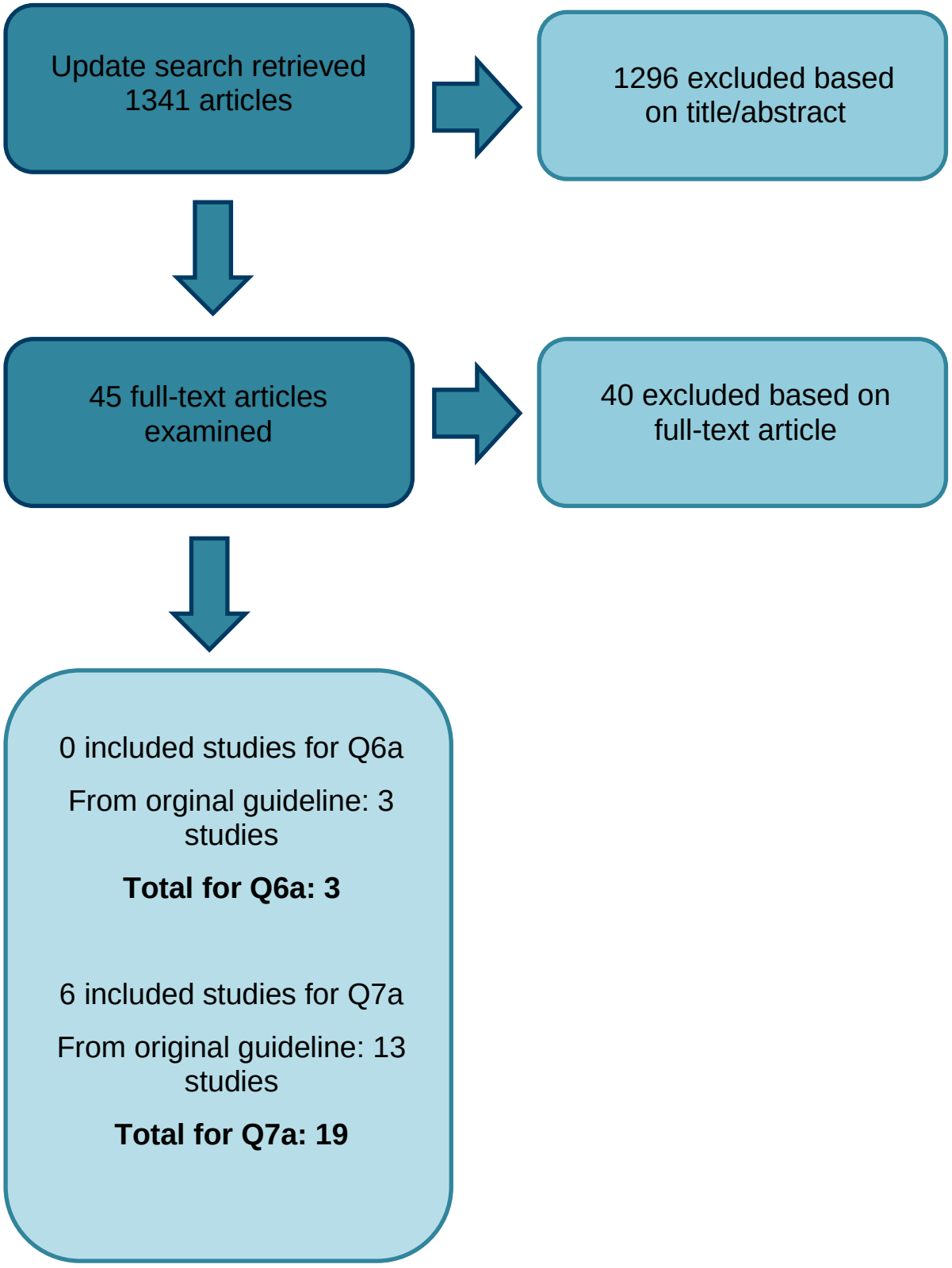
Additional broad search for review question 3:



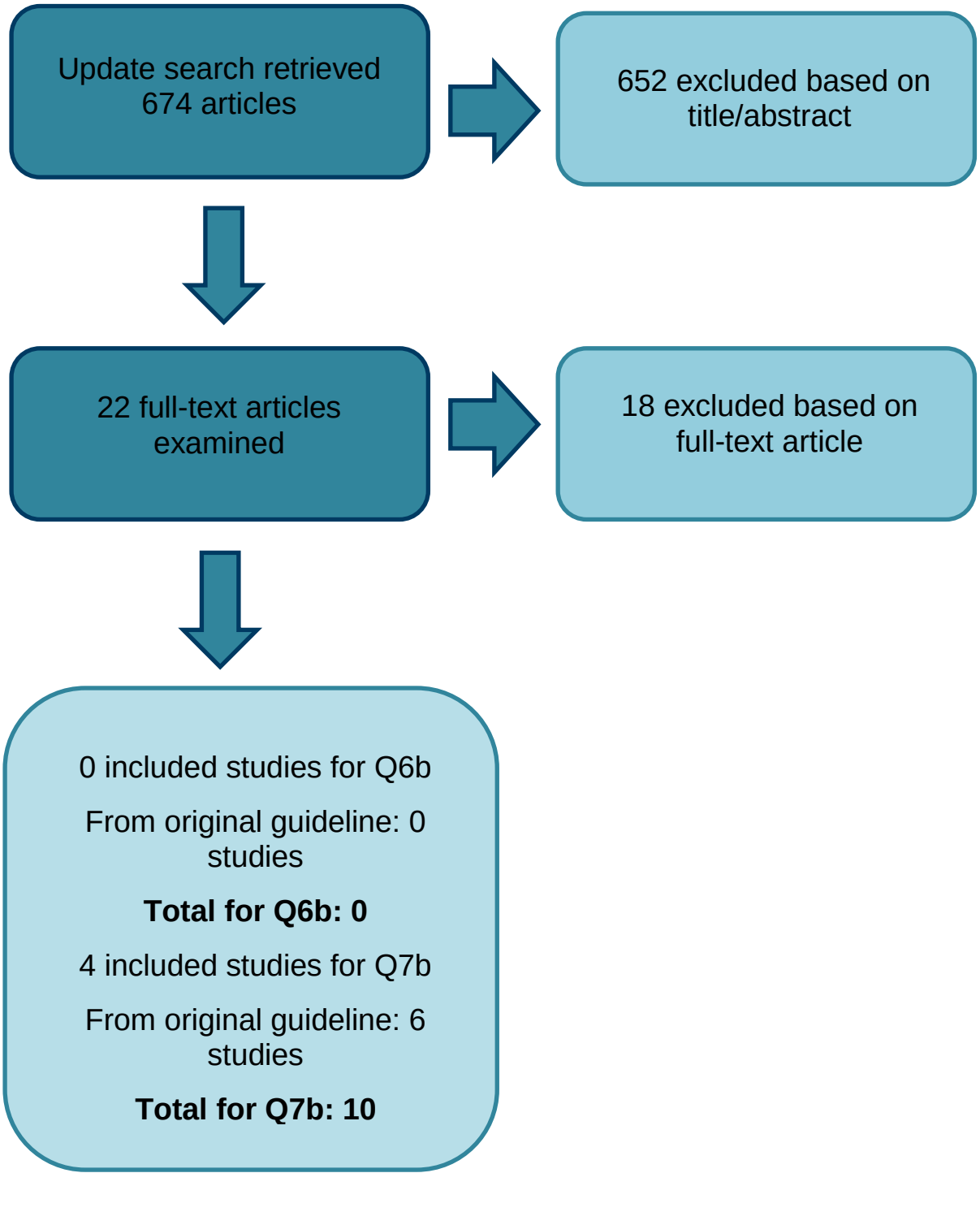
E.4 Review question 5



E.5 Review question 6a and 7a



E.6 Review question 6b and 7b



1 Appendix F: Excluded studies

F.1 2 Overview of epidemiology

Reference	Reason for exclusion
Alestig K, Hogevik H, Olaison L (2000) Infective endocarditis: a diagnostic and therapeutic challenge for the new millennium. [Review] [89 refs]. Scandinavian Journal of Infectious Diseases 32: 343-56.	Not relevant – about diagnostics.
Allen KD, Vardhan MS (2000) Epidemiology of infective endocarditis. Journal of Infection 40: 99-100.	Letter only.
Bashore TM, Cabell C, Fowler V, Jr. (2006) Update on infective endocarditis. [Review] [234 refs]. Current Problems in Cardiology 31: 274-352.	Not relevant – general overview of the condition only.
Baskerville CA, Hanrahan BB, Burke AJ et al. (2012) Infective endocarditis and rheumatic heart disease in the north of Australia. Heart, Lung & Circulation 21: 36-41.	Distribution of clinical features data only, no trend of incidence.
Berlin JA, Abrutyn E, Strom BL et al. (1995) Incidence of infective endocarditis in the Delaware Valley, 1988-1990. American Journal of Cardiology 76: 933-6.	Distribution of clinical features data only, no trend of incidence.
Cecchi E, Imazio M, De Rosa FG et al. (2008) Infective endocarditis in the real world: the Italian Registry of Infective Endocarditis (Registro Italiano Endocardite Infettiva - RIEI). Journal of Cardiovascular Medicine 9: 508-14.	Distribution of clinical features data only, no trend of incidence.
Cecchi E, De Rosa FG, Chirillo F et al. (2010) The prophylaxis of infective endocarditis: a joint position study of the Italian Federation of Cardiologists and the Italian Society of Infectious and Tropical Diseases. [Review] [23 refs]. Journal of Cardiovascular Medicine 11: 419-25.	Commentary on the guideline, no data on the impact of the guideline.
Chen SJ, Liu CJ, Chao TF et al. (2013) Dental scaling and risk reduction in infective endocarditis: a nationwide population-based case-control study. Canadian Journal of Cardiology 29: 429-33.	Not relevant – about risk, not about trend of incidence.
Chirouze C, Hoen B, Duval X (2012) Infective endocarditis prophylaxis: moving from dental prophylaxis to global prevention?. [Review]. European Journal of Clinical Microbiology & Infectious Diseases 31: 2089-95.	Narrative review/commentary
Chirouze C, Athan E, Alla F et al. (2013) Enterococcal endocarditis in the beginning of the 21st century: analysis from the International Collaboration on Endocarditis-Prospective Cohort Study. Clinical Microbiology & Infection 19: 1140-7.	Single hospital study only, not population-based.
Chopra T, Kaatz GW (2010) Treatment strategies for infective endocarditis. [Review] [98 refs]. Expert Opinion on Pharmacotherapy 11: 345-60.	Not relevant – about treatment.
Chugh TD (2004) Pathogenesis of infective endocarditis. [Review] [31 refs]. Indian Journal of Pathology & Microbiology 47: 163-7.	Not relevant – no data on trend of incidence.
Cicalini S, Puro V, Angeletti C et al. (2006) Profile of infective endocarditis in a referral hospital over the last 24 years. Journal of Infection 52: 140-6.	Single hospital study only, not population-based.
Curlier E, Hoen B, Alla F et al. (2014) Relationships between sex, early valve surgery and mortality in patients with left-sided infective endocarditis analysed in a population-based cohort study. Heart 100: 1173-8.	Distribution of clinical features data only, no trend of incidence.
Delahaye F, Alla F, Beguinot I et al. (2007) In-hospital mortality of infective endocarditis: prognostic factors and evolution over an 8-year	Not relevant – about prognosis.

Reference	Reason for exclusion
period. Scandinavian Journal of Infectious Diseases 39: 849-57.	
DeSimone DC, Tleyjeh IM, Correa de Sa DD et al. (2012) Incidence of infective endocarditis caused by viridans group streptococci before and after publication of the 2007 American Heart Association's endocarditis prevention guidelines. Circulation 126: 60-4.	Analysis between 2007 to 2010 were only based on 3 cases of IE.
DeSimone DC, Tleyjeh IM, Correa de Sa DD et al. (2013) Response to letter regarding article, "Incidence of infective endocarditis due to viridans group streptococci before and after publication of the 2007 American Heart Association's endocarditis prevention guidelines". Circulation 127: e521.	Letter only.
Di FS (2012) Prophylaxis of infective endocarditis in patients with congenital heart disease in the context of recent modified guidelines. [Review]. Archives of cardiovascular diseases 105: 454-60.	Narrative review/commentary
Duval X, Alla F, Hoen B (2013) Letter by Duval et al regarding article, "Incidence of Infective endocarditis caused by viridans group streptococci before and after publication of the 2007 American Heart Association's endocarditis prevention guidelines". Circulation 127: e520.	Letter only.
Dzupova O, Machala L, Baloun R et al. (2012) Incidence, predisposing factors, and aetiology of infective endocarditis in the Czech Republic. Scandinavian Journal of Infectious Diseases 44: 250-5.	Distribution of clinical features data only, no trend of incidence.
Erwin JP, Otto CM (2014) Infective endocarditis: old problem, new guidelines and still much to learn. Heart 100: 996-8.	Narrative review/commentary
Fernandez-Hidalgo N, Almirante B, Tornos P et al. (2012) Immediate and long-term outcome of left-sided infective endocarditis. A 12-year prospective study from a contemporary cohort in a referral hospital. Clinical Microbiology & Infection 18: E522-E530.	Single hospital study only, not population-based.
Ferreira JP, Gomes F, Rodrigues P et al. (2013) Left-sided infective endocarditis: analysis of in-hospital and medium-term outcome and predictors of mortality. Revista Portuguesa de Cardiologia 32: 777-84.	Two hospitals study only, not population-based.
Ferreiros E, Nacinovich F, Casabe JH et al. (2006) Epidemiologic, clinical, and microbiologic profile of infective endocarditis in Argentina: a national survey. The Endocarditis Infecciosa en la Republica Argentina-2 (EIRA-2) Study. American Heart Journal 151: 545-52.	Distribution of clinical features data only, no trend of incidence.
Fonager K, Lindberg J, Thulstrup AM et al. (2003) Incidence and short-term prognosis of infective endocarditis in Denmark, 1980-1997. Scandinavian Journal of Infectious Diseases 35: 27-30.	Not relevant – data too old (only between 1980 to 1997), 18 years gap to be deemed as current trend.
Galvez-Acebal J, Rodriguez-Bano J, Martinez-Marcos FJ et al. (2010) Prognostic factors in left-sided endocarditis: results from the Andalusian multicenter cohort. BMC Infectious Diseases 10: 17.	Not relevant – about prognosis.
Giannitsioti E, Skiadas I, Antoniadou A et al. (2007) Nosocomial vs. community-acquired infective endocarditis in Greece: changing epidemiological profile and mortality risk. Clinical Microbiology & Infection 13: 763-9.	Distribution of clinical features data only, no trend of incidence.
Hill EE, Herijgers P, Herregods MC et al. (2006) Evolving trends in infective endocarditis. [Review] [58 refs]. Clinical Microbiology & Infection 12: 5-12.	Narrative review/commentary
Hill EE, Herijgers P, Claus P et al. (2007) Infective endocarditis: changing epidemiology and predictors of 6-month mortality: a prospective cohort study. European Heart Journal 28: 196-203.	Single hospital study only, not population-based.
Hoen B (2006) Epidemiology and antibiotic treatment of infective	Not relevant – about

Reference	Reason for exclusion
endocarditis: an update. [Review] [36 refs]. Heart 92: 1694-700.	treatment.
Hogevik H, Olaison L, Andersson R et al. (1995) Epidemiologic aspects of infective endocarditis in an urban population. A 5-year prospective study. [Review] [69 refs]. Medicine 74: 324-39.	Distribution of clinical features data only, no trend of incidence.
Hricak V, Liska B, Kovackova J et al. (2007) Trends in risk factors and etiology of 606 cases of infective endocarditis over 23 years (1984-2006) in slovakia. Journal of Chemotherapy 19: 198-202.	About risk factors only, no trend of incidence.
Kerr A, Williams M (2014) Infective endocarditis: trends in the disease and how we study them. New Zealand Medical Journal 127: 10-2.	Narrative review/commentary
Kohli V (2002) Infective endocarditis. [Review] [13 refs]. Indian Journal of Pediatrics 69: 333-9.	Narrative review/commentary
Krcmery V, Hricak V, Demitrovicova A et al. (2009) Infective endocarditis in elderly patients. Scandinavian Journal of Infectious Diseases 41: 623-4.	Letter only.
Leone S, Ravasio V, Durante-Mangoni E et al. (2012) Epidemiology, characteristics, and outcome of infective endocarditis in Italy: the Italian Study on Endocarditis. Infection 40: 527-35.	Distribution of clinical features data only, no trend of incidence.
Letaief A, Boughzala E, Kaabia N et al. (2007) Epidemiology of infective endocarditis in Tunisia: a 10-year multicenter retrospective study. International Journal of Infectious Diseases 11: 430-3.	Distribution of clinical features data only, no trend of incidence.
Loupa C, Mavroidi N, Boutsikakis I et al. (2004) Infective endocarditis in Greece: a changing profile. Epidemiological, microbiological and therapeutic data. Clinical Microbiology & Infection 10: 556-61.	Distribution of clinical features data only, no trend of incidence.
Mokhles MM, Ciampichetti I, van DR et al. (2012) Infective endocarditis in a tertiary referral hospital: long-term follow up. Journal of Heart Valve Disease 21: 118-24.	Single hospital study only, not population-based.
Nishimura RA, Carabello BA, Faxon DP et al. (2008) ACC/AHA 2008 Guideline update on valvular heart disease: focused update on infective endocarditis: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Journal of the American College of Cardiology 52: 676-85.	Commentary on the guideline, no data on the impact of the guideline.
Pachirat O, Chetchotisakd P, Klungboonkrong V et al. (2002) Infective endocarditis: prevalence, characteristics and mortality in Khon Kaen, 1990-1999. Journal of the Medical Association of Thailand 85: 1-10.	Distribution of clinical features data only, no trend of incidence.
Prendergast BD (2006) The changing face of infective endocarditis. [Review] [46 refs]. Heart 92: 879-85.	Narrative review/commentary
Rushani D, Kaufman JS, Ionescu-Ittu R et al. (2013) Infective endocarditis in children with congenital heart disease: cumulative incidence and predictors. Circulation 128: 1412-9.	Distribution of clinical features data only, no trend of incidence.
Seto TB (2007) The case for infectious endocarditis prophylaxis: time to move forward. [Review] [42 refs]. Archives of Internal Medicine 167: 327-30.	Narrative review/commentary
Shanson D (2008) New British and American guidelines for the antibiotic prophylaxis of infective endocarditis: do the changes make sense? A critical review. [Review] [55 refs]. Current Opinion in Infectious Diseases 21: 191-9.	Narrative review/commentary
Singh J, Straznicky I, Avent M et al. (2005) Antibiotic prophylaxis for endocarditis: time to reconsider. [Review] [56 refs]. Australian Dental Journal 50: Suppl-8.	Narrative review/commentary
Slipczuk L, Codolosa JN, Davila CD et al. (2013) Infective	Distribution of clinical

Reference	Reason for exclusion
endocarditis epidemiology over five decades: a systematic review. [Review]. PLoS ONE [Electronic Resource] 8: e82665.	features data only, no trend of incidence.
Sousa C, Botelho C, Rodrigues D et al. (2012) Infective endocarditis in intravenous drug abusers: an update. [Review]. European Journal of Clinical Microbiology & Infectious Diseases 31: 2905-10.	Narrative review/commentary
Tak T, Reed KD, Haselby RC et al. (2002) An update on the epidemiology, pathogenesis and management of infective endocarditis with emphasis on Staphylococcus aureus. [Review] [51 refs]. WMJ 101: 24-33.	Distribution of clinical features data only, no trend of incidence.
Thanavaro KL, Nixon JV (2014) Endocarditis 2014: an update. [Review]. Heart & Lung 43: 334-7.	Narrative review/commentary
Thornhill MH, Dayer MJ, Forde JM et al. (2011) Impact of the NICE guideline recommending cessation of antibiotic prophylaxis for prevention of infective endocarditis: before and after study. BMJ 342: d2392.	Part of Thornhill et al (2014) paper
Thornhill MH (2012) Infective endocarditis: the impact of the NICE guidelines for antibiotic prophylaxis. Dental Update 39: 6-10.	Part of Thornhill et al (2014) paper
Tornos P, Iung B, Permanyer-Miralda G et al. (2005) Infective endocarditis in Europe: lessons from the Euro heart survey. Heart 91: 571-5.	Distribution of clinical features data only, no trend of incidence.
Tornos P, Gonzalez-Alujas T, Thuny F et al. (2011) Infective endocarditis: the European viewpoint. [Review]. Current Problems in Cardiology 36: 175-222.	Narrative review/commentary
Tseng WC, Chiu SN, Shao PL et al. (2014) Changing spectrum of infective endocarditis in children: a 30 years experiences from a tertiary care center in Taiwan. Pediatric Infectious Disease Journal 33: 467-71.	Single centre study, clinical features data only, no trend of incidence.
Walls G, McBride S, Raymond N et al. (2014) Infective endocarditis in New Zealand: data from the International Collaboration on Endocarditis Prospective Cohort Study. New Zealand Medical Journal 127: 38-51.	Single centre study, clinical features data only, no trend of incidence.
Wang W, Sun H, Lv T et al. (2014) Retrospective studies on pediatric infective endocarditis over 40 years in a mid-west area of China. Cardiology 128: 88-91.	Distribution of clinical features data only, no trend of incidence.

F.21 Review questions 1a, 1b and 2

Reference	Reason for exclusion
Alsmady,M.M., Ennab,R.M., Hassuneh,S.S., et al. (2010) Early and mid-term evaluation of mechanical heart valve replacement, Kuwait Medical JournalKuwait Med.J., 42, 55-59.	Case series
Alsoufi,Bahaaldin, Al-Halees,Zohair, Fadel,Bahaa et al. (2010) Simultaneous aortic and mitral valve replacement in children: time-related outcomes and risk factors, The Journal of heart valve diseaseJ Heart Valve Dis, 19, 341-348.	Does not answer research question. Case series
Anderson,D.J., Olaison,L., Mcdonald,J.R. et al. (2005) Enterococcal prosthetic valve infective endocarditis: report of 45 episodes from the International Collaboration on Endocarditis-merged database, Eur J Clin Microbiol Infect Dis, 24, 665-70,	Analysis between types of IE only
Ardal,H, Toker,M E, Rabus, M.B. (2006) Does aortic root enlargement impair the outcome of patients with small aortic root? Journal of cardiac surgeryJ Card Surg, 21, 449-453.	Does not answer research question
Ariyaratne,Thathya V., Billah,Baki, Yap,Cheng Hon et al (2011) An Australian risk prediction model for determining early mortality following aortic valve replacement, European journal of cardio-	Does not answer research question

Reference	Reason for exclusion
thoracic surgery : official journal of the European Association for Cardio-thoracic SurgeryEur J Cardiothorac Surg, 39, 815-821.	
Assiri,Abdullah S., (2011) Clinical and microbiological profiles of infective endocarditis in a tertiary hospital in Aseer region, Saudi Arabia, Journal of the Saudi Heart AssociationJ.Saudi Heart Assoc., 23, 207-211.	Case series
Athan, Eugene, Chu, Vivian H., Tattevin, Pierre et al. (2012) ICE-PCS,Investigators, Clinical characteristics and outcome of infective endocarditis involving implantable cardiac devices, JAMA : the journal of the American Medical Association, 307, 1727-1735.	No data on parameters for comparison group
Aydin,Ebuzer, Yapici,Fikri, (2013) A retrospective analysis of factors influencing re-operation in patients undergoing mechanical valve replacement, Cardiovascular journal of AfricaCardiovasc.j.Afr., 24, 251-254.	Case series
Bachour,Khaled, Zmily,Hammam, Kizilbash,Mohammad et al. (2009) Valvular perforation in left-sided native valve infective endocarditis, Clinical cardiologyClin Cardiol, 32, E55-E62.	Does not answer research question
Barker,Gregory M., O'Brien,Sean M., Welke,Karl F et al. (2010) Major infection after pediatric cardiac surgery: a risk estimation model, The Annals of thoracic surgeryAnn Thorac Surg, 89, 843-850.	1) infection after acute surgery 2) IE is grouped with another infection (data not separated)
Barsic,Bruno, Dickerman,Stuart, Krajinovic,Vladimir et al. (2013) International Collaboration on Endocarditis-Prospective Cohort Study Investigators, Influence of the timing of cardiac surgery on the outcome of patients with infective endocarditis and stroke, Clinical infectious diseases : an official publication of the Infectious Diseases Society of AmericaClin Infect Dis, 56, 209-217.	Does not answer research question. Population IE and stroke not reported by cardiac conditions.
Baskerville, Catherine A. Hanrahan, Brendan B. Burke, Andrew J. et al. (2012) Infective endocarditis and Rheumatic Heart Disease in the North of Australia. Heart, Lung and Circulation 21:36-41.	No comparison group
Baumgartner,H. (2011) Infective endocarditis in adults with congenital heart disease: Is it time to change our approach to prophylaxis based on new insights into risk prediction?, European heart journalEur Heart J, 32, 1835-1837.	Editorial
Benito,Natividad, Miro,Jose M., de Lazzari,Elisa et al. (2009) ICE-PCS (International Collaboration on Endocarditis Prospective Cohort Study) Investigators, Health care-associated native valve endocarditis: importance of non-nosocomial acquisition, Annals of internal medicineAnn Intern Med, 150, 586-594.	Does not answer research question
Bernhardt,Alexander M.J., Treede,Hendrik, Rybczynski,Meike et al. (2011) Comparison of aortic root replacement in patients with Marfan syndrome, European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic SurgeryEur J Cardiothorac Surg, 40, 1052-1057.	Not relevant - no comparator
Bin Abdulhak,A.A., Baddour,L.M., Erwin,P.J. et al (2014) Global and regional burden of infective endocarditis, 1990-2010: A systematic review of the literature, Global HeartGlo.Heart, 9, 131-143.	Does not report on incidences of IE in pre-existing cardiac conditions.
Brennan,J.Matthew, Edwards,Fred H., Zhao,Yue et al. (2013) DEcIDE AVR (Developing Evidence to Inform Decisions about Effectiveness-Aortic Valve Replacement) Research Team, Long-term safety and effectiveness of mechanical versus biologic aortic valve prostheses in older patients: results from the Society of Thoracic Surgeons Adult Cardiac Surgery National Database, Circulation, 127, 1647-1655.	Does not answer research question
Brown,Morgan L., Dearani,Joseph A., Danielson,Gordon K. et al. (2009) Comparison of the outcome of porcine bioprosthetic versus	Cardiac procedure

Reference	Reason for exclusion
mechanical prosthetic replacement of the tricuspid valve in the Ebstein anomaly, The American journal of cardiologyAm J Cardiol, 103, 555-561,	
Chirouze,C., Athan,E., Alla,F. et al. (2013) International Collaboration on Endocarditis Study Group, Enterococcal endocarditis in the beginning of the 21st century: analysis from the International Collaboration on Endocarditis-Prospective Cohort Study, Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious DiseasesClin Microbiol Infect, 19, 1140-1147.	Not relevant
Danchin,N., Voiriot,P., Briancon,S. et al. (1989) Mitral valve prolapse as a risk factor for infective endocarditis, The Lancet,1,743-5.	Evaluating the risk of mitral valve prolapse in people with mitral value endocarditis
Chu,V.H., Miro,J.M., Hoen,B., Cabell,C.H. et al. (2009) International Collaboration on Endocarditis-Prospective Cohort Study Group, Coagulase-negative staphylococcal prosthetic valve endocarditis--a contemporary update based on the International Collaboration on Endocarditis: prospective cohort study, Heart (British Cardiac Society)Heart, 95, 570-576.	Outcomes don't match protocol.
d'Alessandro,Cosimo, Vistarini,Nicola, Aubert,Stephane, et al. (2007) European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic SurgeryEur J Cardiothorac Surg, 32, 596-603.	IE reported as outcome but data not reported by group therefore no comparison possible
Deharo,Jean Claude, Quatre,Amandine, Mancini,Julien et al. (2012) Long-term outcomes following infection of cardiac implantable electronic devices: a prospective matched cohort study, Heart (British Cardiac Society)Heart, 98, 724-731.	Inappropriate study population
Desai,Nimesh D., McCarthy,Fenton, Moser,William et al. (2011) Durability of porcine bioroots in younger patients with aortic root pathology: a propensity-matched comparison with composite mechanical roots, The Annals of thoracic surgeryAnn Thorac Surg, 92, 2054-1.	Cardiac procedure
Dhawan,V.K., (2003) Infective Endocarditis in Elderly Patients, Curr.Infect.Dis.Rep., 5, 285-292.	Review article
Doss,Mirko, Wood,Jeffrey P., Kiessling,Arndt H. et al (2011) Comparative evaluation of left ventricular mass regression after aortic valve replacement: a prospective randomized analysis, Journal of cardiothoracic surgeryJ Cardiothorac Surg, 6, 136-,	Does not answer research question
Dzupova,Olga, Machala,Ladislav, Baloun,Rudolf et al. (2012) Incidence, predisposing factors, and aetiology of infective endocarditis in the Czech Republic, Scandinavian journal of infectious diseasesScand J Infect Dis, 44, 250-255.	Case series
Emery,R.W., Krogh,C.C., Jones,D.J. et al. (2004) Five-year follow up of the ATS mechanical heart valve, Journal of Heart Valve DiseaseJ.Heart Valve Dis., 13, 231-238.	Not relevant. Single case of IE
Emery,Robert W., Krogh,Christopher C., McAdams,Sean et al. (2010) Long-term follow up of patients undergoing reoperative surgery with aortic or mitral valve replacement using a St. Jude Medical prosthesis, The Journal of heart valve diseaseJ Heart Valve Dis, 19, 473-484.	Reoperative open heart surgery
Englberger,L., Carrel,T., Schaff,H.V. et al (2001) Differences in heart valve procedures between North American and European centers: A report from the artificial valve endocarditis reduction trial (AVERT), Journal of Heart Valve DiseaseJ.Heart Valve Dis., 10, 562-571.	Does not answer research question
Ennker,Juergen A.C., Albert,Alexander A., Rosendahl,Ulrich P. et al.	Outcomes not reported by

Reference	Reason for exclusion
(2008) Ten-year experience with stentless aortic valves: full-root versus subcoronary implantation, The Annals of thoracic surgeryAnn Thorac Surg, 85, 445-3.	cardiac condition
Fedoruk,Lynn M., Jamieson,W.R.E., Ling,Hilton et al (2009) Predictors of recurrence and reoperation for prosthetic valve endocarditis after valve replacement surgery for native valve endocarditis, The Journal of thoracic and cardiovascular surgeryJ Thorac Cardiovasc Surg, 137, 326-333.	Does not answer research question
Feringa,H.H.H., Shaw,L.J., Poldermans,D. et al (2007) Mitral Valve Repair and Replacement in Endocarditis: A Systematic Review of Literature, Annals of Thoracic SurgeryAnn.Thorac.Surg. 83, 564-570.	Does not answer research question
Fernandez Guerrero,Manuel L., Gonzalez Lopez,Julio J., Goyenechea,Ana et al (2009) Endocarditis caused by Staphylococcus aureus: A reappraisal of the epidemiologic, clinical, and pathologic manifestations with analysis of factors determining outcome, MedicineMedicine (Baltimore), 88, 1-22.	Inadequate comparison group
Fernandez-Hidalgo,N., Almirante,B., Tornos,P. et al (2012) Immediate and long-term outcome of left-sided infective endocarditis. A 12-year prospective study from a contemporary cohort in a referral hospital, Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious DiseasesClin Microbiol Infect, 18, E522-E530.	Indirect population. Hospital vs community acquired. No extractable data, only types of IE
Fernandez-Hidalgo,Nuria, Almirante,Benito, Tornos,Pilar, et al (2008) Contemporary epidemiology and prognosis of health care-associated infective endocarditis, Clinical infectious diseases : an official publication of the Infectious Diseases Society of AmericaClin Infect Dis, 47, 1287-1297.	Indirect population. Hospital vs community aquired
Finkelstein, R. et al (2012). Incidence and risk factors for endocarditis among patients with health care-associated Staphylococcus aureus bacteraemia. Scandinavian Journal of Infectious Diseases.44:934-940.	Population is peole with s.aureus bacteraemia who get IE (inapprorpriate population for comparison). Pre-existing cardiac conditions is a composite risk factor that include pace-makers.
Fisher,M.C. (2001) Changing Risk Factors for Pediatric Infective Endocarditis, Curr.Infect.Dis.Rep., 3, 333-336.	Narrative article
Fitzmaurice,Gerard J., McKenna,Adrian J., Murphy,Jamie et al. (2014) Streptococcus bovis bacteraemia: an evaluation of the long-term effect on cardiac outcomes, General thoracic and cardiovascular surgeryGen Thorac Cardiovasc Surg, 62, 142-148.	Could not tease out the number of different cardiac outcomes
Forcillo,Jessica, El Hamamsy,Ismail, Stevens,Louis Mathieu et al (2014) The perimount valve in the aortic position: twenty-year experience with patients under 60 years old, The Annals of thoracic surgeryAnn Thorac Surg, 97, 1526-1532.	Does not answer research question
Fortun,J., Centella,T., Martin-Davila,P., Lamas,M.J. et al (2013) Infective endocarditis in congenital heart disease: a frequent community-acquired complication, Infection, 41, 167-174.	Case series
Gaca,Jeffrey G., Sheng,Shubin, Daneshmand,Mani A. et al (2011) Outcomes for endocarditis surgery in North America: a simplified risk scoring system, The Journal of thoracic and cardiovascular surgeryJ Thorac Cardiovasc Surg, 141, 98-2.	Does not answer research question
Gamez,Antonio, Castillo,Juan C., Bonilla,Juan L. et al (2011) Infective endocarditis after the Ross procedure, International journal of cardiologyInt J Cardiol, 147, e53-e54.	Case report
Garcia,Mercedes A., Alarcon,Graciela S., Boggio,Gabriela, et al	Does not answer research

Reference	Reason for exclusion
(2014) Grupo Latino Americano de Estudio del Lupus Eritematoso (GLADEL), Primary cardiac disease in systemic lupus erythematosus patients: protective and risk factors--data from a multi-ethnic Latin American cohort, Rheumatology (Oxford, England)Rheumatology (Oxford), 53, 1431-1438.	question
Gersony,W.M., Hayes ,C.J., Driscoll,D.J. et al (1993) Bacterial endocarditis in patients with aortic stenosis, pulmonary stenosis, or ventricular septal defect, Circulation, 87, I-121-I-126.	Prevalence data only, no comparisons.
Girdauskas,Evaldas, Rouman,Mina, Borger,Michael A. et al (2013) Comparison of aortic media changes in patients with bicuspid aortic valve stenosis versus bicuspid valve insufficiency and proximal aortic aneurysm, Interactive cardiovascular and thoracic surgeryInteract Cardiovasc Thorac Surg, 17, 931-936.	Does not answer research question
Gregor,P. (2013) What's new in the prevention of infective endocarditis?, Cor et VasaCor Vasa, 55, e520-e524.	Narrative article
Habib,Ammar, Le,Katherine Y., Baddour,Larry M. et al. (2013) Mayo Cardiovascular Infections Study Group, Predictors of mortality in patients with cardiovascular implantable electronic device infections, The American journal of cardiologyAm J Cardiol, 111, 874-879.	Outcomes not reported by cardiac condition
Hanai,Makoto, Hashimoto,Kazuhiro, Mashiko,Kenoh et al. (2008) Active infective endocarditis: management and risk analysis of hospital death from 24 years' experience, Circulation journal : official journal of the Japanese Circulation SocietyCirc J, 72, 2062-2068.	Outcomes not reported according to pre-existing cardiac condition
Hill E.E., Vanderschueren, S. Verhaegen, J. Herugers, P et al. (2007) Risk Factors for Infective Endocarditis and Outcome of Patients with Staphylococcus aureus Bacteremia. Mayo Clin Proc. 82(10):1165-1169.	Population inadequate (all patients had bacteremia) and comparison was therefore inappropriate.
Holden,E., Bashir,A., Das,I. et al (2014) Staphylococcus aureus bacteraemia in a UK tertiary referral centre: A 'transoesophageal echocardiogram for all' policy, Journal of Antimicrobial ChemotherapyJ.Antimicrob.Chemother., 69, 1960-1965.	Does not answer research question
Jang,W.S., Kim,W.-H., Choi,K. et al (2013) What factors predict long-term survival and valve durability in patients with atrioventricular valve regurgitation in single-ventricle physiology?, Pediatric cardiologyPediatr Cardiol, 34, 1366-1373.	Does not answer research question
Jaussaud,Nicolas, Gariboldi,Vlad, Giorgi,Roch et al (2009) Risk of reoperation for aortic bioprosthesis dysfunction, The Journal of heart valve diseaseJ Heart Valve Dis, 18, 256-261.	Does not answer research question
Johnson,Jennifer A., Boyce,Thomas G., Cetta,Frank, et al (2012) Infective endocarditis in the pediatric patient: a 60-year single-institution review, Mayo Clinic proceedings.Mayo Clinic, 87, 629-635.	Comparison of 2 case series at different time points
Jokinen,Janne J., Hippelainen,Mikko J., Pitkanen,Otto A. et al (2007) Mitral valve replacement versus repair: propensity-adjusted survival and quality-of-life analysis, The Annals of thoracic surgeryAnn Thorac Surg, 84, 451-458.	No report of IE by cardiac risk factors
Kim,H.J., Kim,J.B., Jung,S.-H. et al (2014) Valve replacement surgery for older individuals with preoperative atrial fibrillation: The effect of prosthetic valve choice and surgical ablation, Journal of Thoracic and Cardiovascular SurgeryJ.Thorac.Cardiovasc.Surg., 147, 1907-1917.	Population - AF only and report on cause of death only
Klein,Isabelle, Iung,Bernard, Labreuche,Julien et al (2009) IMAGE Study Group, Cerebral microbleeds are frequent in infective endocarditis: a case-control study, Stroke; a journal of cerebral circulationStroke, 40, 3461-3465.	Risk factors for cerebral microbleeds, did not include pre-existing conditions.
Klieverik,Loes M.A., Bekkers,Jos A., Roos,Jolien W. (2008) Autograft or allograft aortic valve replacement in young adult patients with	Does not answer research question

Reference	Reason for exclusion
congenital aortic valve disease, European heart journalEur Heart J, 29, 1446-1453.	
Klug,Didier, Balde,Mamadou, Pavin,Dominique et al (2007) PEOPLE Study Group, Risk factors related to infections of implanted pacemakers and cardioverter-defibrillators: results of a large prospective study, Circulation, 116, 1349-1355.	Pacemaker infections
Koolbergen,D.R., Manshanden,J.S., Bouma,B.J. et al (2014) Valve-sparing aortic root replacement, Eur.J.Cardiothorac Surg., 8 January 348-54.	Case series
Kratz,J.M., Toole,J.M., (2010) Pacemaker and internal cardioverter defibrillator lead extraction: A safe and effective surgical approach, Annals of Thoracic SurgeryAnn.Thorac.Surg., 90, 1411-1417.	Does not answer research question
Kulik,A., Lam,B.-K., Rubens,F.D. et al (2009) Gender differences in the long-term outcomes after valve replacement surgery, Heart (British Cardiac Society) Heart, 95, 318-326.	No comparison group
Kuwaki,K., Kawaharada,N., Morishita,K. et al (2007) Mitral valve repair versus replacement mitral and aortic valve surgery for rhematic disease, The Society for Thoracic Surgeons, 83, 558-63.	No mention of IE as a long term outcome
Legrand,M., Pirracchio,R., Rosa,A. et al (2013) Incidence, risk factors and prediction of post-operative acute kidney injury following cardiac surgery for active infective endocarditis: An observational study, Critical CareCrit.Care, 17 (5) R220.	No data on pre-existing cardiac conditions
Lehmann,Sven, Walther,Thomas, Leontjev,Sergey et al. (2007) Mid-term results after Epic xenograft implantation for aortic, mitral, and double valve replacement, The Journal of heart valve diseaseJ Heart Valve Dis, 16, 641-648.	Cardiac procedure
Leontyev,Sergey, Borger,Michael A., Davierwala,Piroze et al (2011) Redo aortic valve surgery: early and late outcomes, The Annals of thoracic surgeryAnn Thorac Surg, 91, 1120-1126.	Endocarditis not reported by risk factors of interest
Leontyev,Sergey, Borger,Michael A., Modi,Paul et al (2012) Surgical management of aortic root abscess: a 13-year experience in 172 patients with 100% follow-up, The Journal of thoracic and cardiovascular surgeryJ Thorac Cardiovasc Surg, 143, 332-337.	Outcomes not reported by cardiac condition
Leontyev,Sergey, Borger,Michael A., Modi,Paul et al (2011) Redo aortic valve surgery: Influence of prosthetic valve endocarditis on outcomes, The Journal of thoracic and cardiovascular surgeryJ Thorac Cardiovasc Surg, 142, 99-105.	Does not answer research question
Lesens,O., Hansmann,Y., Storck,D. et al (2003) Risk factors for metastatic infection in patients with Staphylococcus aureus bacteremia with and without endocarditis, European journal of internal medicineEUR.J.INTERN.MED., 14, 227-231.	Does not answer research question
Li,W, Somerville,J. (1998) Infective endocarditis in the grown-up congenital heart (GUCH) population, European Heart Journal, 19, 166-73.	No evaluation on odds of IE with congenital heart disease.
Lopez,Javier, Revilla,Ana, Vilacosta,Isidre et al (2011) Multiple-valve infective endocarditis: clinical, microbiologic, echocardiographic, and prognostic profile, MedicineMedicine (Baltimore), 90, 231-236.	Does not answer research question
Luciani,Giovanni Battista, De Rita,Fabrizio, Lucchese,Gianluca et al (2012) Repair of congenitally dysplastic aortic valve by bicuspidization: midterm results, The Annals of thoracic surgeryAnn Thorac Surg, 94, 1173-1179.	Does not answer research question
Luciani,Giovanni Battista, Viscardi,Francesca, Cresce,Giovanni Domenico et al. (2008) Seven-year performance of the Edwards Prima Plus stentless valve with the intact non-coronary sinus technique, Journal of cardiac surgeryJ Card Surg, 23, 221-226.	Does not answer research question

Reference	Reason for exclusion
Luciani,Giovanni Battista, Viscardi,Francesca, Pilati,Mara et al (2008) Operative risk and outcome of surgery in adults with congenital valve disease, ASAIO journal (American Society for Artificial Internal Organs : 1992)ASAIO J, 54, 458-462.	Cardiac procedure
Maciejewski,Marek, Piestrzeniewicz,Katarzyna, Bielecka-Dabrowa, et al. (2011) Redo surgery risk in patients with cardiac prosthetic valve dysfunction, Archives of medical science : AMSArch.Med.Sci., 7, 271-277.	Case series
Malekzadeh-Milani,S., Ladouceur,M., Iserin,L. et al (2014) Incidence and outcomes of right-sided endocarditis in patients with congenital heart disease after surgical or transcatheter pulmonary valve implantation, Journal of Thoracic and Cardiovascular SurgeryJ.Thorac.Cardiovasc.Surg. 148(6):2809-10.	Comparing cardiac prodecures
Martinez-Quintana,Efren, Rodriguez-Gonzalez,Fayna, Medina-Gil et al (2010) Clinical outcome in Down syndrome patients with congenital heart disease, Cirugia y cirujanosCir Cir, 78, 245-250.	Full article not in English and unclear study design
Math,Ravi S., Sharma,Gautam, Kothari,Shyam Sunder et al (2011) Prospective study of infective endocarditis from a developing country, American heart journalAm Heart J, 162, 633-638.	Case series
McGonigle,Niall C., Jones,J.Mark, Sidhu,Pushpinder et al (2007) Concomitant mitral valve surgery with aortic valve replacement: a 21-year experience with a single mechanical prosthesis, Journal of cardiothoracic surgeryJ Cardiothorac Surg, 2, 24.	Outcomes not reported by cardiac condition
Meszaros,Katharina, Nujic,Sladjan, Sodeck,Gottfried H. et al (2012) Long-term results after operations for active infective endocarditis in native and prosthetic valves, The Annals of thoracic surgeryAnn Thorac Surg, 94, 1204-1210.	No data on comparing pre-existing cardiac conditions and their outcome after IE and treatment
Mirabel,M., Sonneville,R., Hajage,D. et al (2014) Long-term outcomes and cardiac surgery in critically ill patients with infective endocarditis, European heart journalEur Heart J, 35, 1195-1204.	No data on pre-existing cardiac before the IE attack
Morris,C.D., Reller,M.D., Menashe,V.D. (1998) Thirty-year incidence of infective endocarditis after surgery for congenital heart defect, JAMA, 279, 599-603.	Case series
Musci,Michele, Hubler,Michael, Amiri,Aref, et al (2011) Repair for active infective atrioventricular valve endocarditis: 23-year single center experience, Clinical research in cardiology : official journal of the German Cardiac SocietyClin.res.cardiol., 100, 993-1002.	Cardiac procedures
Nadji,Georges, Rusinaru,Dan, Remadi,Jean Paul et al (2009) Heart failure in left-sided native valve infective endocarditis: characteristics, prognosis, and results of surgical treatment, European journal of heart failureEur J Heart Fail, 11, 668-675.	IE population but risk factors did not include pre-existing cardiac conditions
Nazarov,Vladimir M., Zheleznev,Sergey I., Bogachev-Prokophiev,Alexandr V. et al (2014) CardiaMed mechanical valve: mid-term results of a multicenter clinical trial, Asian cardiovascular & thoracic annalsAsian Cardiovasc Thorac Ann, 22, 9-17.	Focuses on safety of 1 valve used in different valve locations
Neragi-Miandoab,S., Skripochnik,E., Michler,R. et al (2014) Risk factors predicting the postoperative outcome in 134 patients with active endocarditis, Heart Surgery ForumHeart Surg.Forum, 17, E35-E41.	No data presented on outcome by risk factor. Cannot back calculate odds ratio
Nishida,T., Sonoda,H., Oishi,Y. et al (2013) Mechanical prosthesis is reasonable for mitral valve replacement in patients approximately 65 years of age, Annals of Thoracic SurgeryAnn.Thorac.Surg., 96, 1614-1620.	Does not answer research question
Onorati,F., Biancari,F., De,Feo M. et al (2014) Mid-term results of aortic valve surgery in redo scenarios in the current practice: results	Cardiac surgery

Reference	Reason for exclusion
from the multicentre European RECORD (REdo Cardiac Operation Research Database) initiative, Eur.J.Cardiothorac Surg. 47(2):269-80.	
Ota,Takeyoshi, Gleason,Thomas G., Salizzoni,Stefano et al (2011) Midterm surgical outcomes of noncomplicated active native multivalve endocarditis: single-center experience, The Annals of thoracic surgeryAnn Thorac Surg, 91, 1414-1419.	Outcomes not reported by cardiac condition
Oz,Bilgehan Savas, Iyem,Hikmet, Akay,Hakki Tankut et al (2006) Risk factors for short- and long-term survival in patients undergoing re-replacement due to prosthetic valve dysfunction, Heart and vesselsHeart Vessels, 21, 339-343.	Cardiac procedure
Pfannmueller,Bettina, Eifert,Sandra, Seeburger,Jorg et al (2013) Gender-dependent differences in patients undergoing tricuspid valve surgery, The Thoracic and cardiovascular surgeonThorac Cardiovasc Surg, 61, 37-41.	Gender not on protocol as sub-group of interest
Pfannmuller,B., Davierwala,P., Misfeld,M et al (2012) Postoperative outcome of isolated tricuspid valve operation using arrested-heart or beating-heart technique, Annals of ThoracicSurgeryAnn.Thorac.Surg. 94, 1218-1222.	Does not answer research question
Preventza,Ourania, Mohamed,Ahmed S., Cooley,Denton A. et al (2014) Homograft use in reoperative aortic root and proximal aortic surgery for endocarditis: A 12-year experience in high-risk patients, The Journal of thoracic and cardiovascular surgeryJ Thorac Cardiovasc Surg, 148, 989-994.	Outcomes not reported by risk factors of interest
Rankin,J.Scott, Thourani,Vinod H., Suri,Rakesh M. et al (2013) Associations between valve repair and reduced operative mortality in 21,056 mitral/tricuspid double valve procedures, European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic SurgeryEur J Cardiothorac Surg, 44, 472-477.	Cardiac procedures
Remadi,J.P., Nadji,G., Goissen,T. et al (2009) Infective endocarditis in elderly patients: clinical characteristics and outcome, European Journal of Cardio-thoracic SurgeryEur.J.Cardio-thorac.Surg.35,123-129.	Age not a protocol sub-group
Remenyi,B., Webb,R., Gentles,T. et al (2013) Improved long-term survival for rheumatic mitral valve repair compared to replacement in the young, World Journal for Pediatric and Congenital Hearth SurgeryWorld J.Pediatr.Congenit.Heart Surg., 4, 155-164.	Cardiac procedure
Riess,Friedrich Christian, Bader,Ralf, Cramer,Eva et al (2011) The Mosaic porcine bioprosthesis: role of age on clinical performance in aortic position, The Journal of thoracic and cardiovascular surgeryJ Thorac Cardiovasc Surg, 141, 1440-1448.	Comparison by age of recipient of porcine bioprosthesis in aortic valve replacement
Rodrigues,Alfredo Jose, Evora,Paulo Roberto Barbosa, Bassetto,Solange et al (2009) Isolated mitral and aortic valve replacement with the St. Jude Medical valve: a midterm follow-up, Arquivos brasileiros de cardiologiaArq Bras Cardiol, 93, 290-298.	Does not answer research question
Roldan,Carlos A., Sibbitt,Wilmer L.J., Qualls,Clifford R. et al (2013) Libman-Sacks endocarditis and embolic cerebrovascular disease, JACC.Cardiovascular imagingJACC Cardiovasc Imaging, 6, 973-983.	Does not answer research question
Roumieh,M., Ius,F., Tudorache,I. et al (2014) Comparison between biological and mechanical aortic valve prostheses in middle-aged patients matched through propensity score analysis: long-term results, Eur.J.Cardiothorac Surg. -	Cardiac procedures
Samad,Zainab, Kaul,Prashant, Shaw,Linda K. et al (2011) Impact of early surgery on survival of patients with severe mitral regurgitation, Heart (British Cardiac Society)Heart, 97, 221-224,	No mention of IE
Sambola,Antonia, Fernandez-Hidalgo,Nuria, Almirante,Benito et al	Gender not a protocol sub-

Reference	Reason for exclusion
(2010) Sex differences in native-valve infective endocarditis in a single tertiary-care hospital, The American journal of cardiologyAm J Cardiol, 106, 92-98.	group
San Martin,Juan, Sarria,Cristina, de las Cuevas,Carmen et al (2010) Relevance of clinical presentation and period of diagnosis in prosthetic valve endocarditis, The Journal of heart valve diseaseJ Heart Valve Dis, 19, 131-138.	Does not answer research question
Sawaki,Sadanari, Usui,Akihiko, Abe,Tomonobu et al (2006) Late mortality and morbidity in elderly patients with mechanical heart valves, Asian cardiovascular & thoracic annalsAsian Cardiovasc Thorac Ann, 14, 189-194.	Cannot tease out those who died from IE by pre-existing cardiac conditions
Saxena,Anita, Aggarwal,Neeraj, Gupta,Pankaj et al (2011) Predictors of embolic events in pediatric infective endocarditis, Indian heart journalIndian Heart J, 63, 237-240.	Case series
Segalote,Rodrigo Coelho, Pomerantzeff,Pablo Maria Alberto, Brandao,Carlos Manuel de Almeida et al (2008) Aortic valve preservation surgery in elderly patients with aortic stenosis, Revista brasileira de cirurgia cardiovascular : orgao oficial da Sociedade Brasileira de Cirurgia CardiovascularRev Bras Cir Cardiovasc, 23, 519-523.	Case series
Shang,Eric, Forrest,Graeme N., Chizmar,Timothy et al (2009) Mitral valve infective endocarditis: benefit of early operation and aggressive use of repair, The Annals of thoracic surgeryAnn Thorac Surg, 87, 1728-1734.	Pre-existing cardiac conditions not a risk factor that was evaluated
Sheikh,Amir M., Elhenawy,Abdelsalam M., Maganti,Manjula, et al (2009) Outcomes of surgical intervention for isolated active mitral valve endocarditis, The Journal of thoracic and cardiovascular surgeryJ Thorac Cardiovasc Surg, 137, 110-116.	Risk factors focused on surgery type not pre-existing cardiac conditions
Shimokawa,Tomoki, Kasegawa,Hitoshi, Matsuyama,Shigefumi et al (2009) Long-term outcome of mitral valve repair for infective endocarditis, The Annals of thoracic surgeryAnn Thorac Surg, 88, 733-739.	Does not answer research question
Shinkawa,Takeshi, Anagnostopoulos,Petros V., Johnson,Natalie C. et al (2010) Performance of bovine pericardial valves in the pulmonary position, The Annals of thoracic surgeryAnn Thorac Surg, 90, 1295-1300.	Case series
Silberman,Shuli, Oren,Avraham, Dotan,Moshe et al (2008) Aortic valve replacement: choice between mechanical valves and bioprostheses, Journal of cardiac surgeryJ Card Surg, 23, 299-306.	Cardiac surgery
Slipczuk,Leandro, Codolosa,J.Nicolas, Davila,Carlos D. et al (2013) Infective endocarditis epidemiology over five decades: a systematic review, PloS one, 8, e82665-,	Does not include pre-existing cardiac conditions.
Sohail,Muhammad R., Uslan,Daniel Z., Khan,Akbar H. et al (2007) Risk factor analysis of permanent pacemaker infection, Clinical infectious diseases : an official publication of the Infectious Diseases Society of AmericaClin Infect Dis, 45, 166-173.	PPMI not the same as IE (confirmed with P.Alderson)
Tang,G.H.L., Maganti,M., David,T.E. et al (2007) Effect of Prior Valve Type on Mortality in Reoperative Valve Surgery, Annals of Thoracic SurgeryAnn.Thorac.Surg., 83, 938-945.	Can't tease out data by pre-existing cardiac condition
Taniguchi,S., Hashizume,K., Ariyoshi,T. et al (2012) Twelve years of experience with the ATS mechanical heart valve prostheses, General thoracic and cardiovascular surgeryGen Thorac Cardiovasc Surg, 60, 561-568.	Endocarditis is not an outcome
Taramasso,M., Denti,P., Buzzatti,N. et al (2012) Mitraclip therapy and surgical mitral repair in patients with moderate to severe left ventricular failure causing functional mitral regurgitation: A single-	Does not answer research question

Reference	Reason for exclusion
centre experience, European Journal of Cardio-thoracic SurgeryEur.J.Cardio-thorac.Surg., 42, 920-926.	
Tjang,Yanto Sandy, van Hees,Yvonne, Korfer,Reiner et al (2007) Predictors of mortality after aortic valve replacement, European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic SurgeryEur J Cardiothorac Surg, 32, 469-474.	No comparator/control group. Reviewing predictors of mortality after aortic valve replacement only.
Tleyjeh,I.M., Steckelberg,J.M., Georgescu,G. et al (2008) The association between the timing of valve surgery and 6-month mortality in left-sided infective endocarditis, Heart (British Cardiac Society)Heart, 94, 892-896.	Not relevant
Tleyjeh,Imad M., Abdel-Latif,Ahmed, Rahbi,Hazim et al (2007) A systematic review of population-based studies of infective endocarditis, Chest, 132, 1025-1035.	Different inclusion criteria to our SR (incl. case series'). Report on change in in proportions of characteristics by decade only.
Tleyjeh,Imad M., Ghomrawi,Hassan M.K., Steckelberg,James M. et al (2010) Conclusion about the association between valve surgery and mortality in an infective endocarditis cohort changed after adjusting for survivor bias, Journal of clinical epidemiologyJ Clin Epidemiol, 63, 130-135.	Does not answer research question - about cardiac surgery as treatment of IE
Toole,J.Matthew, Stroud,Martha R., Kratz,John M. et al (2010) Twenty-five year experience with the St. Jude medical mechanical valve prosthesis, The Annals of thoracic surgeryAnn Thorac Surg, 89, 1402-1409.	Cardiac procedure
Tossios,Paschalis, Reber,Delawer, Oustria,Maria et al (2007) Single-center experience with the On-X prosthetic heart valve between 1996 and 2005, The Journal of heart valve diseaseJ Heart Valve Dis, 16, 551-557.	Cardiac procedures
Tribouilloy,C., Rusinaru,D., Sorel,C. et al (2010) Clinical characteristics and outcome of infective endocarditis in adults with bicuspid aortic valves: a multicentre observational study, Heart (British Cardiac Society)Heart, 96, 1723-1729.	No control
Tzemos,Nikolaos, Therrien,Judith, Yip,James et al (2008) Outcomes in adults with bicuspid aortic valves, JAMAJ.Am.Med.Assoc., 300, 1317-1325.	IE not reported separately. Data not reported by comparison group
Urso,Stefano, Rega,Filip, Meuris,Bart et al (2011) The Contegra conduit in the right ventricular outflow tract is an independent risk factor for graft replacement, European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic SurgeryEur J Cardiothorac Surg, 40, 603-609.	Does not answer research question
Uslan,Daniel Z., Dowsley,Taylor F., Sohail,Muhammad R. et al (2010) Cardiovascular implantable electronic device infection in patients with Staphylococcus aureus bacteremia, Pacing and clinical electrophysiology : PACEPacing Clin Electrophysiol, 33, 407-413.	Does not answer research question
Verheugt,Carianne L., Uiterwaal,Cuno S.P.M., van der Velde,Enno T. et al (2008) Gender and outcome in adult congenital heart disease, Circulation, 118, 26-32.	Gender not a protocol sub-group
Wei,Xufeng, Yi,Wei, Chen,Wensheng et al (2010) Clinical outcomes with the epicholorohydrin-modified porcine aortic heart valve: a 15-year follow-up, The Annals of thoracic surgery Ann Thorac Surg, 89, 1417-1424.	Cardiac procedures
Wang,A., Pappas,P., Anstrom,K.J. et al (2005) The use and effect of surgical therapy for prosthetic valve infective endocarditis: a propensity analysis of a multicenter, international cohort, American	No estimations of associations between pre-existing cardiac conditions

Reference	Reason for exclusion
Heart Journal, 150, 1086-91.	and poorer outcomes from IE
Wiese,L., Mejer,N., Schonheyder,H.C. et al (2013) Danish Staphylococcal Bacteraemia Study Group, A nationwide study of comorbidity and risk of reinfection after Staphylococcus aureus bacteraemia, The Journal of infectionJ Infect, 67, 199-205.	Does not answer research question
Wilbring,Manuel, Tugtekin,Sems Malte, Alexiou,Konstantin et a (2012) Composite aortic root replacement for complex prosthetic valve endocarditis: initial clinical results and long-term follow-up of high-risk patients, The Annals of thoracic surgeryAnn Thorac Surg, 94, 1967-1974.	Outcomes not reported by cardiac condition
Wu,Kuan Sheng, Lee,Susan Shin-Jung, Tsai,Hung Chin et al (2011) Non-nosocomial healthcare-associated infective endocarditis in Taiwan: an underrecognized disease with poor outcome, BMC infectious diseasesBMC Infect Dis, 11, 221.	Does not answer research question
Zhao,D., Zhang,B. (2014) Are valve repairs associated with better outcomes than replacements in patients with native active valve endocarditis?, Interact.Cardiovasc.Thorac.Surg.19(6):1036-9.	Does not answer research question (cardiac surgery)
Zilberszac,R., Gabriel,H., Schemper,M. et al (2013) Outcome of combined stenotic and regurgitant aortic valve disease, Journal of the American College of CardiologyJ Am Coll Cardiol, 61, 1489-1495.	Study focus was to evaluate need for valve replacement between aortic stenosis and regurgitation. Does not answer research question.
Zuzana,H., Katerina,J., Gabriela,D. (2014) Long-term outcome and prosthesis-related complications after valve replacement, Experimental and clinical cardiologyExp.clin.cardiol., 20, 1341-1347.	No report on outcomes by IE status

F.31 Review question 3 and 4

Reference	Reason for exclusion
Q3	
Baltimore R (2008) New recommendations for the prevention of infective endocarditis. Current opinion in pediatrics 20: 85-9.	Not primary study
Coffey S, Nadarasa K, Pan A et al. (2012) The increasing incidence of Streptococcus bovis endocarditis and bacteraemia: A case series from 1997 to 2010. International journal of cardiology 161: 111-3.	Case series.
Durante-Mangoni E, Bradley S, Selton-Suty C et al. (2008) Current features of infective endocarditis in elderly patients: results of the International Collaboration on Endocarditis Prospective Cohort Study. Archives of internal medicine 168: 2095-103.	Not relevant – not about any interventional procedures associated to IE.
Duval X, Delahaye F, Alla F et al. (2012) Temporal trends in infective endocarditis in the context of prophylaxis guideline modifications: Three successive population-based surveys. Journal of the American College of Cardiology 59: 1968-76.	Not relevant.
Forrest GN, Arnold RS, Gammie JS et al. (2011) Single center experience of a vancomycin resistant enterococcal endocarditis cohort. The Journal of infection 63: 420-8.	Not relevant – about antibiotics resistant.
Glenny AM, Oliver R, Roberts GJ et al. (2013) Antibiotics for the prophylaxis of bacterial endocarditis in dentistry. The Cochrane database of systematic reviews 10: CD003813.	Not relevant – about prophylaxis.
Gupta A, Gupta A, Kaul U et al. (2013) Infective endocarditis in an Indian setup: Are we entering the 'modern' era? Indian journal of critical care medicine : peer-reviewed, official publication of Indian Society of Critical Care Medicine 17: 140-7.	Cardiac procedures – excluded from the scope.

Reference	Reason for exclusion
Hsieh J-C, Wang L-Y, Chang H-R et al. (2014) Clinical characteristics and in-hospital prognosis of infective endocarditis in two eastern counties of Taiwan. Acta Cardiologica Sinica 30: 151-6.	Not relevant – only baseline characteristics.
Jain V, Yang M-H, Kovacicova-Lezcano G et al. (2008) Infective endocarditis in an urban medical center: Association of individual drugs with valvular involvement. Journal of Infection 57: 132-8.	Not relevant – about substance misusers.
Lockhart PB, Brennan MT, Thornhill M et al. (2009) Poor oral hygiene as a risk factor for infective endocarditis-related bacteremia. Journal of the American Dental Association (1939) 140: 1238-44.	Not relevant – not about interventional procedures.
Nunes MCP, Gelape CL, Ferrari TCA (2010) Profile of infective endocarditis at a tertiary care center in Brazil during a seven-year period: prognostic factors and in-hospital outcome. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases 14: e394-e398.	About cardiac procedures, which are excluded from the scope.
Werdan K, Dietz S, Loffler B et al. (2014) Mechanisms of infective endocarditis: pathogen-host interaction and risk states. Nature reviews.Cardiology 11: 35-50.	Not primary study
Q3 – From broad search	
Chirouze C, Athan E, Alla F et al. (2013) Enterococcal endocarditis in the beginning of the 21st century: analysis from the International Collaboration on Endocarditis-Prospective Cohort Study. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases 19: 1140-7.	The types of surgical procedures were not clear or defined.
Fernandez-Hidalgo N, Almirante B, Tornos P et al. (2008) Contemporary epidemiology and prognosis of health care-associated infective endocarditis. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 47: 1287-97.	Case series.
Johnson JA, Boyce TG, Cetta F et al. (2012) Infective endocarditis in the pediatric patient: a 60-year single-institution review. Mayo Clinic proceedings.Mayo Clinic 87: 629-35.	Cardiac procedures – not covered by the scope.
Kwang TY, Yin TJ, Naqash N et al. (2013) Infective endocarditis and infected aneurysm of splenic artery post colonoscopy. Annals of Gastroenterology 26: 170-2.	Single case report.
Sambola A, Fernandez-Hidalgo N, Almirante B et al. (2010) Sex differences in native-valve infective endocarditis in a single tertiary-care hospital. The American journal of cardiology 106: 92-8.	Not relevant – the procedures were actually the treatment for the IE>
Q4	
Abu-Sharar Z, Robinson A, Lavoie PM (2010) Incidence of septicemia immediately after elective gastrointestinal contrast procedures in infants: a cohort study. Journal of pediatric surgery 45: 507-12.	Only post-procedure blood sample, no pre-procedure.
Albawardi A, Almarzooqi S, Torab FC (2013) Helicobacter pylori in sleeve gastrectomies: Prevalence and rate of complications. International Journal of Clinical and Experimental Medicine 6: 140-3.	Not relevant
Ali MJ, Ayyar A, Motukupally SR et al. (2014) Bacteremia during dacryocystorhinostomy: results of intra-operative blood cultures. Journal of ophthalmic inflammation and infection 4: 27.	Blood sample only taken pre-procedure, no post-procedure blood sample.
Alsaywid BS, Smith GHH (2013) Antibiotic prophylaxis for transurethral urological surgeries: Systematic review. Urology annals 5: 61-74.	All studies in the review already included in the original guideline.
Bamberger DM (2007) Bacteremia and endocarditis due to methicillin-resistant Staphylococcus aureus: the potential role of daptomycin. Therapeutics and clinical risk management 3: 675-84.	Not primary study.

Reference	Reason for exclusion
Bang JH, Choe HS, Lee DS et al. (2013) Microbiological characteristics of acute prostatitis after transrectal prostate biopsy. Korean journal of urology 54: 117-22.	Not relevant - case series of prostatitis
Barbosa M, Carmona IT, Amaral B et al. (2010) General anesthesia increases the risk of bacteremia following dental extractions. Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics 110: 706-12.	Only post-procedure blood sample, no pre-procedure.
Brennan MT, Kent ML, Fox PC et al. (2007) The impact of oral disease and nonsurgical treatment on bacteremia in children. Journal of the American Dental Association (1939) 138: 80-5.	Blood sample only taken pre-procedure, no post-procedure blood sample.
Burke RE, Halpern MS, Baron EJ et al. (2009) Pediatric and neonatal Staphylococcus aureus bacteremia: epidemiology, risk factors, and outcome. Infection control and hospital epidemiology : the official journal of the Society of Hospital Epidemiologists of America 30: 636-44.	Not about interventional procedures.
Campeggi A, Ouzaid I, Xylinas E et al. (2014) Acute bacterial prostatitis after transrectal ultrasound-guided prostate biopsy: epidemiological, bacteria and treatment patterns from a 4-year prospective study. International journal of urology : official journal of the Japanese Urological Association 21: 152-5.	Not relevant – not about any interventional procedures.
Carignan A, Roussy JF, Lapointe V et al. (2012) Increasing risk of infectious complications after transrectal ultrasound-guided prostate biopsies: time to reassess antimicrobial prophylaxis? European urology 62: 453-9.	Not relevant – about other complications caused by infection.
Casserly P, Kieran S, Phelan E et al. (2010) Bacteremia during adenoidectomy: a comparison of suction diathermy adenoid ablation and adenoid curettage. The Annals of otology, rhinology, and laryngology 119: 526-9.	Only post-procedure blood sample, no pre-procedure.
Chavez-Tapia NC, Barrientos GT, Tellez AF, I et al. (2010) Antibiotic prophylaxis for cirrhotic patients with upper gastrointestinal bleeding. Cochrane Database of Systematic Reviews	Not relevant.
Crasta K, Daly CG, Mitchell D et al. (2009) Bacteraemia due to dental flossing. Journal of clinical periodontology 36: 323-32.	About everyday activities.
de Smet AM, Kluytmans JAJW, Blok HEM et al. (2011) Selective digestive tract decontamination and selective oropharyngeal decontamination and antibiotic resistance in patients in intensive-care units: an open-label, clustered group-randomised, crossover study. The Lancet infectious diseases 11: 372-80.	Not all study population had blood sample taken.
de Smet AM, Bonten MJM, Kluytmans JAJW (2012) For whom should we use selective decontamination of the digestive tract? Current opinion in infectious diseases 25: 211-7.	Not a primary study
Duarte H, Santos C, Capelas ML et al. (2012) Peristomal infection after percutaneous endoscopic gastrostomy: a 7-year surveillance of 297 patients. Arquivos de gastroenterologia 49: 255-8.	Wound culture.
Dubey R, Jalili VP, Jain S et al. (2012) Transient bacteremia consequent to tooth brushing in orthodontic patients. Progress in orthodontics 13: 237-45.	Not relevant – everyday activities.
Eswara JR, Lee H, Dretler SP et al. (2013) The effect of delayed percutaneous nephrolithotomy on the risk of bacteremia and sepsis in patients with neuromuscular disorders. World journal of urology 31: 1611-5.	Not about interventional procedures.
Fernandez-Esparrach G, Sendino O, Araujo I et al. (2014) Incidence of bacteremia in cirrhotic patients undergoing upper endoscopic ultrasonography. Gastroenterologia y Hepatologia 37: 327-33.	Cannot tease out the uncontaminated blood sample from the contaminated ones from

Reference	Reason for exclusion
	the study.
Georgiou I, Farber N, Mendes D et al. (2008) The role of antibiotics in rhinoplasty and septoplasty: a literature review. Rhinology 46: 267-70.	Do not meet review protocol – used as cross reference.
Grabe M, Botto H, Cek M et al. (2012) Preoperative assessment of the patient and risk factors for infectious complications and tentative classification of surgical field contamination of urological procedures. World journal of urology 30: 39-50.	Not relevant.
Guay DR (2012) Antimicrobial prophylaxis in noncardiac prosthetic device recipients. Hospital practice (1995) 40: 44-74.	Not relevant.
Hernandez-Roca JJ, Garcia-Vazquez E, Hernandez A et al. (2013) Bacteraemia at a second level hospital: Epidemiological study, analysis of pronostic factors associated to mortality and economic cost estimation. Revista Espanola de Quimioterapia 26: 119-27.	Not in English.
Horcajada JP, Busto M, Grau S et al. (2009) High prevalence of extended-spectrum beta-lactamase-producing enterobacteriaceae in bacteremia after transrectal ultrasound-guided prostate biopsy: a need for changing preventive protocol. Urology 74: 1195-9.	Only selected blood samples, not whole study population.
Horliana ACRT, Chambrone L, Foz AM et al. (2014) Dissemination of periodontal pathogens in the bloodstream after periodontal procedures: A systematic review. PloS one 9	Do not match the review protocol – used as cross checking.
Ibrahim AIA, Rashid M (2002) Comparison of local povidone-iodine antisepsis with parenteral antibacterial prophylaxis for prevention of infective complications of TURP: A prospective randomized controlled study. European urology 41: 250-6.	Only post-procedure blood sample, no pre-procedure.
Jeremiah CJ, Spelman DW, Royce PL et al. (2013) Gentamicin and norfloxacin prophylaxis for transrectal ultrasound-guided prostate biopsy. Healthcare Infection 18: 67-71.	Unclear whther blood sample or urine sample.
Jones DJ, Munro CL, Grap MJ et al. (2010) Oral care and bacteremia risk in mechanically ventilated adults. Heart & lung : the journal of critical care 39: S57-S65.	About everyday activities.
Jongerden IP, Buiting AG, Leverstein-Van Hall MA et al. (2011) Effect of open and closed endotracheal suctioning on cross-transmission with Gram-negative bacteria: A prospective crossover study. Critical care medicine 39: 1313-21.	No blood sample, only aspirate sample.
Juanjuan D, Zhiyong Z, Xiaoju L et al. (2007) Retrospective analysis of bacteremia because of Enterobacter cloacae compared with Escherichia coli bacteremia. International journal of clinical practice 61: 583-8.	Not relevant – not about any interventional procedures.
Kamizono K, Sakuraba M, Nagamatsu S et al. (2014) Statistical analysis of surgical site infection after head and neck reconstructive surgery. Annals of Surgical Oncology 21: 1700-5.	Not relevant – about surgical site infection.
Kanjanawongdeengam P, Viseshsindh W, Santanirand P et al. (2009) Reduction in bacteremia rates after rectum sterilization before transrectal, ultrasound-guided prostate biopsy: a randomized controlled trial. Journal of the Medical Association of Thailand = Chotmaihet thangphaet 92: 1621-6.	Not relevant – study population had prophylaxis.
Kava BR, Kanagarajah P, Ayyathurai R (2011) Contemporary revision penile prosthesis surgery is not associated with a high risk of implant colonization or infection: a single-surgeon series. The journal of sexual medicine 8: 1540-6.	No blood sample.
Khatib R, Sharma M (2013) Echocardiography is dispensable in uncomplicated Staphylococcus aureus bacteremia. Medicine 92: 182-8.	Cardiac procedures – excluded from the scope.
Klug TE, Henriksen JJ, Rusan M et al. (2012) Bacteremia during	Only post-procedure blood

Reference	Reason for exclusion
quinsy and elective tonsillectomy: an evaluation of antibiotic prophylaxis recommendations for patients undergoing tonsillectomy. Journal of cardiovascular pharmacology and therapeutics 17: 298-302.	sample, no pre-procedure.
Kusachi S, Sumiyama Y, Takahashi Y et al. (2012) Evaluation of the efficacy and safety of intravenous ciprofloxacin versus meropenem in the treatment of postoperative infection. Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy 18: 152-9.	Not relevant – about surgical site infection.
Lee BS, Hwang J-H, Lee SH et al. (2013) Risk factors of organ failure in patients with bacteremic cholangitis. Digestive diseases and sciences 58: 1091-9.	Not relevant – not about any interventional procedures.
Lee MK, Ide M, Coward PY et al. (2008) Effect of ultrasonic debridement using a chlorhexidine irrigant on circulating levels of lipopolysaccharides and interleukin-6. Journal of clinical periodontology 35: 415-9.	No extractable data on blood sample.
Lin Y-T, Jeng Y-Y, Lin M-L et al. (2010) Clinical and Microbiological Characteristics of Chryseobacterium indologenes Bacteremia. Journal of Microbiology, Immunology and Infection 43: 498-505.	Not about interventional procedures.
Llach J, Bordas JM, Almela M et al. (2006) Prospective assessment of the role of antibiotic prophylaxis in ERCP. Hepato-gastroenterology 53: 540-2.	About prophylaxis.
Lodi G, Figini L, Sardella A et al. (2012) Antibiotics to prevent complications following tooth extractions. The Cochrane database of systematic reviews 11: CD003811.	Not relevant – not about bacteraemia.
Loffler C, Bohmer F, Hornung A et al. (2014) Dental care resistance prevention and antibiotic prescribing modification-the cluster-randomised controlled DREAM trial. Implementation science : IS 9: 27.	Not relevant
Lorente L, Jimenez A, Martin MM et al. (2009) Influence of tracheostomy on the incidence of central venous catheter-related bacteremia. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology 28: 1141-5.	Unclear data on blood samples.
Matveychuk A, Guber A, Talker O et al. (2014) Incidence of bacteremia following bronchoscopy with argon plasma coagulation: A prospective study. Lung 192: 615-8.	Only post-procedure blood sample, no pre-procedure.
Nishigaki E, Abe T, Yokoyama Y et al. (2014) The detection of intraoperative bacterial translocation in the mesenteric lymph nodes is useful in predicting patients at high risk for postoperative infectious complications after esophagectomy. Annals of surgery 259: 477-84.	Not relevant – study population had prophylaxis.
Oliver R, Roberts GJ, Hooper L et al. (2008) Antibiotics for the prophylaxis of bacterial endocarditis in dentistry. The Cochrane database of systematic reviews : CD003813.	About prophylaxis.
Rochlen GK, Keenan AV (2014) Value of prophylactic antibiotics for invasive dental procedures unclear. Evidence-based dentistry 15: 12-3.	About prophylaxis.
Saha S, Jagannath GV, Sahana S et al. (2012) Relationship between periodontal infections and atherosclerosis - A review. Indian Journal of Public Health Research and Development 3: 111-3.	Not a primary research.
Sang JK, Sun IK, Hyun SA et al. (2010) Risk factors for acute prostatitis after transrectal biopsy of the prostate. Korean journal of urology 51: 426-30.	Unclear whether blood sample or urine sample.
Schaeffer AJ, Montorsi F, Scattoni V et al. (2007) Comparison of a 3-day with a 1-day regimen of an extended-release formulation of	No blood sample.

Reference	Reason for exclusion
ciprofloxacin as antimicrobial prophylaxis for patients undergoing transrectal needle biopsy of the prostate. BJU international 100: 51-7.	
Segers P, Speekenbrink RGH, Ubbink DT et al. (2006) Prevention of nosocomial infection in cardiac surgery by decontamination of the nasopharynx and oropharynx with chlorhexidine gluconate: A randomized controlled trial. Journal of the American Medical Association 296: 2460-6.	Cardiac procedures – excluded from the scope.
Steinfort DP, Johnson DF, Irving LB (2010) Incidence of bacteraemia following endobronchial ultrasound-guided transbronchial needle aspiration. The European respiratory journal 36: 28-32.	Only post-procedure blood sample, no pre-procedure.
Templeton A, Schlegel M, Fleisch F et al. (2008) Multilumen central venous catheters increase risk for catheter-related bloodstream infection: prospective surveillance study. Infection 36: 322-7.	Not relevant – not about any interventional procedures.
Tomas C, I, Alvarez M, Limeres J et al. (2007) Effect of a chlorhexidine mouthwash on the risk of postextraction bacteremia. Infection Control and Hospital Epidemiology 28: 577-82.	Already in the original guideline.
Tomas I, Diz P, Tobias A et al. (2012) Periodontal health status and bacteraemia from daily oral activities: systematic review/meta-analysis. Journal of clinical periodontology 39: 213-28.	Not relevant – about daily activities.
Wagenlehner FME, van Oostrum E, Tenke P et al. (2013) Infective complications after prostate biopsy: outcome of the Global Prevalence Study of Infections in Urology (GPIU) 2010 and 2011, a prospective multinational multicentre prostate biopsy study. European urology 63: 521-7.	Not relevant – not about bacteraemia.
Yang M, Zhao X, Wu Z et al. (2009) Meta-analysis of antibiotic prophylaxis use in transrectal prostatic biopsy. Zhong nan da xue xue bao.Yi xue ban = Journal of Central South University.Medical sciences 34: 115-23.	Not relevant – about prophylaxis.

F.41 Review question 5

Study	Reason for Exclusion
Crasta K, Daly CG., Mitchell D, Curtis B, Stewart D, Heitz-Mayfield L. (2009) Bacteraemia due to dental flossing, Journal of clinical periodontologyJ Clin Periodontol, 36, 323-332.	Study does not assess an everyday activity specified in the protocol but flossing instead
Dubey R, Jalili VP, Jain S, Dubey A. (2012) Transient bacteremia consequent to tooth brushing in orthodontic patients, Progress in orthodonticsProg Orthod, 13, 237-245.	No outcomes of interest - study focuses on microbial identity but numbers of each bacteria detected are unclear (poor reporting). Also, unclear whether the different arms of the study did toothbrushing as an isolated procedure before any orthodontic treatment, thus increasing the possibility for confounding bacteraemia from other procedures.
Elram T, Livne A, Oren A, Gross I, Shapiro M, Mankuta D. (2008) Labor as a bacteriuric event--assessment and risk factors, The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal ObstetriciansJ Matern Fetal Neonatal Med, 21, 483-486.	Study assesses labour which is not an everyday activity
Garcia S, McKenzie J, Patterson T, Rohde R (2012) Snapshot prevalence and characterization of Staphylococcus species,	Study does not assess an everyday activity specified in the protocol but bacteria levels found on various exercise equipment within a

including MRSA, in a student athletic facility: an undergraduate research project, Clinical laboratory science : journal of the American Society for Medical TechnologyClin Lab Sci, 25, 156-164	student athletic facility
Gondhalekar R, Richard,K.M.J., Jayachandra,M.G., Aslam S, Reddy V, Barabde A (2013) Effect of tongue cleaning methods and oral mutans streptococci level, The journal of contemporary dental practiceJ Contemp Dent Pract, 14, 119-122.	Study does not assess an everyday activity specified in the protocol and also does not examine bacteraemia but bacteria in the saliva.
Ipe D, Sundac L, Benjamin W, Moore K, Ulett,G (2013) Asymptomatic bacteriuria: prevalence rates of causal microorganisms, etiology of infection in different patient populations, and recent advances in molecular detection, FEMS microbiology lettersFEMS Microbiol Lett, 346, 1-10	Study requested for reference purposes (does not meet the criteria specified in protocol)
Jones DJ, Munro CL (2008) Oral care and the risk of bloodstream infections in mechanically ventilated adults: A review, Intensive & critical care nursing : the official journal of the British Association of Critical Care NursesIntensive Crit Care Nurs, 24, 152-161	Review requested for reference purposes
Lear A, McCord G, Peiffer J, Watkins R, Parikh A, Warrington S (2011) Incidence of Staphylococcus aureus nasal colonization and soft tissue infection among high school football players, Journal of the American Board of Family Medicine : JABFMJ Am Board Fam Med, 24, 429-435	Study does not assess an everyday activity specified in the protocol and is also of case series design
Lockhart P, Brennan M, Thornhill M, Michalowicz B, Noll J, Bahrani-Mougeot F, Sasser H (2009) Poor oral hygiene as a risk factor for infective endocarditis-related bacteremia, Journal of the American Dental Association (1939)J Am Dent Assoc, 140, 1238-1244	Further results of a previously published study (Lockhart et al., 2008) - no other outcomes of interest were identified in this later publication.
Matthews D (2012) Impact of everyday oral activities on the risk of bacteraemia is unclear, Evidence-based dentistryEvid.- based dent., 13, 80	Commentary of a review article (Tomas et al.,2012) requested for reference purposes
Rupesh,S., Winnier,J.J., Nayak,U.A., Rao,Ap, Reddy,V., Peter,J. (2012) The comparative evaluation of the effects of tongue cleaning on salivary levels of mutans streptococci in children, International journal of dental hygieneInt.j.dent.hyg., 10, 107-112	Study does not assess bacteraemia but bacteria in the saliva instead - therefore this study does not meet the criteria specified in the protocol
Schechter-Perkins,EM, Mitchell,PM, Murray K A., Rubin-Smith JE, Weir S, Gupta K (2011) Prevalence and predictors of nasal and extranasal staphylococcal colonization in patients presenting to the emergency department, Annals of emergency medicineAnn Emerg Med, 57, 492-499	Study looks at contact sports as a risk factor for bacteria colonisation - this is not an everyday activity of interest and bacteraemia is not assessed either.
Tomas I, Diz P, Tobias A, Scully C, Donos N (2012) Periodontal health status and bacteraemia from daily oral activities: systematic review/meta-analysis, Journal of clinical	Review for reference purposes: individual studies checked for inclusion

periodontologyJ Clin Periodontol, 39, 213-228	
Zhang W, Daly CG, Mitchell D, Curtis B (2013) Incidence and magnitude of bacteraemia caused by flossing and by scaling and root planing, Journal of clinical periodontologyJ Clin Periodontol, 40, 41-52	Study does not assess an everyday activity specified in the protocol but flossing compared with scaling and root planning instead

F.51 Review question 6a and 7a

Study	Reason for Exclusion
ACOG practice bulletin No. 104 (2009) Antibiotic prophylaxis for gynecologic procedures, Obstetrics and GynecologyObstet.Gynecol., 113, 1180-1189	Narrative review
Aghamir,S.M., Hamidi,M., Salavati,A., Mohammadi,A., Farahmand,H., Meysamie,A.P., Ghorbani,B (2011) Is antibiotic prophylaxis necessary in patients undergoing ureterolithotripsy?, Acta Medica Iranica, 49, 513-516	Blood cultures only taken in subjects with fever (n=1) therefore bacteraemia not assessed in all subjects
Allison,M.C., Sandoe,J.A.T., Tighe,R., Simpson,I.A., Hall,R.J., Elliott,T.S.J. (2009) Antibiotic prophylaxis in gastrointestinal endoscopy, Gut, 58, 869-880	Summary of various existing guidelines
Alsaywid,B.S., Smith,G.H., (2013) Antibiotic prophylaxis for transurethral urological surgeries: Systematic review, Urology annals, 5, 61-74	Review article: relevant studies included in this review have been checked for inclusion/exclusion
Anitua,E., Aguirre,J.J., Gorosabel,A., Barrio,P., Errazquin,J.M., Roman,P., Pla,R., Carrete,J., de,Petro J., Orive,G., (2009) A multicentre placebo-controlled randomised clinical trial of antibiotic prophylaxis for placement of single dental implants, European Journal of Oral Implantology, 2, 283-29	Study does not assess bacteraemia nor IE
Bach,D.S., (2010) Antibiotic prophylaxis for infective endocarditis: ethical care in the era of revised guidelines, Methodist DeBakey cardiovascular journal, 6, 48-52	Narrative review requested for reference
Baecher,L., Grobman,W., (2008) Prenatal antibiotic treatment does not decrease group B streptococcus colonization at delivery, International Journal of Gynaecology & Obstetrics, 101, 125-128	Study does not assess bacteraemia nor IE
Bai,Y., Gao,F., Gao,J., Zou,D.W., Li,Z.S., (2009) Prophylactic antibiotics cannot prevent endoscopic retrograde cholangiopancreatography-induced cholangitis: a meta-analysis, Pancreas, 38, 126-130	Meta-analysis - no studies of interest
Brand,M., Bizos,D., O'Farrell,P.,Jr., (2010) Antibiotic prophylaxis for patients undergoing elective endoscopic retrograde cholangiopancreatography. [Review], Cochrane Database of Systematic Reviews	Review article: relevant studies included in this review have been checked for inclusion/exclusion
Brennan,M.T., Kent,M.L., Fox,P.C., Norton,H.J., Lockhart,P.B., (2007) The impact of oral disease and nonsurgical treatment on bacteremia in children, Journal of the American Dental	Secondary analysis of Lockhart 2004 (same data)

Association (1939)J Am Dent Assoc, 138, 80-85	
Brooks,N., (2009) Prophylactic antibiotic treatment to prevent infective endocarditis: New guidance from the national institute for health and clinical excellence, Heart.95 (9) (pp 774-780)	Summary of NICE 2008 guidance
CADTH (2013) Antibiotic prophylaxis for patients with cardiac or orthopedic implants undergoing dental procedures: a review of the clinical effectiveness and guidelines (Structured abstract), Health Technology Assessment Database	Review article: relevant studies included in this review have been checked for inclusion/exclusion
Dinsbach,N.A., (2008) Antibiotics in dentistry: Bacteremia, antibiotic prophylaxis, and antibiotic misuse. [Review], General Dentistry, 60, 200-207	Review article requested for reference
Diz,P., Alvarez,J., Limeres,J., Feijoo,J.F., Castro,M., Vazquez,E., (2013) A new antimicrobial prophylactic regimen to prevent bacteraemia following dental procedures [abstract], European heart journal, Conference: European Society of Cardiology, ESC Congress 2013 Amsterdam Netherlands. Conference Start: 20130831 Conference End: 20130904. Conference Publication:, 861-862	Conference abstract
Ellervall,E., Vinge,E., Rohlin,M., Knutsson,K., (2010) Antibiotic prophylaxis in oral healthcare - the agreement between Swedish recommendations and evidence. [Review] [32 refs], British Dental Journal, 208, E5-E5	Review article: relevant studies included in this review have been checked for inclusion/exclusion
Esposito,M., Cannizzaro,G., Bozzoli,P., Consolo,U., Felice,P., Ferri,V., Landriani,S., Leone,M., Magliano,A., Pellitteri,G., Todisco,M., Torchio,C., (2008) Efficacy of prophylactic antibiotics for dental implants: a multicentre placebo-controlled randomised clinical trial, European Journal of Oral Implantology, 1, 23-31	Study does not assess bacteraemia nor IE
Esposito,M., Grusovin,M.G., Coulthard,P., Oliver,R., Worthington,H.V., (2008) The efficacy of antibiotic prophylaxis at placement of dental implants: a Cochrane systematic review of randomised controlled clinical trials. [Review] [18 refs], European Journal of Oral Implantology, 1, 95-103	Review article - studies included do not assess bacteraemia nor IE
Farbod,F., Kanaan,H., Farbod,J., (2009) Infective endocarditis and antibiotic prophylaxis prior to dental/oral procedures: latest revision to the guidelines by the American Heart Association published April 2007, International Journal of Oral and Maxillofacial SurgeryInt.J.Oral Maxillofac.Surg., 38, 626-631	Review of existing guidelines
Glenny,Anne Marie, Oliver,Richard, Roberts,Graham J., Hooper,Lee, Worthington,Helen,V, (2013) Antibiotics for the prophylaxis of bacterial endocarditis in dentistry, Cochrane Database of Systematic ReviewsCochrane Database Syst.Rev.,	No relevant studies
Gopalakrishnan,P.P., Shukla,S.K., Tak,T.,	Narrative review: comparison of existing

(2009) Infective endocarditis: Rationale for revised guidelines for antibiotic prophylaxis, Clinical Medicine and Research, 7, 63-6	guidelines
Gregoriou,O., Bakas,P., Grigoriadis,C., Creatsa,M., Sofoudis,C., Creatsas,G., (2012) Antibiotic prophylaxis in diagnostic hysteroscopy: is it necessary or not?, European Journal of Obstetrics, Gynecology, & Reproductive Biology, 163, 190-192	Study does not assess bacteraemia nor IE
Gregoriou,O., Vlahos,N., Bakas,P., Grigoriadis,C., Gregoriou,V., Liapis,A., Creatsas,G., (2012) The role of antibiotic prophylaxis in operative hysteroscopy, Gynecological surgery, 9, S99-	Abstract only (also does not assess bacteraemia)
Harrison,J.L., Hoen,B., Prendergast,B.D., (2008) Antibiotic prophylaxis for infective endocarditis, Lancet, 371, 1317-1319	Commentary
Juthani-Mehta,M., (2013) Should antibiotic prophylaxis after urinary catheter removal be standard practice?, BMJ (Online).346 (7914)	Narrative review, no data of interest to this review question
Kanazawa,H., (2007) Efficacy of azithromycin administration in prevention of respiratory tract infection after bronchoscopic biopsy: a randomized, controlled trial, Respirology (Carlton, Vic.), 12, 70-75	Study does not assess bacteraemia nor IE
Legout,L., Beltrand,E., Migaud,H., Senneville,E., (2012) Antibiotic prophylaxis to reduce the risk of joint implant contamination during dental surgery seems unnecessary. [Review], Orthopaedics & traumatology, surgery & research, 98, 910-914	Literature review for reference
Llach,J., Bordas,J.M., Almela,M., Pellise,M., Mata,A., Soria,M., Fernandez-Esparrach,G., Gines,A., Elizalde,J.I., Feu,F., Pique,J.M., (2006) Prospective assessment of the role of antibiotic prophylaxis in ERCP, Hepato-gastroenterologyHepatogastroenterology, 53, 540-542	Comparator not as specified in protocol
Lodi,G., Figini,L., Sardella,A., Carrassi,A., Del,Fabbro M., Furness,S., (2012) Antibiotics to prevent complications following tooth extractions. [Review], Cochrane Database of Systematic Reviews, 11, CD003811-	Review article: relevant studies included in this review have been checked for inclusion/exclusion
Niederau C, Pohlmann U, Lubke H et al. (1994) Prophylactic antibiotic treatment in therapeutic or complicated diagnostic ERCP: results of a randomized controlled clinical study.[see comment]. Gastrointestinal Endoscopy 40: 533-7	This study is included in the Harris 1999 meta-analysis
Oliver,R., Roberts,G.J., Hooper,L., Worthington,H.V., (2008) Antibiotics for the prophylaxis of bacterial endocarditis in dentistry, Cochrane Database of Systematic Reviews	Review article: relevant studies included in this review have been checked for inclusion/exclusion
Pitak-Arnnop,P., Pausch,N.C., Dhanuthai,K., Neff,A., (2013) Oral amoxicillin as antibiotic prophylaxis before dental surgery - "faux pas" or "dernier cri"?, Revue de Stomatologie, de Chirurgie Maxillo-faciale et de Chirurgie Orale,	Narrative review

114, 338-340	
Rochlen,G.K., Keenan,A.V., (2014). Value of prophylactic antibiotics for invasive dental procedures unclear, Evidence-Based Dentistry, 15, 12-13	Commentary
Schaeffer,A.J., Montorsi,F., Scattoni,V., Perroncel,R., Song,J., Haverstock,D.C., Pertel,P.E., (2007) Comparison of a 3-day with a 1-day regimen of an extended-release formulation of ciprofloxacin as antimicrobial prophylaxis for patients undergoing transrectal needle biopsy of the prostate, BJU internationalBJU Int, 100, 51-57	Comparator not as specified in protocol. Also, study does not assess bacteraemia nor IE.
Sauter G, Grabein B, Huber G et al. (1990) Antibiotic prophylaxis of infectious complications with endoscopic retrograde cholangiopancreatography. A randomized controlled study. Endoscopy 22: 164-7.	This study is included in the Harris 1999 meta-analysis.
Smaill,F.M., Gyte,G.M., (2010) Antibiotic prophylaxis versus no prophylaxis for preventing infection after cesarean section. [Review] [177 refs], Cochrane Database of Systematic Reviews, CD007482	Review article: relevant studies included in this review have been checked for inclusion/exclusion
Smaill,Fiona M., Grivell,Rosalie M., (2014) Antibiotic prophylaxis versus no prophylaxis for preventing infection after cesarean section, Cochrane Database of Systematic Reviews	Review - studies included in this review do not assess bacteraemia nor incidence of IE as an outcome
Strom BL AEBJeal (1998) Dental and cardiac risk factors for infective endocarditis: a population- based case-control study. Ann Int Med 1998	It is not clear whether those with and without antibiotics were those with underlying cardiac conditions; therefore population not met.
Tempelhof,M.W., Reeves,G., (2012) Infective endocarditis and antibiotic prophylaxis: A systematic review of efficacy and safety of the AHA guidelines, Research Journal of Medical SciencesRes.J.Med.Sci., 6, 193-202	Review of AHA guidelines
Tomas,Carmona,I, Diz,Dios P., Scully,C., (2007) Efficacy of antibiotic prophylactic regimens for the prevention of bacterial endocarditis of oral origin. [Review] [175 refs], Journal of Dental Research, 86, 1142-1159	Review requested for reference
Wagenlehner,F.M.E., Wagenlehner,C., Schinzel,S., Naber,K.G., Bach,D., Basting,R., Bruns,T., Friesen,A., Hofstetter,A.G., Keller,H.J., Peters,H.J., Rothenberger,K.H., Schmitz,H.J., Seiter,H.-J., Sinagowitz,E., Tauber,R., Wittenberger,R., (2005) Prospective, randomized, multicentric, open, comparative study on the efficacy of a prophylactic single dose of 500 mg levofloxacin versus 1920 mg trimethoprim/sulfamethoxazole versus a control group in patients undergoing TUR of the prostate, European urologyEur Urol, 47, 549-556	Study does not assess bacteraemia but bacteruria
Xu,H.W., Wang,J.H., Tsai,M.S., Wu,K.L., Chiou,S.S., Changchien,C.S., Hu,T.H., Lu,S.N., Chuah,S.K., (2011) The effects of cefazolin on cirrhotic patients with acute variceal hemorrhage	Study design not as specified in protocol. This was a cross sectional retrospective chart review.

after endoscopic interventions, Surgical Endoscopy, 25, 2911-2918	
Yang,M., Zhao,X., Wu,Z., Xiao,N., Lu,C., 2009, Meta-analysis of antibiotic prophylaxis use in transrectal prostatic biopsy, Zhong Nan da Xue Xue Bao, Yi, 115-123	Meta-analysis: no new (post 2008) relevant studies
Zani,E.L., Clark,O.A., Rodrigues,Netto N.,Jr., (2011) Antibiotic prophylaxis for transrectal prostate biopsy. [Review], Cochrane Database of Systematic Reviews, CD006576-	Review article: relevant studies included in this review have been checked for inclusion/exclusion
Hall, G., Nord, CE., Heimdahl, A. (1996) Elimination of bacteraemia after dental extraction: comparison of erythromycin and clindamycin for prophylaxis of infective endocarditis. Journal of Antimicrobial Chemotherapy, 37, 783-795, [included in CG64]	Comparator not as specified in protocol
Roberts, G., Holzel, H.(2002) Intravenous antibiotic regimens and prophylaxis of odontogenic bacteremia. British Dental Journal, 193, 525-527 [included in CG64]	Comparator not as specified in protocol
Brewster, SF., Macgowan, AP., Gingell, JC. (1995) Antimicrobial prophylaxis for transrectal prostatic biopsy: a prospective randomised trial of cefuroxime versus piperacillin/tazobactam, 76, 351-354 [included in CG64]	Comparator not as specified in protocol
Duvall, X., Alla, F et al (2006) Estimated risk of endocarditis in adults with predisposing cardiac conditions undergoing dental procedures with or without antibiotic prophylaxis. Clinical infectious diseases, 42 [included in CG64]	Cross sectional study
Van der Meer, JTM. et al (1992) Epidemiology of bacterial endocarditis in the Netherlands. Arch Intern Med. 152, 1869-1873 [included in CG64]	Case series study design
Glenny, AM., Oliver, R., Roberts, GJ., Hooper, L., Worthington, HV (2004) Antibiotics for the prophylaxis of bacterial endocarditis in dentistry [Review], Cochrane Database of Systematic Reviews, CD003813-[included in CG64]	Study included in this Cochrane review has been reviewed separately

F.61 Review question 6b and 7b

Study	Reason for Exclusion
Attin,R., Yetkiner,E., Aykut-Yetkiner,A., Knosel,M., Attin,T., (2013) Effect of chlorhexidine varnish application on streptoococcus mutans colonisation in adolescents with fixed orthodontic appliances, Australian Orthodontic Journal, 29, 52-57	Study does not assess bacteraemia nor IE
Bebek,B., Bago,I., Skaljac,G., Plecko,V., Miletic,I., Anic,I., (2009) Antimicrobial effect of 0.2% chlorhexidine in infected root canals, Collegium Antropologicum, 33, 1159-1163	Study does not assess bacteraemia nor IE
Beus,C., Safavi,K., Stratton,J., Kaufman,B., (2012) Comparison of the effect of two endodontic irrigation protocols on the elimination of bacteria from root canal system: a prospective, randomized clinical trial, Journal of Endodontics, 38, 1479-1483	Study does not assess bacteraemia nor IE

Cabov,T., Macan,D., Husedzinovic,I., Skrlin-Subic,J., Bosnjak,D., Sestan-Crnek,S., Peric,B., Kovac,Z., Golubovic,V., (2010) The impact of oral health and 0.2% chlorhexidine oral gel on the prevalence of nosocomial infections in surgical intensive-care patients: a randomized placebo-controlled study, Wiener Klinische Wochenschrift, 122, 397-404	Study does not assess bacteraemia nor did the subjects undergo an interventional procedure
Cosyn,J., Sabzevar,M.M., (2007) Subgingival chlorhexidine varnish administration as an adjunct to same-day full-mouth root planing. II. Microbiological observations, Journal of periodontologyJ Periodontol, 78, 438-445	Study does not assess bacteraemia nor IE
Devker,N.R., Mohitey,J., Vibhute,A., Chouhan,V.S., Chavan,P., Malagi,S., Joseph,R., (2012), A study to evaluate and compare the efficacy of preprocedural mouthrinsing and high volume evacuator attachment alone and in combination in reducing the amount of viable aerosols produced during ultrasonic scaling procedure, Journal of Contemporary Dental Practice [Electronic Resource], 13, 681-689	Study does not assess bacteraemia nor IE
Diz,P., Tomas,I., Barbosa,M., Amaral,B., Cerqueira,C., Limeres,J., Alvarez,M., A (2007) chlorhexidine mouthwash reduces the risk of bacteraemia following dental extractions performed unter either general or local anaesthesia, Clinical research in cardiology, 96, 443	Abstract only
Duss,C., Lang,N.P., Cosyn,J., Persson,G.R., (2010) A randomized, controlled clinical trial on the clinical, microbiological, and staining effects of a novel 0.05% chlorhexidine/herbal extract and a 0.1% chlorhexidine mouthrinse adjunct to periodontal surgery, Journal of Clinical Periodontology, 37, 988-997	Comparator not as specified in protocol. Also, study does not assess bacteraemia.
Fedorowicz,Zbys, Nasser,Mona, Sequeira,Byron Patrick, de-Souza,Raphael Freitas, Carter,Ben, Heft,Marc, Irrigants for non-surgical root canal treatment in mature permanent teeth, Cochrane Database of Systematic Reviews, -, 2012	No relevant studies
Feres,M., Figueiredo,L.C., Faveri,M., Stewart,B., de,Vizio W., (2010) The effectiveness of a preprocedural mouthrinse containing cetylpyridinium chloride in reducing bacteria in the dental office, Journal of the American Dental Association, 141, 415-422	Study does not assess bacteraemia nor IE
Guarnelli,M.E., Franceschetti,G., Manfrini,R., Trombelli,L., (2008) Adjunctive effect of chlorhexidine in ultrasonic instrumentation of aggressive periodontitis patients: a pilot study, Journal of Clinical Periodontology, 35, 333-341	Study does not assess bacteraemia nor IE
Jolly,M., Singh,N., Rathore,M., Tandon,S., Banerjee,M., (2013) Propolis and commonly used intracanal irrigants: comparative evaluation of antimicrobial potential, Journal of Clinical Pediatric Dentistry, 37, 243-249	Study does not assess bacteraemia nor IE
Kusahara,D.M., Friedlander,L.T., Peterlini,M.A.,	Study does not assess bacteraemia nor did the

Pedreira,M.L., (2012). Oral care and oropharyngeal and tracheal colonization by Gram-negative pathogens in children, Nursing in Critical Care, 17, 115-122	subjects undergo an interventional procedure
Lee,M.K., Ide,M., Coward,P.Y., Wilson,R.F., (2008) Effect of ultrasonic debridement using a chlorhexidine irrigant on circulating levels of lipopolysaccharides and interleukin-6, Journal of Clinical Periodontology, 35, 415-419	Study does not assess bacteraemia specifically but a surrogate outcome (lipopolysaccharide levels)
Matesanz,P., Herrera,D., Echeverria,A., O'Connor,A., Gonzalez,I., Sanz,M., (2013) A randomized clinical trial on the clinical and microbiological efficacy of a xanthan gel with chlorhexidine for subgingival use, Clinical Oral Investigations, 17, 55-66	Study does not assess bacteraemia nor IE
Paiva,S.S., Siqueira,J.F.,Jr., Rocas,I.N., Carmo,F.L., Ferreira,D.C., Curvelo,J.A., Soares,R.M., Rosado,A.S., (2012) Supplementing the antimicrobial effects of chemomechanical debridement with either passive ultrasonic irrigation or a final rinse with chlorhexidine: a clinical study, Journal of Endodontics, 38, 1202-1206	Study does not assess bacteraemia nor IE
Paolantonio,M., Perinetti,G., D'Ercole,S., Graziani,F., Catamo,G., Sammartino,G., Piccolomini,R., (2008) Internal decontamination of dental implants: an in vivo randomized microbiologic 6-month trial on the effects of a chlorhexidine gel, Journal of Periodontology, 79, 1419-1425	Study does not assess bacteraemia nor IE
Swierkot,K., Nonnenmacher,C.I., Mutters,R., Flores-de-Jacoby,L., Mengel,R,. (2009) One-stage full-mouth disinfection versus quadrant and full-mouth root planing, Journal of Clinical Periodontology, 36, 240-249	Study does not assess bacteraemia nor IE

1

1 Appendix G: Evidence tables

G.1 2 Review question 1a and 1b

3 **Table 33: THIS STUDY IS ALSO INCLUDED FOR Q2.**

Bibliographic reference	**Alagna, L et al. (2014) Repeat endocarditis: analysis of risk factors based on the International collaboration of Endocarditis – Prospective Cohort Study. Clinical Microbiology and Infection. 20: 566-575.**
Study type	Prospective cohort study
Aim	Describe clinical characteristics, identify risk factors and examine 1 year mortality of patients with repeat IE.
Patient characteristics	Patients enrolled in International Collaboration on Endocarditis – Prospective Cohort Study (ICE-PCS) with definite diagnosis of native (NVE) or prosthetic valve IE (PVE) (Duke Criteria) and 1 year follow-up data. New IE cases occurring within 10 weeks from initial episode were included (arbitrary threshold). ***Relapse*** defined as new episode caused by same bacterial species, within 6 months of the first episode. ***Presumed new infection*** was defined as new IE caused by a different bacterial species OR by the same bacterial species >6 months from the initial episode. **Exclusion Criteria** Missing data at one year (2521/5594), intra-cardiac lead IE (N=270) as repeat IE could be related to a retained device, missing information on IE type (n=49), bacterial culture negative for the suspected second episode as it was impossible to differentiate between relapse and new infection (n=8).
Number of patients	1874 patients had a complete data set. Of these 174 patients had repeat IE, minus exclusions, 91 patients (4.8%) with repeat IE were included. Presumed relapse (n=17), presumed new infection (n=74).
Outcomes	Single episodes of IE and Recurrent IE
Predictors/risk factors and effect estimates	**Bivariate and multivariate analysis comparing patients with single episode IE with repeat IE patients**

Bibliographic reference	**Alagna, L et al. (2014) Repeat endocarditis: analysis of risk factors based on the International collaboration of Endocarditis – Prospective Cohort Study. Clinical Microbiology and Infection. 20: 566-575.**

	Single episode IE	**Repeat IE (Recurrence or relapse)**	**P-value**	**Multivariate model odds ratio (95%CI)**
Sample	1783 (95)	91 (4.8)		Not reported
Male sex	1213 (68)	63 (69)	0.90	Not reported
Age median (25-75th percentiles), yr.	58.7 (45-71)	50.9 (38-66)	0.001	Not reported
Type of valve IE				
Native valve IE	1352 (76)	75 (82)	0.17	Not reported
Prosthetic valve IE 447/1874	431 (24)	16 (18)		
History of previous endocarditis	135 (7.4)	17 (19)	0.001	2.8 (1.5-5.1)
History of congenital heart disease 173/1874	165 (9.2)	8 (8.7)	1.00	Not reported

FOR QUESTION 2

Clinical characteristics of patients with repeat endocarditis: bivariate analysis comparing presumed relapse vs. presumed new infection.

	Repeat IE Total	**Presumed new infection**	**Presumed relapse**	**p-value**
Sample [n (%)]	91 (4.8)	74 (4)	17 (0.8)	Not reported
Age [median (25-75th percentiles)]	51 (37-66)	51 (37-66)	49 (33-66)	0.48
Type of Valve IE [n (%)]				
Native valve	75 (82)	58 (78)	17 (100)	**0.03**
Prosthetic Valve	16 (18)	16 (22)	0	
History of previous	17 (19)	17 (23)	0	**0.03**

Bibliographic reference	**Alagna, L et al. (2014) Repeat endocarditis: analysis of risk factors based on the International collaboration of Endocarditis – Prospective Cohort Study. Clinical Microbiology and Infection. 20: 566-575.**
	endocarditis | | | | | History of congenital heart disease | 8 (8.7) | 7 (9) | 1 (6) | 1 Statistically significant increase in recurrence with history of IE on native valve vs prosthetic valve.
Analysis used	Bivariate analysis using Fisher's exact test. Multiple logistic regression used to determine factors associated with repeat IE as well as for mortality. Variables in final adjusted regression models were selected according to statistical significance and clinical judgement.
Length of follow-up	1 year
Location	Data from 64 sites in 28 countries worldwide
Source of funding	The work was supported in part by grants from the American Heart Association and various non-commercial Spanish research organisations.
Comments	**Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))** Study Participation – Y Study attrition – N Authors cite a limitation in the amount of missing data. Prognostic factor measurement – Y. Outcome measurement – Y although follow-up status beyond 1 year was not collected – long enough? Confounding measurement and account – N No data on medical treatment (e.g. antibiotic type/duration) by study arm is provided which could be an important influencer of outcome. Analysis – N Reviewer had to back calculate unadjusted ORs. No sample size calculation. 3/6 met = HIGH RISK OF BIAS

1 **Table 34**

Bibliographic reference	**Ammar, W et al. (2013) Case-Control study of potential culprit procedures for infective endocarditis in an Egyptian tertiary care centre. The Egyptian Heart Journal. 65, 153-157**
Study type	Retrospective case-control study
Aim	To test the hypothesis that underlying medical conditions, not culprit procedures, are the most important risk factor for development of IE.

Bibliographic reference	**Ammar, W et al. (2013) Case-Control study of potential culprit procedures for infective endocarditis in an Egyptian tertiary care centre. The Egyptian Heart Journal. 65, 153-157**
Patient characteristics	175 patients with definite IE (Duke Criteria) from the IE database of the Cardiology Department, Cairo University Hospital (between March 2005 and June 2008) were matched with 175 control cases without IE, matched for age, sex, and underlying heart disease (including prosthetic valves and intra cardiac devices).
Number of patients	350.
Outcomes	IE
Predictors/risk factors and effect estimates	**Clinical characteristics and underlying heart disease between cases and controls**

Variable	IE Case N (%)	Control N (%)	P-value
Number of patients	175	175	n/a
Age (Mean ±SD)	32.13 ±13.76	32.90 ±12.12	NS
Male	102 (58.3)	103 (58.9)	NS
Female	73 (41.7)	72 (41.1)	NS
Known structural heart disease	117 (66.9)	111 (63.4)	NS
Valvular heart disease	53 (30.3)	54 (30.9)	NS
Prosthetic valve	49 (28.0)	45 (25.7)	NS
Congenital heart disease	15 (8.6)	12 (6.9)	NS
No structural heart disease	58 (33.1)	64 (36.6)	NS

Medical co-morbidities associated with increased risk of IE.

Host related risk factors	IE cases N (%)	Controls N (%)	P value	Odds Ratio (95%CI)
Prior endocarditis	9 (5.1)	2 (1.1)	0.032	4.69 (0.998-22.027)

Significant Predictors of IE (adjusted for age and sex)

Predictors for IE	P value	Odds ratio (95%CI)
Prior IE	0.029	**5.841 (1.201-28.411)**

Bibliographic reference	**Ammar, W et al. (2013) Case-Control study of potential culprit procedures for infective endocarditis in an Egyptian tertiary care centre. The Egyptian Heart Journal. 65, 153-157**
Analysis used	Comparisons - continuous variables (normally distributed) - t-tests; categorical variables Pearson's Chi-square test Correlations measured using Pearson's correlation coefficient. No correction for multiple testing.
Length of follow-up	Study duration 2 years 9 months
Location	Cairo
Source of funding	Not specified.
Comments	**Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))** Study Participation – U Retrospective design. Study attrition – Y Prognostic factor measurement – N Clinical data was collected by telephone r/v and this was patient reported for controls. No mention of verification of this data. Outcome measurement – Y Confounding measurement and account – Y Analysis – N Reviewer had to back calculate ORs. No sample size calculation regarding number of controls required. 3/6 met = HIGH RISK OF BIAS

1 **Table 35**

Bibliographic reference	**[from CG64]** **Clemens JD, Horwitz RI, Jaffe CC, et al. (1982) A controlled evaluation of the risk of bacterial endocarditis in persons with mitral-valve prolapse. N Engl J Med 307: 776–81.**
Study type	Case-control
Aim	To evaluate whether mitral valve prolapse is an important risk factor for bacterial endocarditis
Patient characteristics	Cases – n=51. people with bacterial endocarditis and Controls –n=153 people without bacterial endocarditis selected from a group of 4335 adult inpatients. hospital in-patients who had undergone echocardiography and who lacked any known cardiovascular risk factors for endocarditis apart from mitral valve prolapse and isolated mitral-regurgitant murmurs; age ≥15 yrs. at the time of hospital admission [a] **Inclusion:**

Bibliographic reference	[from CG64] **Clemens JD, Horwitz RI, Jaffe CC, et al. (1982) A controlled evaluation of the risk of bacterial endocarditis in persons with mitral-valve prolapse. N Engl J Med 307: 776–81.**
	cases: data extracted from medical records, who fulfilled the diagnostic and/or pathological criteria for bacterial endocarditis controls: selected from those who had undergone echocardiography during the period covered by the study; matched with age, sex and nearest date of echocardiography (excluded those with antecedent heart disease) using first 3 eligible candidates. **Exclusion:** cases: antecedent heart disease acting as a risk factor for endocarditis; discharge diagnosis referable only to episodes occurring in previous admissions; inadequate diagnostic evidence of BE; no echocardiogram controls: antecedent heart disease acting as a risk factor for endocarditis; medical records not located MVP was defined by either auscultatory or echocardiographic data The cases and controls were similar in age and sex, the cases groups had higher proportions of those with a history of parenteral drug use, recommendations for prophylaxis before instrumentation and high-risk cardiovascular lesions that were unsuspected before echocardiography, adjustment was made for these inequalities [b] **Mitral valve prolapse** n = 13 (25%) of the cases and n = 10 (7%) of the controls had mitral valve prolapse. **Bacterial endocarditis diagnosis** was based on pathological documentation and clinical criteria (existence of a heart murmur and at least two blood cultures obtained at separate time indicating the same organism).
Number of patients	n = 204 (cases 51, controls 153)
Predictors	Mitral valve prolapse
Outcomes	Bacterial endocarditis
Analysis used	Calculation of Odds ratios from matched analyses.
Length of follow-up	4yrs of cases Between 1 Nov 1976 and 1 Nov 1980
Location	USA
Effect estimates	In 16 matched sets, the cases and controls were discordant for the presence or absence of mitral-valve prolapse; the matched OR for the association was 8.2 (2.4 to 28.4, CI 95%), p<0.001

Bibliographic reference	**[from CG64]** **Clemens JD, Horwitz RI, Jaffe CC, et al. (1982) A controlled evaluation of the risk of bacterial endocarditis in persons with mitral-valve prolapse. N Engl J Med 307: 776–81.**
	Indicating a substantially higher risk of endocarditis for people with MVP than those without it. Analysis was completed using only the echocardiographic criteria for MVP (the association was unaffected – OR 7.2 (2.1-25.5). and also to adjust for risk factors for endocarditis that were unequally distributed between the cases and the controls - the association remained substantial for both addicts and non addicts. No drug users (per protocol population) Matched **OR 4.7 (1.1-19.5).** (the authors consider that these results demonstrate a substantial association between MVP and BE)
Source of funding	Not stated
Comments	**Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))** Study Participation – N Retrospective. Cases selected from people having had echocardiography during study period, without endocarditis. Unclear other criteria for selection of cases. No sample size calculation although 3 cases were selected for each case. Study attrition – Y Prognostic factor measurement – Y Outcome measurement – Y although study conducted before Duke Criteria developed diagnosis was confirmed with echo. Confounding measurement and account – Y Analysis – N although IVDUs were included, adjustment was made for this. Adjusted ORs were not calculated. No sample size calculation. 4/6 criteria met = LOW RISK OF BIAS

(a)The one exception was the inclusion of those with antecedent findings of isolated mitral regurgitation, since mitral valve prolapse is commonly accompanied by auscultatory findings of mitral regurgitation

(b)The eligibility of patients was determined by a 'blinded' researcher, without knowledge of the echocardiograph findings

Table 36

Bibliographic reference	**[from CG64]** **Hickey AJ, MacMahon SW, Wilcken DE, et al. (1985) Mitral valve prolapse and bacterial endocarditis: when is antibiotic prophylaxis necessary? American Heart Journal 109: 431–35.**
Study type	Case-control
Aim	To investigate the association between mitral valve prolapse (MVP) and bacterial endocarditis.

Bibliographic reference	**[from CG64]** **Hickey AJ, MacMahon SW, Wilcken DE, et al. (1985) Mitral valve prolapse and bacterial endocarditis: when is antibiotic prophylaxis necessary? American Heart Journal 109: 431–35.**
Patient characteristics	**Cases** n = 56 cases [c] (n = 66 met the criteria, n = 10 excluded due to antecedent lesions) Inclusion: cases ≥15yrs admitted to hospital, all who had echocardiography, met the criteria set for diagnosis for endocarditis **Controls** n = 168 controls matched for age, sex and date of echocardiography (n = 4620 met the criteria) Inclusion: inpatients who did not have bacterial endocarditis and underwent echocardiography during the period of the study, 3 controls were chosen for each case Exclusion: for both cases and controls, known to have had antecedent cardiovascular lesions warranting antibiotic prophylaxis Prevalence of mitral valve prolapse MVP was identified in n = 11/56(20%) of cases and in n = 7/168 (4%) of controls 11 sets had BE and MVP were present, in one of these MVP was also present in a control 39 sets had BE without MVP, in 6 of these MVP was present in a control [a]
Number of patients	n = 224
Predictors	MVP
Outcomes	Endocarditis
Analysis used	Odds ratios for matched sets together with Chi squared values and 95% CIs
Length of follow-up	Between Jan 1976 to Jan 1984
Location	Australia
Effect estimates	OR for the association of MVP and BE was 5.3 (2.0 to 14.4, 95% CI) Systolic murmur In n = 9/11 of those with MVP and BE, there were pre-existing systolic murmurs OR for the association between BE and MVP with pre-existing systolic murmurs was **6.8 (2.1 to 22.0, 95%CI)**

Bibliographic reference	**[from CG64]** **Hickey AJ, MacMahon SW, Wilcken DE, et al. (1985) Mitral valve prolapse and bacterial endocarditis: when is antibiotic prophylaxis necessary? American Heart Journal 109: 431–35.**
	Probability of developing endocarditis (the incidence of BE in the adult population of New South Wales in 1980 was 145 out of 3,852,638 [b] , also assuming that 15% of patients with BE had known high-risk lesions other than MVP and mitral regurgitation, as was the case in this study) The probability of BE occurring in a person with MVP in a 1-year period is 0.00014, this is x4.7 greater than in the general population Results suggest that 14 out of every 100,000 adult patients with MVP will develop BE over a 1-year period, compared with 3 people in every 100,000 in the general population
Source of funding	Not stated
Comments	**Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))** Study Participation – N haemodialysis patients and IVDUs were included in the cases (not protocol). Retrospective design. Study attrition – Y Prognostic factor measurement – Y Outcome measurement – Y (pre-Duke criteria) Confounding measurement and account – N no reporting on other pre-existing cardiac conditions between the cases and controls. Analysis – N - no adjusted ORs. No sample size calculation. 3/6 criteria met = HIGH RISK OF BIAS

(a) In no set was MVP present in more than one of the 3 controls
(b) Taken from the New South Wales State hospital morbidity and mortality statistics for 1980
(c) 7 of the cases were on chronic haemodialysis and 6 were parenteral drug users

Table 37

Bibliographic reference	**Richet, H. et al (2008). Development and assessment of a new early scoring system using non-specific clinical signs and biological results to identify children and adult patients with a high probability of infective endocarditis on admission. Journal of Antimicrobial Chemotherapy; 62:1434-1440.**
Study type	Prospective cohort study (the collection of data was prospective but the study itself was retrospective).
Aim	To assess whether non-specific clinical signs or biological results can identify patients with a high probability of infective endocarditis (IE) to improve outcomes.
Patient characteristics	All patients consulting or hospitalised with suspected IE were screened.

<table>
<tr><td>Bibliographic reference</td><td>Richet, H. et al (2008). Development and assessment of a new early scoring system using non-specific clinical signs and biological results to identify children and adult patients with a high probability of infective endocarditis on admission. Journal of Antimicrobial Chemotherapy; 62:1434-1440.</td></tr>
<tr><td></td><td>Definite IE diagnosed in 409 of 2039 participants (Modified Duke Criteria).
Patients with rejected IE served as controls.
All definite or suspected IE patients underwent blood cultures and other blood tests. Suspected IE patients also were assessed according to presence of one major Duke Criterion or trans-oesophageal echocardiographic abnormalities.
A standardized questionnaire was used to prospectively collect data on all patients with suspected IE.
1870 patients subjected to 2039 diagnostic episodes/assessments.

Of this initial population, mean age 61, 60% were male and 1206 (59.4%) had prior valvular damage (PVD) 11% had a bio-prosthesis, 12.3% had a mechanical prosthesis and 13% had a pacemaker. Most frequently damaged valve was the mitral valve 595 (37.3%) followed by the aortic valve 544 (34%) and the tricuspid valve 64 (4.3%).

Adults and children were included in the study of 402 patients. Mean age was 63±17 (range not provided by definite IE).

After exclusion of 66 patients with possible endocarditis, 1152 of the remaining patients had PVD. (This included patients with prosthetic heart valves, pacemaker or congenital heart disease), 288 (69.7% were male) and mean age was 63±17, median 67 (range 4-95)</td></tr>
<tr><td>Number of patients</td><td>402</td></tr>
<tr><td>Outcomes</td><td>IE</td></tr>
<tr><td>Predictors/risk factors and effect estimates</td><td>Multivariate analysis for risk factors of IE
<table>
<tr><th>Variable</th><th>Odds ratio (95%) CI</th><th>P-value</th></tr>
<tr><td>Prior valve damage 1152/1939</td><td>8.2 (5-13.3)</td><td><0.00001</td></tr>
</table></td></tr>
<tr><td>Analysis used</td><td>Univariate and multivariate analysis were performed.</td></tr>
<tr><td>Length of follow-up</td><td>1 October 1999 to 31 January 2006.</td></tr>
<tr><td>Location</td><td>Marseille, France.</td></tr>
<tr><td>Source of funding</td><td>No funding was sought or obtained for this study.</td></tr>
<tr><td>Comments</td><td>Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))
Study Participation – N. Although the collection of data was prospective the study itself was retrospective. Adults</td></tr>
</table>

Bibliographic reference	**Richet, H. et al (2008). Development and assessment of a new early scoring system using non-specific clinical signs and biological results to identify children and adult patients with a high probability of infective endocarditis on admission. Journal of Antimicrobial Chemotherapy; 62:1434-1440.**
	and children mixed population. Study attrition – Y Prognostic factor measurement – Y Outcome measurement – Y Confounding measurement and account – Y Analysis – N While multivariate analysis was carried out, there is limited detail of the description of the methods and no adjusted odds ratios are reported. 4/6 met = LOW RISK OF BIAS

1 **Table 38**

Bibliographic reference	**Rushani, D. et al. (2013) Infective Endocarditis in Children with congenital heart disease. Cumulative incidence and predictors. Circulation. 128:1412-1419.**
Study type	Population based cohort including nested case-control design to analyse predictors of IE
Aim	Identify cumulative incidence and predictors for the development of IE in children with CHD.
Patient characteristics	Children (0-18 years) between 1988 and 2010 in the Quebec CHD database. Matched each on calendar time with 20 controls. IE diagnosis during observation period. **Distribution of CHD Lesions in Children Followed Since Birth, 1988 to 2010**

CHD Lesions	No. of Children (%)	Person-Years of Follow-Up
Cyanotic CHD	2196 (6)	21 757
Endocardial cushion defects	975 (3)	10 389
Left-sided lesions	2811 (8)	31 974
Right-sided lesions	2201 (6)	20 574
Patent ductus arteriosus	2170 (6)	17 329
Ventricular septal defect	8646 (25)	84 386
Atrial septal defect	12 343 (36)	111 989
Other CHD	2937 (9)	29 787

Bibliographic reference	**Rushani, D. et al. (2013) Infective Endocarditis in Children with congenital heart disease. Cumulative incidence and predictors. Circulation. 128:1412-1419.**

Total	34 279 (100)	328 185

Numbers may not add up because of rounding. The absolute numbers in this table do not reflect the birth prevalence of CHD lesions. Some defects may be asymptotic early in life and only captured after an extended observation period. CHD indicates congenital heart disease.

Number of patients

All CHD children during above time frame n=47,518

Predictors of IE evaluated in 47,518 children with CHD – IE cases 185, controls n=3,700.

Incidence - Total children followed from birth N=34,279. IE cases 136.

Outcomes

IE

Predictors/risk factors and effect estimates

Incidence

Lesion Group-Specific Cumulative Incidence and Incidence Rate of IE in Children with CHD

Cumulative Incidence (95% CI) per 1000 Children				
CHD Lesions	**0–6 y**	**0–12 y**	**0–18 y**	**Incidence Rate (95% CI) per 10 000 Person-Years**
Cyanotic CHD	16.8 (11.9–23.8)	23.3 (17.0–31.8)	31.0 (22.5–42.7)	20.7 (15.4–27.7)
Endocardial cushion defects	5.5 (2.3–13.1)	8.7 (4.1–18.6)	11.1 (5.4–22.9)	7.7 (3.9–15.4)
Left-sided lesions	2.7 (1.3–5.7)	4.8 (2.6–8.7)	7.9 (4.4–14.0)	4.4 (2.6–7.4)
Right-sided lesions	2.3 (1.0–5.5)	2.3 (1.0–5.5)	4.2 (1.5–11.5)	2.9 (1.3–6.5)
Patent ductus arteriosus*	3.2 (1.4–7.1)	3.2 (1.4–7.1)	3.2 (1.4–7.1)	3.5 (1.6–7.7)
Ventricular septal defect	2.0 (1.2–3.2)	2.4 (1.5–3.8)	3.2 (1.9–5.3)	2.4 (1.5–3.7)
Atrial septal defect	1.9 (1.3–2.9)	2.2 (1.5–3.4)	3.0 (1.9–4.8)	2.3 (1.6–3.4)
Other CHD	2.9 (1.4–5.8)	3.7 (1.8–7.3)	5.5 (2.9–10.6)	3.7 (2.0–6.7)
Overall	3.2 (2.6–3.9)	4.2 (3.5–5.1)	6.1 (5.0–7.5)	4.1 (3.5–4.9)

*No IE events were observed in children with PDA past 4 years of age.

Bibliographic reference	Rushani, D. et al. (2013) Infective Endocarditis in Children with congenital heart disease. Cumulative incidence and predictors. Circulation. 128:1412-1419.

Predictors

Characteristics of Children (0–18 Years of Age) With IE and Their Calendar Time–Matched Controls (from the full population of children with CHD)

Characteristic	IE cases (n=185), n (%)	Controls (n=3700), n (%)	Unadjusted Rate Ratio (95% CI)	Adjusted rate ratio (95% CI)
Cardiac surgery 6 mo before*	17 (9)	25 (1)	15.52 (8.08–29.80)	**5.34 (2.49-11.43)**
Valve surgery 6 mo before	3 (2)	8 (0)	7.50 (1.28–31.25)†‡	Not reported
Shunt surgery 6 mo before	13 (7)	13 (0)	21.06 (9.59–46.25)†	Not reported
Other cardiac surgery 6 mo before	13 (7)	25 (1)	11.67 (5.76–23.63)†	Not reported
CHD type				
Cyanotic CHD	62 (34)	348 (9)	6.38 (4.02–10.13)	**6.44 (3.95-10.50)**
Endocardial cushion defects	18 (10)	154 (4)	4.37 (2.35–8.15)	**5.47 (2.89-10.36)**
Left-sided lesions	18 (10)	414 (11)	1.57 (0.86–2.88)	**1.88 (1.01-3.49)**
Right-sided lesions	7 (4)	216 (6)	1.12 (0.49–2.59)	1.22 (0.52-2.86)
Patent ductus arteriosus	6 (3)	161 (4)	1.33 (0.54–3.27)	1.25 (0.50-3.13)
Ventricular septal defect	27 (15)	988 (27)	0.95 (0.56–1.62)	0.97 (0.56-1.66)
Atrial septal defect	29 (16)	1004 (27)	Reference**	Not reported
Other CHD	18 (10)	415 (11)	1.54 (0.84–2.81)	**1.86 (1.01-3.42)**
Age, y				
Median (IQR)	3.5 (0.6–10.2)	7.6 (3.6–12.2)		
0–3	89 (48)	788 (21)	3.30 (2.40–4.53)	
3–6	20 (11)	698 (19)	0.84 (0.51–1.39)	
6–18	76 (41)	2214 (60)	Reference	
Male sex	97 (52)	1761 (48)	1.22 (0.90–1.64)	

Cardiac surgery subcategories do not add up to the total because the procedures performed in 1 operation may

Bibliographic reference	Rushani, D. et al. (2013) Infective Endocarditis in Children with congenital heart disease. Cumulative incidence and predictors. Circulation. 128:1412-1419.

fall under >1 category. Percentages do not add to 100% because of rounding. CHD indicates congenital heart disease; CI, confidence interval; IE, infective endocarditis; and IQR, interquartile range.

* 6 mo before is with respect to the index date for cases and the time of matching for controls.

** This figure was not reported but was used as a reference category (see below). Reviewer calculated **OR 0.449 (0.33-0.75).**

† These are combined into a single variable in the multivariate model.

‡ Estimated with exact logistic regression owing to sparse data.

Results are reported comparing the above characteristics to atrial septal defect as reference category as this defect was the most common CHD (36%). Relative to ASD, the following lesions were most strongly associated with an elevated risk of IE: Cyanotic CHD (adjusted RR, 6.44; 95%CI, 3.95, 10.50), endocardial cushion defects (aRR, 5.47; 2.89,10.36) and left-sided lesions (aRR, 1.88; 1.01, 3.49).

Young age was a strong predictor of IE: in comparison with those aged 6 to 18, children <3 years of age were at higher risk of IE (aRR 3.53, 2.53-4.96) but not those 3 to 6 years (aRR 0.91; 0.54-1.51).

Male sex and IE (aRR 1.09, 0.80-1.50)

CHD Lesions at Elevated Risk of IE Stratified by History of Cardiac Surgery

CHD Lesions	IE Cases, n (%)	Controls, n (%)	Adjusted Rate Ratio (95% CI)
Cyanotic CHD	45	178	
Unoperated	27 (60)	100 (56)	7.56 (4.03–14.18)
Operated	18 (40)	78 (44)	9.22 (4.39–19.34)
Endocardial cushion defects	8	84	
Unoperated	5 (63)	51 (61)	3.00 (1.06–8.51)
Operated	3 (37)	33 (39)	–*
Left-sided lesions	14	253	
Unoperated	13 (93)	233 (92)	2.35 (1.16–4.73)
Operated	1 (7)	20 (8)	–*

Analysis was performed in the subset of children followed since birth. History of cardiac surgery was measured

Bibliographic reference	**Rushani, D. et al. (2013) Infective Endocarditis in Children with congenital heart disease. Cumulative incidence and predictors. Circulation. 128:1412-1419.**
	from birth to 6 months before time of matching and did not include catheterization procedures. Adjustment was for age, sex, and cardiac surgery in the previous 6 months. CHD categories not stratified by history of cardiac surgery (right-sided lesions, VSD, PDA, and other CHD) are not shown. The reference CHD category is atrial septal defects (26 IE cases, 928 controls). CHD indicates congenital heart disease; CI, confidence interval; IE, infective endocarditis; PDA, patent ductus arteriosus; and VSD, ventricular septal defect. * Covariate adjustment is impossible because of sparse data.
Analysis used	IE estimated using Kaplan-Meier estimator. Incidence rate = cumulative incidence (first cases of IE) divided by the total person-time at risk with CIs computed using Poisson distribution. Predictors analysed using conditional and exact logistic regression. Wald test used to evaluate differences in risk of IE between different CHD lesions.
Length of follow-up	1 January 1988 – 31 March 2010 (22years)
Location	Quebec, Canada.
Source of funding	Dr Kaufman is funded by the Canada Research Chairs program. Drs Marelli, Ionescu-Ittu, and Pilote are funded by the Fonds de la recherche en santé du Québec. Drs Marelli and Mackie are funded by the Heart and Stroke Foundation of Canada and the Canadian Institutes of Health Research. Dr Pilote holds a James McGill Chair at McGill University.
Comments	**Potential bias (Hayden)** Study Participation – Y Study attrition – Y Prognostic factor measurement – Y Outcome measurement – Y Confounding measurement and account – Y Analysis - U. No sample size calculation and N for each variable <20. 5/6 met - Low risk of bias

1 **Table 39**

Bibliographic reference	**[from CG64]** **Strom BL, Abrutyn E, Berlin J et al (1998) Dental and cardiac risk factors for infective endocarditis: a population-based case-control study. Ann Int Med; 129:761-9.**

Bibliographic reference	**[from CG64]** **Strom BL, Abrutyn E, Berlin J et al (1998) Dental and cardiac risk factors for infective endocarditis: a population-based case-control study. Ann Int Med; 129:761-9.**
Study type	Population based Case-control. Retrospective interviews/data collection
Aim	To quantify the risk of endocarditis from dental treatment and cardiac abnormalities.
Patient characteristics	Surveillance completed for IE in 54 hospitals. **Cases**; Community acquired IE not associated with IVDU - defined from self-reporting structured telephone interviews, dental visit (information was obtained from dental records) **Controls:** Controls were community residents. Case-patients were matched for age, sex and neighbourhood of residence. One control from the community selected for each case-patient (using a modification of the Waksberg random-digit dialling method) Information was obtained from case-patients by a structured telephone interview, medical and dental records were subsequently requested. Case records were examined and classified by experts in IE. Host characteristics were collected and the following conditions were classified as a variable called “any valvular heart abnormality” mitral valve prolapse, congenital heart disease, rheumatic fever with heart involvement, cardiac valvular surgery, previous episode of endocarditis and other valvular heart disease, those reporting >1 of these factors were only reported once Case-patients and controls were similar for age (range 18-98yrs, mean 59.1±17.1 and 59.1±17.0, respectively), sex, ethnicity, education, occupation, and dental insurance status. Excluded: <18yrs, IV drug users, those who developed endocarditis in the hospital Interviewers and medical records abstractors were not blinded but were extensively trained in good interviewing and abstracting techniques.
Number of patients	416 enrolled potential case-patients. 287 community acquired IE not associated with IV drug use. Of these 287 included patients, 273 patients completed the interview.
Predictors	Pre-existing cardiac condition / Valvular abnormality
Outcomes	Endocarditis

Bibliographic reference	**[from CG64]** **Strom BL, Abrutyn E, Berlin J et al (1998) Dental and cardiac risk factors for infective endocarditis: a population-based case-control study. Ann Int Med; 129:761-9.**
Analysis used	Conditional logistical regression. Variables were included in multiple regression models if they were significant (P<0.2) in unadjusted (matched) analyses if there inclusion had a substantial effect (>15 change) on coefficients for variables in the model or if they were strongly suspected confounders. Adjusted ORs and 95% CIs were provided.
Length of follow-up	From August 1988 – November 1990
Location	Philadelphia, USA
Effect estimates	**Cardiac risk factors** Patient-reported history of any cardiac valvular abnormality was highly associated with IE (adjusted odds ratio 16.7, CI 7.4 to 37.4) (Adjusted for socioeconomic status variables (ethnic group, education, occupation, health insurance status, and dental insurance status))

Risk factor	Cases (n = 273)	Controls (n = 273)	Adjusted OR[1] (CI 95%)
Mitral valve prolapse	52(19.0%)	6(2.2%)	19.4 (6.4 to 58.4)
Congenital heart disease	26(9.5%)	7(2.6%)	6.7 (2.3 to 19.4)
Rheumatic fever	32(11.7%)	10(3.7%)	13.4 (4.5 to 39.5)
Cardiac valvular surgery	37(13.6%)	2(0.7%)	74.6 (12.5 to 447)
Other valvular heart disease *	12(4.4%)	1(0.4%)	131 (6.9 to 2489)
Heart murmur	37(13.6%)	14(5.1%)	4.2 (2.0 to 8.9)
Any cardiac valvular abnormality **	104 (38.1%)	17(6.2%)	16.7 (7.4 to 37.4)
(previous episode of endocarditis)	17(6.2%)	1(0.4%)	37.2 (4.4 to 317)

*defined as patient reported “other valvular disease”

**includes any of; mitral valve prolapse, congenital heart disease, rheumatic fever with heart involvement, cardiac valvular surgery, previous episode of endocarditis and other valvular heart disease, those reporting >1 of these factors were only reported once

[1] Adjusted for socioeconomic status variables (ethnic group, education, occupation, health insurance status, and dental insurance status), diabetes mellitus and severe kidney disease)

Bibliographic reference	**[from CG64]** **Strom BL, Abrutyn E, Berlin J et al (1998) Dental and cardiac risk factors for infective endocarditis: a population-based case-control study. Ann Int Med; 129:761-9.**
	Case patients were substantially more likely than controls to report previous known mitral valve prolapse; history of CHD; rheumatic fever; cardiac valvular surgery; previous endocarditis; other valvular heart disease; heart murmur without other known cardiac abnormalities
Source of funding	National Heart, Lung and Blood Institute
Comments	**Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))** Study Participation – N Data Were collected retrospectively and case selection insufficiently describe to limit potential bias. Study attrition – Y although only 58% of recruited controls completed questionnaire Prognostic factor measurement – Y Includes cardiac conditions that were patient reported but made efforts to validate reports and indicated 90% agreement. Outcome measurement – Y Confounding measurement and account – Y Analysis – Y adjusted rate ratios provided 5/6 = LOW RISK OF BIAS

G.2 Review question 2

Table 40

<table>
<tr><td>Bibliographic reference</td><td>Aksoy, O. et al (2007). Early surgery in patients with infective endocarditis: A propensity score analysis. Clinical Infectious diseases; 44:364-72.</td></tr>
<tr><td>Study type</td><td>Longitudinal cohort study</td></tr>
<tr><td>Aim</td><td>Prospective evaluation of predictors of long term mortality after IE</td></tr>
<tr><td>Patient characteristics</td><td>Data was obtained from Duke University Prosthetic Cohort Study on endocarditis.
426 adult patients with infective endocarditis (modified Duke criteria for definite or possible endocarditis)
Initial analysis L or R-sided involvement. Patients with >1 occurrence only the 1st was included in analysis as well as IE of native or prosthetic valve. Cardiac device related IE was also included.
Matched cohort - LSA IE did not undergo surgery (n=255), underwent surgery (n=78)

Patient characteristic/risk factors of interest as per outcome tables.</td></tr>
<tr><td>Number of patients</td><td>426</td></tr>
<tr><td>Outcomes</td><td>Surgery
All-cause mortality at 5 years after discharge.</td></tr>
<tr><td>Predictors/risk factors and effect estimates</td><td>Characteristics of IE cohort according to whether SURGERY was performed.
<table>
<tr><th rowspan="2">Characteristic</th><th rowspan="2">Total cohort (n=426)</th><th rowspan="2">Total Patients with LSA* IE (n=333)</th><th colspan="2">Matched Cohort</th><th rowspan="2">P-value</th></tr>
<tr><th>LSA IE no surgery (n=255)</th><th>LSA IE surgery (n=78)</th></tr>
<tr><td>Age (y) mean SD</td><td>58.3±26,2</td><td>56.6±25.3</td><td>58.4±26.8</td><td>54.2±20.6</td><td>0.089</td></tr>
<tr><td>Male</td><td>242 (56.8)</td><td>186 (55.9)</td><td>134 (52.6)</td><td>52 (66.7)</td><td>0.028</td></tr>
<tr><td>Female</td><td>184 (43.2)</td><td>147 (44.1)</td><td>121 (47.5)</td><td>26 (33.3)</td><td>0.028</td></tr>
<tr><td>Type of IE</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Native valve</td><td>295 (69.3)</td><td>248 (74.5)</td><td>192 (75.3)</td><td>56 (71.8)</td><td>0.535</td></tr>
<tr><td>Prosthetic valve</td><td>81 (19.0)</td><td>57 (17.1)</td><td>38 (14.9)</td><td>19 (24.4)</td><td>0.052</td></tr>
<tr><td>Other</td><td>50 (11.7)</td><td>28 (8.4)</td><td>25 (9.8)</td><td>3 (3.9)</td><td>0.097</td></tr>
<tr><td>Previous episode</td><td>20 (4.7)</td><td>12 (3.6)</td><td>11 (4.3)</td><td>1 (1.3)</td><td>0.209</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Aksoy, O. et al (2007). Early surgery in patients with infective endocarditis: A propensity score analysis. Clinical Infectious diseases; 44:364-72.**

of IE					
Congenital heart disease	45 (10.6)	36 (10.8)	26 (10.2)	10 (12.8)	0.514

P-value analysis based on comparison of the non-surgical cohort with the surgical cohort.
*LSA = left sided association without concomitant intra-cardiac devices.

With the exception of gender, there were no significant differences between those having surgery vs no surgery (medical therapy only) in the above characteristics/risk factors.

5year mortality of patients with L-sided IE by characteristic

Characteristic (Total n=333)	**Patients who survived (total n=171) (%)**	**Patients who died (total n=162) (48.6%)**	**P-value**
Age, mean years± SD	53.2 ±26.1	62.6 ±24.8	**<0.001**
Male	102 (59.7)	784 (51.9)	0.152
Aortic Valve IE	0	5 (3.1)	**0.003**
Congenital heart disease	26 (15.2)	10 (6.2)	**0.008**

Older patients as well as those with history of congenital heart disease and those with aortic valve IE were significantly more likely to be dead at 5 years post event.

Analysis used	Chi-square test for categorical variables. Wilcoxon rank-sum test for continuous variables. Patients were matched to patients who did not undergo surgery using individual propensity scores (using minimum absolute distance) between propensities for surgery. Matching tolerance was a score difference of 0.075.
Length of follow-up	5 year follow up period. duration 1 April 1996 - 31 December 2002
Location	North Carolina, USA
Source of funding	Financial support: National Institutes of Health grant.
Comments	**Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))** Study Participation – Y Study attrition – Y Based on numbers reported on 5 year follow-up this appears that follow-up was 100%. Prognostic factor measurement – Y Outcome measurement – Y

Bibliographic reference	**Aksoy, O. et al (2007). Early surgery in patients with infective endocarditis: A propensity score analysis. Clinical Infectious diseases; 44:364-72.**
	Confounding measurement and account – N some concern as although the propensity score matching reduces the effect of treatment bias it does not completely control for confounding. ? potential for confounding by referral bias. Analysis – N Odds ratios needed to be back calculated by reviewer. 4/6 met = LOW RISK OF BIAS

1 **Table 41:**

Bibliographic reference	**Alonso-valle, H. et al. (2010). Clinical course and predictors of death in prosthetic valve endocarditis over a 20-year period. The Journal of Thoracic and Cardiovascular Surgery. 139:4887-893**
Study type	Retrospective observational study.
Aim	To compare early and late outcome of patients with prosthetic valve endocarditis (PVE) over 20 year period.
Patient characteristics	133 episodes (in 122 adult patients). 112 patients had 1 episode, 9 patients had 2 episodes and 1 patient had 3 episodes). PVE defined by Duke criteria. Early PVE = within 60 days of implantation. Late onset 2 or more months from replacement. In hospital death was recorded according to various parameters. Data were collected using retrospective review of patient records. There were 24 cases of early and 109 cases of late PVE (total 133). 64/133 cases had a mechanical prosthesis. Mechanical PVE was more frequent in early onset group (78% vs. 22%). Bioprosthetic PVE was more frequent in late onset group (58% vs. 42%). Men n=87, women n=34, mean age 59y (95%CI 56-62).
Number of patients	133 episodes (in 122 patients).
Outcomes	(e.g. mortality, 10-year survival, event rate of interest e.g. number of heart attack, no. of sudden infant death, etc.) Mortality 39 patients died (in-hospital mortality rate of 29.3%). Of the 94 patients who were discharged alive, 26 (27%) died during mean follow-up period of 31 months.

<table>
<tr><td>Bibliographic reference</td><td>Alonso-valle, H. et al. (2010). Clinical course and predictors of death in prosthetic valve endocarditis over a 20-year period. The Journal of Thoracic and Cardiovascular Surgery. 139:4887-893</td></tr>
<tr><td></td><td>Recurrence
Recurrent PVE was observed in 12 cases (9%). (Recurrent episode n=10, relapse 2).
50% of patients with recurrence were carriers of mechanical valve prosthesis.</td></tr>
<tr><td>Predictors/risk factors and effect estimates</td><td>Actual data (numbers/percentages) with outcome were not provided by risk factor.

Univariate analyses: risk factors for in-hospital death in 133 episodes of PVE
<table>
<tr><th rowspan="2">Variable</th><th colspan="3">Crude Mortality (in-hospital death)</th></tr>
<tr><th>RR</th><th>95%CI</th><th>P Value</th></tr>
<tr><td>Age >75 y</td><td>1.6</td><td>0.6-4.3</td><td>NS</td></tr>
<tr><td>Female gender</td><td>1.2</td><td>0.4-1.9</td><td>NS</td></tr>
<tr><td>Previous IE</td><td>1.7</td><td>0.7-4.4</td><td>NS</td></tr>
<tr><td>Previous valve replacement</td><td>0.9</td><td>0.4-2.1</td><td>NS</td></tr>
<tr><td>Mechanical Prosthesis implantation</td><td>1.1</td><td>0.5-2.4</td><td>NS</td></tr>
</table>

Multivariate analyses was conducted but the variables of interest were clearly not in the model. (Adjusted for age, sex, year of PVE onset, referral hospital, nosocomial infection after original valve replacement).

Recurrence was observed in a total of 12 patients (9%). These data were not provided by outcome/risk factor.

Long-term mortality was not reported by risk factor.</td></tr>
<tr><td>Analysis used</td><td>Logistic regression model was used to identify prognostic factors of in-hospital mortality.
Mortality rates were derived evaluated by plotting survival distribution derived from Kaplan-Meier estimates and differences evaluated using log-rank test.
Cox regression analysis was used to assess the effect of different variables on risk of death.</td></tr>
<tr><td>Length of follow-up</td><td>Duration January 1986 – December 2005. Mean follow up was 32.2 months (SD 46.8, range 0-212 months).</td></tr>
<tr><td>Location</td><td>Santander, Spain. (single centre)</td></tr>
<tr><td>Source of funding</td><td>No external funding was received.</td></tr>
</table>

Bibliographic reference	**Alonso-valle, H. et al. (2010). Clinical course and predictors of death in prosthetic valve endocarditis over a 20-year period. The Journal of Thoracic and Cardiovascular Surgery. 139:4887-893**
Comments	**Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))** Study Participation – N Retrospective design. Selection bias could also occur regarding treatment options (medical vs. medical & surgical) and this could bias the outcomes. Study attrition – U No final numbers were reported. Prognostic factor measurement – Y Surgery rates were higher than usual in this study due to referral from other hospitals of patients with complicated clinical course, although in-hospital mortality was lower in surgical group (NS). Survival after 12 months was markedly different in favour of surgically treated patients (71% vs. 42%) but Multivariate analysis included referral bias as a covariate to reduce the likelihood of referral bias. Outcome measurement – Y Confounding measurement and account – Y. Analysis – N No adjusted odds ratios/risk ratios were provided by predictor despite them being calculated. No sample size calculation. 3/6 = HIGH RISK OF BIAS

1 **Table 42**

Bibliographic reference	**Bannay, A et al. (2011) The impact of valve surgery on short- and long-term mortality in left-sided infective endocarditis: do differences in methodological approaches explain previous conflicting results? European Heart Journal; 32, 2003-2015..**
Study type	Long term prospective follow up study
Aim	Evaluate the effect of valve surgery (VS) in infective endocarditis on 5 year mortality
Patient characteristics	Adult patients with IE were selected from a prospective, population based study. Original study - Cases were collected during a cross-sectional prospective population-based survey between 1 December 1998 and 31 March 2000. 559 patients with definite IE (Duke Criteria). Of these 449 with left sided IE were included in the current study. Inclusion criteria included IVDUs. See results tables for baseline characteristics of interest.
Number of patients	449 with L-sided IE
Outcomes	Surgery Mortality
Predictors/risk factors and effect estimates	Previous cardiac conditions were not found to be independent predictors of valve surgery after IE.

Bibliographic reference	**Bannay, A et al. (2011) The impact of valve surgery on short- and long-term mortality in left-sided infective endocarditis: do differences in methodological approaches explain previous conflicting results? European Heart Journal; 32, 2003-2015..**

Characteristics (pre-existing cardiac conditions) of 449 patients by those undergoing valve SURGERY

	Total sample N (%)	**Valve surgery (n=240)**	**No valve surgery (n=209)**	**P-value**
Age y (mean, SD)	60.8 (14.0)	57.6 (13.5)	64.4 (15.6)	**<0.0001**
Male	344 (74.4)	188 (78.3)	146 (69.9)	0.051
History of Predisposing cardiac diseases (Valvular diseases with/without prosthesis)	257 (57.2)	142 (59.2)	115 (55.0)	0.446
History of Valvular disease (both native and prosthetic valves)	233 (51.9)	Not reported	Not reported	N/A
Valvular prosthesis	71 (15.8)	37 (15.4)	34 (16.3)	0.897
Native valve disease (no prosthesis)	162 (36.1)	105 (43.8)	81 (38.8)	0.292
Intracardiac device	15 (3.3)	5 (2.1)	10 (4.8)	0.123
History of previous IE	38 (8.5)	24 (10.0)	14 (6.7)	0.237

Mortality

In hospital mortality reported as overall percentage only – 19%. Not reported separately by risk factor.

160 patients died in total (including in-hospital deaths) resulting in a 41% 5-year mortality rate. (61 (25.4%) in surgical group vs 99 (47.4%) in non-surgical group).

5-year survival rates were thus 69.6% and 48.0% respectively (crude P<0.0001) (log rank).

Independent prognostic factors of 5 year death rate (449 patients with a definitely left sided IE, adjusted Cox model n=449)

Characteristic	**HR (95% CI)**	**P-value**
Age (years)	1.04 (1.02-1.05)	**<0.0001**
Number of serious comorbid diseases*	1.40 (1.23-1.58)	**<0.0001**
History of valvular disease		
No previously known valvular disease	1.00	
Native valve disease	0.67 (0.46-0.97)	**0.032**

Bibliographic reference	**Bannay, A et al. (2011) The impact of valve surgery on short- and long-term mortality in left-sided infective endocarditis: do differences in methodological approaches explain previous conflicting results? European Heart Journal; 32, 2003-2015..**
	Valvular prosthesis | 1.09 (0.72-1.67) | 0.677 *Serious comorbid diseases: ischaemic cardiomyopathy, heart failure, peripheral vascular disease, previous stroke, chronic pulmonary disease, renal insufficiency, connective tissue disease, immunodeficiency, liver disease and malignant disease. (All covariates fulfilled proportional hazard assumption). Length of stay was reported as mean of total sample only (42 days) and not by risk factor.
Analysis used	Categorical variables – Fisher's exact test Continuous variables – unpaired t-test or median test. Bivariable and multivariable ascending stepwise Cox proportional hazard model was used to determine independent predictors of valve surgery and independent 5-year survival predictors. Unclear which variables adjusted for. ? ask Toni to check.
Length of follow-up	5 years. Median follow up was 5.0 years (loss to follow-up rate was 12.5% at 5 years.
Location	7 centres in France
Source of funding	Funded by the Programme Hospitalier de Recherche Clinique.
Comments	**Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))** Study Participation – Y Study attrition – U reported loss to follow-up of 12.5% could be a potential source of bias Prognostic factor measurement – Y Outcome measurement – Y Confounding measurement and account – Y IVDUs were included (non- protocol criteria)but not grouped with those with pre-existing cardiac conditions Analysis – N Odds ratios were not provided and needed to be back calculated by reviewer. No sample size calculation. 4/6 = LOW RISK OF BIAS

1 **Table 43**

Bibliographic reference	**Da COSTA, M.A.C. et al. (2007) Risk index for death by infective endocarditis: a multivariate logistic model. Brazilian Journal of Cardiovascular Surgery. 22(2):192-200.**

<table>
<tr><td>Bibliographic reference</td><td>Da COSTA, M.A.C. et al. (2007) Risk index for death by infective endocarditis: a multivariate logistic model. Brazilian Journal of Cardiovascular Surgery. 22(2):192-200.</td></tr>
<tr><td>Study type</td><td>Retrospective observational study</td></tr>
<tr><td>Aim</td><td>To identify predictive variables for in-hospital mortality after IE and create a risk index for death.</td></tr>
<tr><td>Patient characteristics</td><td>186 consecutive episodes of IE confirmed using Duke criteria in 179 patients.
Adults and children included. Mean age 7 – 70 years (mean 33.9 years, no SD.</td></tr>
<tr><td>Number of patients</td><td>186 episodes (179 patients)</td></tr>
<tr><td>Outcomes</td><td>Mortality after IE</td></tr>
<tr><td>Predictors/risk factors and effect estimates</td><td>Post IE Mortality in univariate analysis of quantitative variables
<table>
<tr><th>Characteristic</th><th>Total (N=186)</th><th>Death (n=49 = 26.3%) (n)</th><th>Mortality (%)</th><th>P-value</th><th>Odds ratio (95% CI)</th></tr>
<tr><td><40 Years old</td><td>133</td><td>23</td><td>9.1</td><td><0.0001</td><td>4.61 (2.28, 9.29)</td></tr>
<tr><td>40 or over</td><td>53</td><td>26</td><td>49.1</td><td></td><td></td></tr>
<tr><td>Male</td><td>12</td><td>29</td><td>25.9</td><td>0.867</td><td>Not reported</td></tr>
<tr><td>Prosthesis</td><td>56</td><td>20</td><td>35.7</td><td>0.3965</td><td>Not reported</td></tr>
<tr><td>Prosthesis (from Echo)</td><td>55</td><td>20</td><td>36.4</td><td>0.0008</td><td>4.57 (1.89, 11.07)</td></tr>
<tr><td>Rheumatic
(fever in table, disease in text)</td><td>45</td><td>9</td><td>20.0</td><td>0.3652</td><td>Not reported</td></tr>
</table>
After multivariate analysis, complicated valve or valve prosthesis were significantly associated with mortality - OR 4.77 (1.44, 15.76), p<0.01.

ROC Curve for probability of death – area under the curve 0.872.</td></tr>
<tr><td>Analysis used</td><td>Univariate inference analysis using Chi-square test, Fisher’s exact test, logistic regression and Mann-Whitney U test. Multivariate inference analysis using logistic regression with the stepwise procedure by the forward method. (independent variables had to be significant at p<0.20 to be included. To remain in the model p needed to be <0.05).
A formula was developed to calculate the risk of death and a Receiver Operating Characteristic (ROC) curve was developed.</td></tr>
<tr><td>Length of follow-up</td><td>January 1988-december 1998. Patients followed-up until discharge.</td></tr>
</table>

Bibliographic reference	**Da COSTA, M.A.C. et al. (2007) Risk index for death by infective endocarditis: a multivariate logistic model. Brazilian Journal of Cardiovascular Surgery. 22(2):192-200.**
Location	Curitiba, Brazil.
Source of funding	Not mentioned
Comments	**Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))** Study Participation – N Retrospective design. Adults and children grouped together. Mean but no SD for age reported. Study attrition – Y. Prognostic factor measurement – N Age is separated with 40 years as the threshold. Those <40 include children but it is not reported how many and what ages. Lack of clarity about rheumatic fever/rheumatic heart disease – inconsistently reported. Outcome measurement – Y Confounding measurement and account – Y Analysis – Y No sample size calculation but n= min 20 for some variables. 4/6 met = LOW RISK OF BIAS

1 **Table 44**

Bibliographic reference	**Delahaye, F. et al. (2007) In-hospital mortality of infective endocarditis: Prognostic factors and evaluation over an 8-year period. Scandinavian Journal of Infectious Diseases. 39:849-857.**
Study type	Prospective population based survey
Aim	To report on in-hospital mortality from IE
Patient characteristics	Age >15 years living in one of the study regions. Physician lead patient selection (faxed notification form to study centre for each IE patient treated) and the physician and microbiologist were asked to complete a questionnaire. 653 cases of IE (Duke Criteria) were entered into database. Exclusions – no evidence of diagnosis according to Duke Criteria (n=94). 559 cases included. (390 were retained for case description and 1 yr. incidence calculation in the original manuscript (published previously) based on 1999 data only). Data was also collected in 1991 to enable comparison of mortality rates between 1991 and 1999. The current study included all 559 cases. Mean Age 59±16.8 y. 72% male.

Bibliographic reference	**Delahaye, F. et al. (2007) In-hospital mortality of infective endocarditis: Prognostic factors and evaluation over an 8-year period. Scandinavian Journal of Infectious Diseases. 39:849-857.**

Variable	Percentage
Underlying heart disease	
Native valve disease	34
Prosthetic valve	15
Congenital heart disease	1
No previously known underlying disease	46

Number of patients: 559

Outcomes: Mortality

Predictors/risk factors and effect estimates

In-hospital mortality rate in this study period was 17% (95/559).

Univariate analysis in-hospital mortality after IE by patient characteristics

Variable		% deaths	p-value
Age (y)	<60	11.2	
	60-70	18.0	
	70-80	25.2	
	>80	21.6	**0.004**
Gender	Not		
History of prosthetic valve	No	15.6	
	Yes	24.7	**0.04**
Rheumatological manifestations	No	8.9	
	Yes	14.1	**0.01**

Multiple regression (stepwise logisitic) was carried out for baseline variables but the above variables of interest were not reported as they were not retained in the model.

Analysis used: Prognostic influence of variables on in-hospital mortality tested first in univariate analysis (Pearson's X^2 test) then multivariate analysis (stepwise logistic regression, variables with $p<0.10$ in univariate analysis).

Bibliographic reference	**Delahaye, F. et al. (2007) In-hospital mortality of infective endocarditis: Prognostic factors and evaluation over an 8-year period. Scandinavian Journal of Infectious Diseases. 39:849-857.**
Length of follow-up	Launched 1 December 1998 and stopped 31 March 2000. (Plus cross-sectional incidence carried out 1999).
Location	France
Source of funding	Funded by a Programme Hospitalier de Recherche Clinicque grant, the Federation Francaise de Cardiologie and the Aventis and GlaxoSmithKline laboratories, France.
Comments	**Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))** Study Participation - N Inclusion was based on physician referrals of patients with IE which could introduce a source of bias Study attrition – U study reports outcomes for 100% of participants but the data on percentages with mortality does not add up to 100%. Prognostic factor measurement – Y Outcome measurement – Y Confounding measurement and account – Y Analysis – N Odds ratios inconsistently reported and insufficient data provided to enable back calculation by reviewer. No sample size calculation. 3/6 met = HIGH RISK OF BIAS

Table 45

Bibliographic reference	**Erbay, A.R. et al. (2010). Risk Factors for In-Hospital Mortality in Infective Endocarditis: Five years' Experience at a Tertiary Care Hospital in Turkey. Journal Heart Valve Disease; 19:2:216-224.**
Study type	Retrospective cohort design
Aim	To determine the clinical, laboratory and echocardiographic features of IE and evaluate the risk factors for in-hospital mortality.
Patient characteristics	All adult patients (≥18y) admitted to hospital with IE – Modified Duke criteria for definitive IE. >1 episode of IE only the first episode was included. People with pacemakers were excluded. TEE was carried out for all patients with suspected IE and PVE Data obtained from medical records and computerised database. (79 male, 28 female, mean age 45±16 years)
Number of patients	107
Outcomes	In-hospital mortality

Bibliographic reference

Erbay, A.R. et al. (2010). Risk Factors for In-Hospital Mortality in Infective Endocarditis: Five years' Experience at a Tertiary Care Hospital in Turkey. Journal Heart Valve Disease; 19:2:216-224.

Predictors/risk factors and effect estimates

Risk factors associated with in-hospital mortality after infective endocarditis, based on univariate analysis

Risk Factor	Total (n=107)	Survived (n=78)	Died (n=29) (27%)	p-value
Age (y)	45± 16	45±16	44±17	0.736
Male gender	79 (74)	55(71)	24(83)	0.200
Previous IE history	10 (9)	4(5)	6(21)	**0.023**
Predisposing heart disease	87 (81)	62(80)	25(86)	0.312
Prosthetic valve	47 (44)	37(47)	10(35)	0.230
Native Valves				
Degenerative valve disease	15(14)	11(14)	4(14)	0.608
Rheumatic heart disease	11(10)	6(8)	5(17)	0.148
Congenital heart disease	7(7)	5(6)	2(7)	0.613
Bicuspid aortic valve	3(3)	1(1)	2(7)	0.178
Other	4(4)	2(3)	2(7)	0.296

Estimated Standard Error (SE), p-value and hazard ratio (HR) as a function of the risks of the variables for IE according to Cox proportional hazards model.

Risk Factor	SE	p-value	HR	95%CI
Previous IE history	2.1	0.026	3.5	1.2-11.0

Analysis used

Categorical variables/proportions - Chi-square or Fisher's exact test

Continuous variables – independent Student's t-test or Wilcoxon rank sum test.

A cox regression was used to model in-hospital mortality.

For multivariate analysis, only variables with a p-value of <0.05 were entered into the model. Stepwise selection procedure applied.

HRs were computed from estimated parameters of the final regression model.

Length of follow-up

January 2004 - December 2008.

Bibliographic reference	**Erbay, A.R. et al. (2010). Risk Factors for In-Hospital Mortality in Infective Endocarditis: Five years' Experience at a Tertiary Care Hospital in Turkey. Journal Heart Valve Disease; 19:2:216-224.**
Location	Ankara, Turkey
Source of funding	Not mentioned
Comments	**Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))** Study Participation – N Retrospective design. Relatively small numbers. May have been subjected to referral bias (data collected at a referral and tertiary-care hospital) as the patients referred to specialized units tend to be more complex and severe. Study attrition – Y Prognostic factor measurement – Y Outcome measurement – Y Confounding measurement and account – Y Analysis – N no odds ratios were reported and needed to be back calculated by the reviewer. No sample size calculation. 4/6 met = LOW RISK OF BIAS

1 **Table 46**

Bibliographic reference	**Fernandez Guerrero, M.L. et al. (2007). Enterococcal endocarditis on native and prosthetic valves. A review of clinical and prognostic factors with emphasis on hospital-acquired infections as a major determinant of outcome. Medicine. 86:6:363-377**
Study type	Retrospective observational study
Aim	To determine the risk factors for mortality in patients with enterococcal endocarditis on native vs prosthetic valves
Patient characteristics	Data collected from patient records from a database. Diagnosis was based on strict case definitions using modified Duke criteria. Methods for blood cultures changed over the years but at least 3 sets of cultures were taken from each patient with suspected endocarditis. IVDUs were included. Median age 58 years (noted by authors to be younger than other published studies) Predisposing heart conditions were observed in 38/47 (86.3%) patients. 17 had prosthetic valve (of which 13 were metallic valves and 4 bioprosthetic) endocarditis. 10 had degenerative valvular disease

<table>
<tr><td>Bibliographic reference</td><td>Fernandez Guerrero, M.L. et al. (2007). Enterococcal endocarditis on native and prosthetic valves. A review of clinical and prognostic factors with emphasis on hospital-acquired infections as a major determinant of outcome. Medicine. 86:6:363-377</td></tr>
<tr><td></td><td>4 had rheumatic valve disease
3 had congenital cardiac disease (1 ductus arteriosus and 2 bicuspid aortic valves).
3 had previous endocarditis and
1 had mitral valve prolapse.

Only the first episode of endocarditis was considered in the analysis of the risk factors for mortality.
Mortality related to either in-hospital mortality or within 30 days of discharge. Patients were also followed up in outpatient clinics with visits at 1, 3, 6 and 12 months after discharge. (Unclear if mortality figure includes deaths after 30 days of discharge).</td></tr>
<tr><td>Number of patients</td><td>47 episodes in 44 patients</td></tr>
<tr><td>Outcomes</td><td>Mortality - occurred in 8 cases (18.1%).
Brain emboli (9 cases)
Surgery (Valve replacement due to cardiac failure) (18 cases)</td></tr>
<tr><td>Predictors/risk factors and effect estimates</td><td>Clinical findings of 44 patients with Enterococcal Endocarditis
<table>
<tr><th>Variable</th><th>Native Valve endocarditis (N=27 patients) N (%)</th><th>Prosthetic Valve endocarditis (N=17) N (%)</th><th>P value</th></tr>
<tr><td>Mortality</td><td>6 (22.2)</td><td>2 (11.7)</td><td>NS</td></tr>
<tr><td>Brain emboli</td><td>5 (18.5)</td><td>4(23.5)</td><td>NS</td></tr>
<tr><td>Valve replacement (due to cardiac failure)</td><td>12 (44.4)</td><td>6 (35.2)</td><td>NS</td></tr>
</table></td></tr>
<tr><td>Analysis used</td><td>Continuous variables – Student t test or nonparametric test
Categorical variables – Chi-square or Fisher’s exact test.
Stepwise logistic regression was applied to variables the yielded significant results in the univariate analysis to identify risk factors for mortality.</td></tr>
<tr><td>Length of follow-up</td><td>January 1988 to December 2005</td></tr>
<tr><td>Location</td><td>Single centre, Madrid, Spain.</td></tr>
</table>

Bibliographic reference	**Fernandez Guerrero, M.L. et al. (2007). Enterococcal endocarditis on native and prosthetic valves. A review of clinical and prognostic factors with emphasis on hospital-acquired infections as a major determinant of outcome. Medicine. 86:6:363-377**
Source of funding	Not mentioned.
Comments	**Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))** Study Participation – N Retrospective design. Enterococcal endocarditis only. Small number over long study period – ?changing practices in that time. No sample size calculation Study attrition – Y Prognostic factor measurement – Y Outcome measurement – U follow up periods were not explicit for mortality and complications (brain emboli) Confounding measurement and account – Y Analysis – N did not report odds ratios for mortality or complications as listed in results. Back calculation by reviewer was necessary. No sample size calculation. 3/6 met = HIGH RISK OF BIAS

1 **Table 47**

Bibliographic reference	**Fernandez Guerrero, M.L. et al (2010) Left-sided Endocarditis caused by staphylococcus aureus. A comparison of clinical and prognostic factors of patients with native and prosthetic valve endocarditis. Infectious Diseases in Clinical Practice; 18:308-312.**
Study type	Retrospective observational study
Aim	To compare the epidemiology, manifestations and outcome of patients with NVE and PVE due to S. aureus and to assess the risk factors associated with mortality.
Patient characteristics	Review of records of all patients with a definite diagnosis of endocarditis (modified Duke's criteria). 533 cases of IE. 151 were definite S. aureus endocarditis. Exclusion : R-sided endocarditis (n=67). 84 patients with definite L-Sided endocarditis caused by S. aureas were included. Incidence ranged from 2 to 4 cases per 10,000 admissions per year. 54 patients (64%) had a pre-determined valve condition (not specified by type of endocarditis nor by protocol outcomes). Mean age was 57 in those with NVE and 61 in those with PVE. No SD Reported.
Number of patients	**84**
Outcomes	Mortality Surgery (Valve-replacement)

<table>
<tr><td>Bibliographic reference</td><td>Fernandez Guerrero, M.L. et al (2010) Left-sided Endocarditis caused by staphylococcus aureus. A comparison of clinical and prognostic factors of patients with native and prosthetic valve endocarditis. Infectious Diseases in Clinical Practice; 18:308-312.</td></tr>
<tr><td></td><td>Stroke (CNS complications including brain bleeding)</td></tr>
<tr><td>Predictors/risk factors and effect estimates</td><td>Overall mortality n=28

Mortality by IE valve type in Patients with L-Sided endocarditis caused by S. aureus.
<table>
<tr><th>All n=84</th><th>Mortality</th><th>OR (95% CI)</th><th>P-value</th></tr>
<tr><td>NVE (Total n=56)</td><td>16 (28)</td><td rowspan="2">0.53 [0.21-1.37]</td><td rowspan="2">Not reported</td></tr>
<tr><td>PVE Total n=28)</td><td>12 (43)</td></tr>
</table>
Subsequent Surgery (valve replacement) by IE valve type in Patients with L-Sided endocarditis caused by S. aureus
<table>
<tr><th>All n=84</th><th>Surgery (Valve Replacement)</th><th>OR (95% CI)</th><th>P-value</th></tr>
<tr><td>NVE (Total n=56)</td><td>21 (37)</td><td rowspan="2">0.24 [0.09-0.64]</td><td rowspan="2">Not reported</td></tr>
<tr><td>PVE Total n=28)</td><td>20 (71)</td></tr>
</table>
Stroke (CNS complications including brain bleeding) by IE valve type in Patients with L-Sided endocarditis caused by S. aureus
<table>
<tr><th>All n=84</th><th>Stroke</th><th>OR (95% CI)</th><th>P-value</th></tr>
<tr><td>NVE (Total n=56)</td><td>16 (28)</td><td rowspan="2">0.72 [0.27-1.89]</td><td rowspan="2">Not reported</td></tr>
<tr><td>PVE Total n=28)</td><td>10 (36)</td></tr>
</table>
(percentage only reported)</td></tr>
<tr><td>Analysis used</td><td>Association of continuous variables – Fisher’s exact test.
Strength of association – odds ratio (OR) or Haldane’s estimator for small sample 2 x 2 tables.</td></tr>
<tr><td>Length of follow-up</td><td>1987-2009</td></tr>
<tr><td>Location</td><td>Madrid, Spain</td></tr>
<tr><td>Source of funding</td><td>Not mentioned</td></tr>
</table>

Bibliographic reference	**Fernandez Guerrero, M.L. et al (2010) Left-sided Endocarditis caused by staphylococcus aureus. A comparison of clinical and prognostic factors of patients with native and prosthetic valve endocarditis. Infectious Diseases in Clinical Practice; 18:308-312.**
Comments	**Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))** Study Participation – N Retrospective design. ? age of population/adults only? – mean age but no SD reported. S aureus population only. Study attrition – Y. Prognostic factor measurement – U The author's state that a limitation could be the length of time over which the data were collected in that substantial medical improvements in medical practice occurred. Outcome measurement – P the authors could not control for selection of surgical versus medical therapy. Confounding measurement and account – Y Analysis – N multivariate regression analysis has been carried out but aOR not reported. No sample size calculation 2/6 met = HIGH RISK OF BIAS

1 **Table 48**

Bibliographic reference	**Galvez-Acebal, J. et al (2010). Prognostic factors in left-sided endocarditis: results from the Andalusian multicentre cohort. BMC Infectious diseases. 10:17.**
Study type	Observational multi-centre study
Aim	To identify predictors of in-hospital mortality
Patient characteristics	Left sided IE (Duke criteria) for definite and possible IE. 624 (88%) were definite IE and 81 (12%) possible cases. 46 (7%) were IVDUs. Consecutively registered to a database during study period. (5 tertiary referral hospitals, 2 community hospitals). Patients registered before 1994 where retrospectively assigned diagnostic criteria. For relapses, only the first episode was included. Excluded : patients with insufficient follow-up data (not longer than 1 month). 5patients were ≤15 years old. 486 (69%) patients were male.
Number of patients	705
Outcomes	In-hospital mortality
Predictors/risk factors and effect estimates	Overall In-hospital mortality n=208, 29.5%

<table>
<tr><td>Bibliographic reference</td><td>Galvez-Acebal, J. et al (2010). Prognostic factors in left-sided endocarditis: results from the Andalusian multicentre cohort. BMC Infectious diseases. 10:17.</td></tr>
<tr><td></td><td>Univariate analysis of in-hospital mortality: patient characteristics and etiology.
<table>
<tr><th colspan="2">Variable</th><th>Alive (n=497)
N (%)</th><th>Deaths (n=208)
N (%)</th><th>RR (95%CI)</th><th>P-value</th></tr>
<tr><td>Age (y)</td><td>Mean±SD</td><td>51.6 ±17</td><td>28.8 ±16</td><td>-</td><td><0.001</td></tr>
<tr><td>Gender</td><td>Male</td><td>345 (71)</td><td>141 (29)</td><td rowspan="2">1.07 (0.76-1.52)</td><td rowspan="2">0.367</td></tr>
<tr><td></td><td>Female</td><td>152 (69.4)</td><td>67 (30.6)</td></tr>
<tr><td rowspan="2">Valve type</td><td>Prosthetic</td><td>104 (60.8)</td><td>67 (39.2)</td><td rowspan="2">1.48 (1.17-1.87)</td><td rowspan="2">0.001</td></tr>
<tr><td>Native</td><td>393 (73.6)</td><td>141 (26.4)</td></tr>
</table>
Multivariate analysis
Prosthetic endocarditis, β 0.688, OR 1.99 (1.26-3.14), p=0.003

Recurrence and relapse was reported as overall percentages only and not according to variables of interest.</td></tr>
<tr><td>Analysis used</td><td>Categorical variables – Chi-Square or Fisher’s exact test
Continuous variables – Student’s T test or Mann-Whitney U test.
Univariate analysis (RR) for mortality was performed followed by multivariate analyses using logistic regression. (model built including all variables with a significant association in univariate analysis and those considered potentially clinically relevant. Modification between variables were also studied and selection of variables was performed using stepwise backward procedure.</td></tr>
<tr><td>Length of follow-up</td><td>January 1984 – December 2006</td></tr>
<tr><td>Location</td><td>Andalusia, Spain. (7 hospitals)</td></tr>
<tr><td>Source of funding</td><td>Supported by Spanish Network for the Research in infectious diseases.</td></tr>
<tr><td>Comments</td><td>Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))
Study Participation – N Retrospective analysis. Age – 5 patients children, grouped with adults.
Study attrition – Y
Prognostic factor measurement – Y
Outcome measurement – Y
Confounding measurement and account – N Included all patients with definite and possible IE.
Analysis – Y
4/6 met = LOW RISK OF BIAS</td></tr>
</table>

1 **Table 49**

<table>
<tr><td>Bibliographic reference</td><td>Lin, Y-T. et al (2013) Infective endocarditis in children without underlying heart disease. Journal of Microbiology, Immunology and Infection. 46, 121-128.</td></tr>
<tr><td>Study type</td><td>Retrospective analysis</td></tr>
<tr><td>Aim</td><td>To review the clinical and laboratory characteristics of paediatric IE patients with and without underlying heart disease</td></tr>
<tr><td>Patient characteristics</td><td>January 1991 – April 2011.
All consecutive paediatric patients (age≤18years) with a diagnosis of definite or possible IE (Modified Duke criteria) were enrolled. Data collected from medical records.
Mean age was 9.2 years (range 3 days to 18.7 years)</td></tr>
<tr><td>Number of patients</td><td>47 (with 48 episodes of IE). Of these 31 (64.6%) had CHD, 6 (12.5%) had non CHD chronic disease and 11 (22.9%) were previously healthy adolescents.</td></tr>
<tr><td>Outcomes</td><td>IE, Need for surgery (incl. valve surgery), in-hospital death, microbial pathogens (not reported here as non-protocol outcome)</td></tr>
<tr><td>Predictors/risk factors and effect estimates</td><td>IE in children with and without CHD
<table>
<tr><td rowspan="2"></td><td rowspan="2">CHD (n=31)</td><td colspan="2">NON CHD (n=17)</td><td rowspan="2">P-value (CHD vs non CHD)</td><td rowspan="2">P-value (CHD vs healthy)</td></tr>
<tr><td>Chronic disease (n=6)</td><td>Previously healthy (n=11)</td></tr>
<tr><td>Definite/Possible IE</td><td>19 / 12</td><td>4 / 2</td><td>11 / 0</td><td>0.095</td><td>0.018</td></tr>
</table>
(Protocol) Outcomes in Children with IE by health status (For Q2)
<table>
<tr><td rowspan="2"></td><td rowspan="2">CHD (n=31) (%)</td><td colspan="2">NON CHD (n=17)</td><td rowspan="2">P-VALUE</td></tr>
<tr><td>Chronic disease (n=6)</td><td>Previously healthy (n=11)</td></tr>
<tr><td>Need for cardiac surgery (total = 17)</td><td>9/31 (29)</td><td>0 (0)</td><td>8/11 (72.7)</td><td>Not calculated</td></tr>
<tr><td>Valve replacement surgery specifically (total = 11/17)</td><td>3 / 9 (33.3%)</td><td>0</td><td>8 / 8 (100)</td><td>Not calculated</td></tr>
<tr><td>In-hospital mortality (total deaths =7)</td><td>6 / 7</td><td>0</td><td>1 / 7</td><td>Not calculated</td></tr>
</table>
No odds ratios reported.</td></tr>
</table>

Bibliographic reference	Lin, Y-T. et al (2013) Infective endocarditis in children without underlying heart disease. Journal of Microbiology, Immunology and Infection. 46, 121-128.
Analysis used	Categorical variables were compared using Pearson Chi-square test or Fisher's exact test in univariate analysis.
Length of follow-up	20 years 3 months study duration
Location	Kaohsiung Hospital, Taiwan
Source of funding	This work was supported by a grant from the Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan
Comments	**Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))** Study Participation – U retrospective design (but consecutive enrolment) Study attrition – Y Prognostic factor measurement – Y Outcome measurement – N Diagnosis of IE included possible and definite. Confounding measurement and account – Y Analysis – N No odds ratios. Reviewer needed to back calculate. No sample size calculations. 3/6 met = HIGH RISK OF BIAS

1 **Table 50**

Bibliographic reference	Murakami, T. et al (2012) Factors associated with surgery for active endocarditis in congenital heart disease. International Journal of Cardiology 157; 59-62.
Study type	Retrospective observational cohort (multi-centre)
Aim	To determine the surgical indications for active infective endocarditis in congenital heart diseases.
Patient characteristics	N=239 paediatric and adult patients with IE surveyed. (Children n=170) 216 had congenital heart diseases, 23 were not diagnosed. Of these 147 had CHD and 23 without apparent CHD) 61 underwent surgical therapy for active IE. Age Children 7.4 years±5.7 years (range 14 days to17 years). Adults 32.5±14.1 years (range 18-69years) Diagnoses of underlying congenital diseases given as single number/percentage of total.
Number of patients	239
Outcomes	Surgery

<table>
<tr><td>Bibliographic reference</td><td>Murakami, T. et al (2012) Factors associated with surgery for active endocarditis in congenital heart disease. International Journal of Cardiology 157; 59-62.</td></tr>
<tr><td>Predictors/risk factors and effect estimates</td><td>7 deaths (11%).

Number of patients that underwent surgery with active endocarditis with or without each risk factor, odds ratio and p values by univariate regression analysis.
<table>
<tr><th>Risk Factor</th><th>Surgery</th><th>No surgery</th><th>Odds Ratio (95% CI)</th><th>P value</th></tr>
<tr><td>Male</td><td>42/143 (29)</td><td>19/96 (20)</td><td>1.69 (0.91-3.13)</td><td>0.13</td></tr>
<tr><td>Diagnosis of underlying heart disease before IE</td><td>49/216 (23)</td><td>12/23 (52)</td><td>0.27 (0.11-0.65)</td><td>0.0044</td></tr>
<tr><td>Previous surgery for CHD</td><td>26/119 (22)</td><td>35/120 (29)</td><td>0.68 (0.38-1.22)</td><td>0.24</td></tr>
<tr><td>History of IE</td><td>4/21 (19)</td><td>57/218 (26)</td><td>0.67 (0.22-2.06)</td><td>0.61</td></tr>
</table>
Data are expressed as number of operated patients during active infective endocarditis period of the group of the presence or absence of the risk factors and the ratio of operated patients in parenthesis.

Lack of diagnosis of CHD before onset of IE was significantly associated with need for surgical intervention.</td></tr>
<tr><td>Analysis used</td><td>Univariate logistic regression analysis to evaluate risk factors associated with need for surgical intervention for IE
Multivariate analysis (stepwise approach) was conducted.</td></tr>
<tr><td>Length of follow-up</td><td>Duration : January 1997 to December 2001</td></tr>
<tr><td>Location</td><td>Japan (66 separate institutions)</td></tr>
<tr><td>Source of funding</td><td>Not reported</td></tr>
<tr><td>Comments</td><td>Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))
Study Participation – N retrospective design
Study attrition – Y
Prognostic factor measurement – Y
Outcome measurement – Y
Confounding measurement and account – Y
Analysis – N unadjusted OR reported only. Multivariate analysis conducted but results not provided for each predictor evaluated.</td></tr>
</table>

Bibliographic reference	**Murakami, T. et al (2012) Factors associated with surgery for active endocarditis in congenital heart disease. International Journal of Cardiology 157; 59-62.**
	4/6 met = LOW RISK OF BIAS

1 **Table 51**

Bibliographic reference	**Murdoch, D.R. et al. (2009). Clinical presentation, etiology, and outcome of Infective endocarditis in the 21st century. Archives of Internal Medicine; 169:5:463-473**
Study type	Prospective Cohort Study
Aim	To provide a picture of the presentation, etiology and outcome of infective endocarditis (IE) in a large cohort from multiple locations worldwide.
Patient characteristics	Adult patients with definite IE (Modified Duke Criteria) Median age 57.9 (IQR 43.2-71.8)y. 72.1% had native valve IE. Site of enrolment minimum criteria – 12 cases per year, access to cardiac surgery, consecutive enrolment and to minimise ascertainment bias, high quality data and institutional review board approval. Data submitted to main co-ordinating centre – Duke University.
Number of patients	2781 (with definite IE out of a total of 3284 who were screened).
Outcomes	IE Complications from IE including mortality
Predictors/risk factors and effect estimates	**Predisposing conditions of people with definite IE** / **Total cohort** Prosthetic valve IE: 563/2636 (21) Previous IE: 222/2780 (8) Congenital heart disease: 311/2656 (12) There was no reporting of associations between risk factors of interest and IE. In hospital mortality was 17.7% **Results of multivariable regression modelling of associations with in-hospital death in 2781 patients** **Variable** / **OR (95% CI)** / **P-value** Prosthetic valve endocarditis / 1.47 (1.13-1.90) / **0.004**

Bibliographic reference	**Murdoch, D.R. et al. (2009). Clinical presentation, etiology, and outcome of Infective endocarditis in the 21st century. Archives of Internal Medicine; 169:5:463-473**
	Congenital heart disease | 1.22 (0.74-2.02) | 0.44
Analysis used	Univariable comparisons made using Chi-square or Kruskal-Wallis test. Those with P<0.10 were entered into final explanatory model.
Length of follow-up	Duration June 1, 2000 – September 1, 2005.
Location	58 hospitals in 25 countries
Source of funding	Supported in part by grants from NIH, American Heart Association and Ministerio de Sanidad y Consumo, Madrid, Spain and two other Spanish research centres.
Comments	**Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))** Study Participation – Y Study attrition – U Unclear why numbers of total sample (denominator) changes during reporting of pre-existing cardiac condition. Prognostic factor measurement – Y Outcome measurement – Y Confounding measurement and account –U All participating centres were referral centres which may mean the results to do not fully reflect those of the general population as referral centres tend to see more complex cases. The weighting of geographical distribution is towards wealthier countries in Europe, North America and Australasia. Analysis – Y 4/6 met = LOW RISK OF BIAS.

1 **Table 52**

Bibliographic reference	**San Roman, J A. et al. (2007) Prognostic Stratification of patients with left sided endocarditis determined at admission. The American Journal of Medicine; 120, 369.e1-369.e7.**
Study type	Prospective study
Aim	To identify high risk patients with first few days after admission with IE.
Patient characteristics	441 Patients who met Duke criteria (406 with definite and 35 with possible IE) were included. Consecutive enrolment during study period. N=333 had L-sided IE. Exclusions : (n= 16) patients with septic shock at admission due to it being an absolute indication for urgent surgery.

<table>
<tr><td>Bibliographic reference</td><td>San Roman, J A. et al. (2007) Prognostic Stratification of patients with left sided endocarditis determined at admission. The American Journal of Medicine; 120, 369.e1-369.e7.</td></tr>
<tr><td></td><td>In patients with more than one event, only the first was considered.
Not specified if adults only.</td></tr>
<tr><td>Number of patients</td><td>N=317</td></tr>
<tr><td>Outcomes</td><td>Events – (death or active phase surgery)</td></tr>
<tr><td>Predictors/risk factors and effect estimates</td><td>Of the 130 who had events, 65 died and 65 underwent operation in the active phase.

There were no significant differences in death or operation in those with left sided IE according to previous cardiopathy or previous endocarditis.

Univariate analysis of clinical characteristics by event (death or active phase surgery)
<table>
<tr><th>Clinical characteristics</th><th>Total (n=317) N (%)</th><th>No Events* (n=187) N (%)</th><th>Events* (n=130) N (%)</th><th>P value</th></tr>
<tr><td>Age (y)</td><td>57 ±16</td><td>57 ±16</td><td>58 ±16</td><td>0.82</td></tr>
<tr><td>Male gender</td><td>209 (66)</td><td>128 (68)</td><td>81 (62)</td><td>0.26</td></tr>
<tr><td>Previous cardiopathy</td><td>202 (65)</td><td>121 (66)</td><td>81 (64)</td><td>0.26</td></tr>
<tr><td>Degenerative</td><td>29 (9)</td><td>16 (9)</td><td>13 (10)</td><td>0.65</td></tr>
<tr><td>Prosthesis</td><td>124 (40)</td><td>72 (39)</td><td>52 (41)</td><td>0.76</td></tr>
<tr><td>Rheumatic</td><td>32 (10)</td><td>17 (9)</td><td>15 (12)</td><td>0.47</td></tr>
<tr><td>Previous endocarditis</td><td>28 (9)</td><td>16 (9)</td><td>12 (9)</td><td>0.80</td></tr>
<tr><td colspan="5">Echocardiographic Characteristics (relating to pre-existing cardiac conditions)</td></tr>
<tr><td>Prosthetic</td><td>114 (36)</td><td>63 (34)</td><td>51 (39)</td><td>0.31</td></tr>
<tr><td>Aortic mechanical prosthesis</td><td>36 (11)</td><td>17 (9)</td><td>19 (15)</td><td>0.13</td></tr>
<tr><td>Mitral mechanical prosthesis</td><td>55 (17)</td><td>35 (19)</td><td>20 (15)</td><td>0.44</td></tr>
<tr><td>Mitral bioprosthesis</td><td>16 (5)</td><td>30 (18)</td><td>25 (17)</td><td>0.80</td></tr>
<tr><td>Aortic bioprosthesis</td><td>10 (3)</td><td>7 (4)</td><td>9(7)</td><td>0.31</td></tr>
</table>
*Death and surgery in the active phase were regarded as events. Elective surgery (after antibiotic regimen was completed) were not classed as events.</td></tr>
</table>

Bibliographic reference	**San Roman, J A. et al. (2007) Prognostic Stratification of patients with left sided endocarditis determined at admission. The American Journal of Medicine; 120, 369.e1-369.e7.**
	Results provided for statistically significant variables only (after multivariate analysis) associated with an event (death or surgery). None of the protocol characteristics of interested remained significant.
Analysis used	2 group analysis using 2 tailed Student t-tests or Wilcoxon rank-sum tests and Chi-square or Fisher's exact tests where appropriate. Univariate and multivariate analysis (logistic regression model) including a backward stepwise method were performed with events as the dependent variable. In consecutive steps variables that were statistically significant in the univariate analysis were analysed further. Max 1 variable per 10 outcomes was entered into models. Hosmer-Lemeshow test and model was used to examine goodness of fit of the final model.
Length of follow-up	Duration : 1996 and 2003
Location	5 tertiary care centres Spain
Source of funding	Financed in part by the red de centros cardiovasculares which is supported by the Instituo de Salud Carlos III
Comments	**Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))** Study Participation – Y. Study attrition – Y Prognostic factor measurement – Y Outcome measurement – N classification of the outcome as event vs no event, and defining event as death OR surgery (and counting only the first event if there were more than one) introduces potential bias. If surgery was performed and then patients died this could affect the significance of the identified predictors. Confounding measurement and account – Y. Analysis – N aOR were not reported. Reviewer needed to back calculate odds ratios. No sample size calculation. 4/6 met = LOW RISK OF BIAS

1 **Table 53**

Bibliographic reference	**Smith MJ, So RR, Engel AM. (2007) Clinical predictors of mortality from infective endocarditis. International journal of Surgery. 5, 31-34.**
Study type	Prospective cohort
Aim	To determine which risk factors and outcome variables are statistically significant predictors of mortality from IE.
Patient characteristics	Original cohort of prospective hospitalisation n=11,230. This study included patients from this original cohort who had IE diagnosed between October 1993 and Feb 2004,

<table>
<tr><td>Bibliographic reference</td><td>Smith MJ, So RR, Engel AM. (2007) Clinical predictors of mortality from infective endocarditis. International journal of Surgery. 5, 31-34.</td></tr>
<tr><td></td><td>adults, (≥18y). N=87.
No exclusion criteria given</td></tr>
<tr><td>Number of patients</td><td>87</td></tr>
<tr><td>Outcomes</td><td>Mortality</td></tr>
<tr><td>Predictors/risk factors and effect estimates</td><td>Univariate analysis of risk factors for death
<table>
<tr><th></th><th>Deceased N (%)
(Total n =10 (11.5%)</th><th>Alive N (%)
(n=77)</th><th>P-value</th></tr>
<tr><td>Age (y)</td><td>65.1±15.5</td><td>53.9±14.2</td><td>0.023</td></tr>
<tr><td>Male</td><td>7 (13)</td><td>45 (86)</td><td>0.734</td></tr>
<tr><td>Previous cardiac surgery</td><td>3 (12)</td><td>21 (88)</td><td>1.00</td></tr>
<tr><td>Type of prosthesis (mechanical)</td><td>2 (9)</td><td>20 (91)</td><td>0.665</td></tr>
</table>
(unclear if type of prosthesis relates to inserted post IE or if was present prior to diagnosis)

Multivariate regression was used to generate the adjusted risk for the significant risk factors. There was no significant difference in mortality for endocarditis patients for any of the risk factors of interest.</td></tr>
<tr><td>Analysis used</td><td>Risk Factors – (unadjusted) chi squire or Fisher’s exact tests where appropriate and t-tests comparing survival and non-survival. Multivariate regression was used to generate the adjusted risk for the significant risk factors.
Outcome variables – survival vs non survival comparisons were conducted using chi-square or Fisher’s exact test and t-tests.</td></tr>
<tr><td>Length of follow-up</td><td>Not specified. Mortality is defined as in-house.</td></tr>
<tr><td>Location</td><td>Cincinnati, USA</td></tr>
<tr><td>Source of funding</td><td>No specified</td></tr>
<tr><td>Comments</td><td>Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))
Study Participation – U Exclusion criteria not specified (? Reported elsewhere)
Study attrition – Y sample population accounted for the study period (sub population)
Prognostic factor measurement – Y
Outcome measurement – Y
Confounding measurement and account – Y
Analysis – N no odds ratios or adjusted ORs were reported. The former were back calculated by the reviewer.</td></tr>
</table>

Bibliographic reference	**Smith MJ, So RR, Engel AM. (2007) Clinical predictors of mortality from infective endocarditis. International journal of Surgery. 5, 31-34.**
	No sample size calculation. 4/6 met = LOW RISK OF BIAS

1 **Table 54**

Bibliographic reference	**Ternhag A et al. (2013) A nationwide cohort study of mortality risk and long-term prognosis in infective endocarditis in Sweden. 8, 7, e67519.**
Study type	Retrospective cohort study
Aim	To investigate the incidence of IE as well as associated short and long term mortality rates
Patient characteristics	IE patients (hospitalised and treated) identified from Swedish National inpatient register and linked to population register to identify deaths. Not specified if adults only. Crude mortality rates were obtained at different time intervals. These were standardized using age and sex matched controls in the general population. IVDUs were included (5%)
Number of patients	7063 with 7817 episodes of IE during study period.
Outcomes	Mortality (all cause attributable IE Mortality by the end of the follow-up period). Surgery (cardiac, i.e. valve surgery)
Predictors/risk factors and effect estimates	Average annual incidence 7.7 cases of IE per 100000 Of these 12% had prosthetic valve IE (80% had native valve, remainder were IVDUs). All cause 30 day crude mortality rate was 10.4%

	No of patients (% men)	**Age, mean (IQR)**	**Crude 30 day mortality (%)**
Total	7609 (59.2)	65.7 (55-79)	788 (10.4)
Native Valve	6138 (57.6)	66.8 (57-80)	642 (10.5)
Prosthetic Valve	890 (62.7)	70.4 (65-79)	100 (11.2)
Native valve surgery	778 (72.1)	55.8 (47-67.8)	42 (5.4)
Native Valve non surgery	5360 (55.5)	68.4 (60-81)	600 (11.2)
Prosthetic Valve surgery	104 (74)	61.3 (56.8-72)	16 (15.4)
Prosthetic Valve non Surgery	786 (61.2)	71.6 (67-80)	84 (10.7)

<table>
<tr><td>Bibliographic reference</td><td>Ternhag A et al. (2013) A nationwide cohort study of mortality risk and long-term prognosis in infective endocarditis in Sweden. 8, 7, e67519.</td></tr>
<tr><td></td><td>No significant differences in absolute or relative mortality risks were found between patients with native valve and prosthetic valve IE during 1 year follow up but those with prosthetic valve IE had a lower 5 year survival.

Long term mortality in the infective endocarditis cohort compared to the age and sex matched Swedish General Population (n=7603).
<table>
<tr><th></th><th colspan="2">Time 1-5 years</th><th>SMR</th><th>95%CI</th></tr>
<tr><th></th><th>Obs No. of deaths (%)</th><th>Expected number of deaths</th><th></th><th></th></tr>
<tr><td>Total</td><td>1117 (14.7)</td><td>518.6</td><td>2.2</td><td>2.0-2.3</td></tr>
<tr><td>Native valve</td><td>894 (14.6)</td><td>441.9</td><td>2.0</td><td>1.9-2.2</td></tr>
<tr><td>Prosthetic valve</td><td>154 (17.3)</td><td>67.9</td><td>2.3</td><td>1.9-2.7</td></tr>
<tr><td>Age≤65 years</td><td>228 (7.4)</td><td>36.3</td><td>6.3</td><td>5.4-7.2</td></tr>
<tr><td>Age >65</td><td>889 (19.6)</td><td>482.3</td><td>1.8</td><td>1.7-2.0</td></tr>
<tr><td>Men</td><td>623 (13.9)</td><td>296.1</td><td>2.1</td><td>1.9-2.3</td></tr>
<tr><td>Women</td><td>494 (15.9)</td><td>222.5</td><td>2.2</td><td>2.0-2.5</td></tr>
</table></td></tr>
<tr><td>Analysis used</td><td>Comparisons of mortality for each category were stratified using and sex Mantel-Haenszel estimates of the OR. Time trend for incidence and mortality rate of IE was evaluated using linear regression model using quasi-poisson distribution and t-test for significance.</td></tr>
<tr><td>Length of follow-up</td><td>Duration 1997-1007.</td></tr>
<tr><td>Location</td><td>Sweden</td></tr>
<tr><td>Source of funding</td><td>Not specified</td></tr>
<tr><td>Comments</td><td>Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))
Study Participation – N Retrospective design. IVDUs were included (analysed separately). The authors cite a possible selection bias that explains the divergent results concerning mortality after surgery among different types of IE (native or prosthetic valve). Also the younger and those with fewer morbidities were probably more likely to have surgery than the oldest and most vulnerable individuals.
Study attrition – Y All patients were accounted for in analysis.
Prognostic factor measurement – Y
Outcome measurement – Y
Confounding measurement and account – Y</td></tr>
</table>

Bibliographic reference	**Ternhag A et al. (2013) A nationwide cohort study of mortality risk and long-term prognosis in infective endocarditis in Sweden. 8, 7, e67519.**
	Analysis – Y 4/6 met = LOW RISK OF BIAS

1 **Table 55**

Bibliographic reference	**Thuny, F et al. (2012) Excess mortality and morbidity in patients surviving infective endocarditis. Valvular and congenital heart disease. 164:94-101.**
Study type	Observational cohort study (majority of data collected retrospectively).
Aim	To evaluate survival in people with IE who survive the acute phase and had treatment completed.
Patient characteristics	Consecutive patients admitted with a first definite diagnosis of IE (Duke Criteria) were eligible for participation. Those who survived the inpatient episode were retrospectively included. Not specified if adults only. Exclusion criteria : absence of data after hospitalisation and an isolated pacemaker or defibrillator leads IE. Early surgery was defined as valve surgery performed during the course of antibiotic therapy.
Number of patients	328 (followed up for 731 person-years, median 2.2 years, range, 6 days to 7 years).
Outcomes	All-cause mortality (after completion of treatment for acute IE) Recurrence of IE (includes relapses and reinfections defined by the European guidelines for Cardiology). Need for late surgery (surgery indicated as consequence of the initial or recurrent IE episode.
Predictors/risk factors and effect estimates	**Characteristics of the 328 patients surviving the acute phase of IE**

Characteristic	Overall (n=328)	Alive (n-273)	Died (n=55)	p-value
Age (y) mean ±SD	61 ±16	60±16	68±13	0.0003
Sex ratio male/female	233/95	199/74	34/21	0.10
Underlying heart disease	206(63)	176 (64)	30 (55)	0.16
Prosthetic valve	93 (28)	80 (29)	13 (24)	0.39

Recurrence and late surgery are reported but not included here as they are not reported by characteristic (i.e. underlying cardiac condition).

Predictors of IE excess mortality in the univariate excess hazard mortality analysis adjusted for age and sex.

Bibliographic reference	**Thuny, F et al. (2012) Excess mortality and morbidity in patients surviving infective endocarditis. Valvular and congenital heart disease. 164:94-101.**
	<table><tr><th>Predictor</th><th>Age and sex adjusted EHR</th><th>95% CI</th><th>P value</th></tr><tr><td>Underlying heart disease</td><td>NOT REPORTED</td><td></td><td></td></tr><tr><td>Prosthetic valve</td><td>0.72</td><td>0.35-1.50</td><td>0.39</td></tr></table> No significant differences in death directly attributable to IE by characteristics of interest.
Analysis used	Statistical test not specified for baseline characteristics although univariate and multivariate analysis (adjusted for age and sex) using excess mortality hazard regression model. (Although results not reported here for the latter). Expected survival was calculated acco0rding to Hakulinen method by applying age, sex and calendar year specific mortality hazard rates of the Bouche-du-Rhone French district population (2002-2006) to the number of person years of follow-up in the study cohort. Excess mortality hazard model for individual data was used with a generalized linear model and Poisson error structure. This enabled calculation of specific IE mortality hazard in the absence of other causes of death.
Length of follow-up	Duration January 2002 to December 2008. Follow up period was restricted to 7 years.
Location	Marseille, France
Source of funding	No extramural funding was used.
Comments	**Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))** Study Participation – N Retrospective design (although consecutive). ? Referral bias as was performed in referral centres. Study attrition – Y Prognostic factor measurement – Y Outcome measurement – Y Confounding measurement and account – Y Analysis – N Reviewer had to back calculate ORs as none were reported. No sample size calculation. 4/6 = LOW RISK OF BIAS

1 **Table 56**

Bibliographic reference	**Thuny F, et al (2007) Impact of cerebrovascular complications on mortality and neurologic outcome during infective endocarditis: a prospective multicentre study. 28, 1155-1161.**
Study type	Prospective Study

<table>
<tr><td>Bibliographic reference</td><td>Thuny F, et al (2007) Impact of cerebrovascular complications on mortality and neurologic outcome during infective endocarditis: a prospective multicentre study. 28, 1155-1161.</td></tr>
<tr><td>Aim</td><td>To analyse the risk of death according to the type of cerebrovascular complication during infective endocarditis and to analyse the determinants of outcome.</td></tr>
<tr><td>Patient characteristics</td><td>496 patients with definite IE (Duke criteria)
Consecutive patients admitted with IE were eligible for entry (n=545). 49 patients were excluded due to pacemaker IE.
Diagnosis of CVC was based on clinical and CT scan data or both. 453 patients had a CT scan. CVC included stroke, TIA and silent cerebral embolism.</td></tr>
<tr><td>Number of patients</td><td>496</td></tr>
<tr><td>Outcomes</td><td>CVC (cerebro-vascular complications)</td></tr>
<tr><td>Predictors/risk factors and effect estimates</td><td>CVC (n=109) complications were
Silent cerebral embolism n=17, ischaemic stroke n=50, TIA n=30, Primary intracerebral haemorrhage n=12.

<table>
<tr><th></th><th>All patients (n=496)</th><th>CVC* (n=109)</th><th>Without CVC (n=387)</th><th>p-value</th></tr>
<tr><td>Age (mean ±SD, y)</td><td>58±16</td><td>59±16</td><td>58±16</td><td>0.61</td></tr>
<tr><td>Male</td><td>364(73)</td><td>81(74)</td><td>283(73)</td><td>0.80</td></tr>
<tr><td>Prosthetic Valve</td><td>110 (22)</td><td>24(22)</td><td>86(22)</td><td>0.96</td></tr>
<tr><td>Underlying heart disease[b]</td><td>275 (55)</td><td>59(54)</td><td>216(56)</td><td>0.75</td></tr>
</table>
*222 patients (45%) had ≥1 embolic event.
[b]Including Rheumatic valve disease, non-rheumatic valve disease, congenital heart disease and degenerative cardiac disease.</td></tr>
<tr><td>Analysis used</td><td>Categorical variables – Chi-Square test, Fisher’s exact test (two-tailed), Student’s t-test or Mann Whitney U test.</td></tr>
<tr><td>Length of follow-up</td><td>January 1990-March 2005. Median follow up was 2.9yrs (IQR 1.4-5.8 yrs.).</td></tr>
<tr><td>Location</td><td>Two referral centres, Marseille, France</td></tr>
<tr><td>Source of funding</td><td>Not mentioned.</td></tr>
<tr><td>Comments</td><td>Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))
Study Participation – Y
Study attrition – Y
Prognostic factor measurement – Y</td></tr>
</table>

Bibliographic reference	**Thuny F, et al (2007) Impact of cerebrovascular complications on mortality and neurologic outcome during infective endocarditis: a prospective multicentre study. 28, 1155-1161.**
	Outcome measurement – U authors cite that the predictive value of a mechanical valve PVE on risk of neurological death in patients with CVC could be explained by the potential effect of anticoagulant therapy in these patients. The potential of referral bias was also cited by the authors as these two centres have an early surgery policy. This could have reduced the incidence of CVC. Definition of CVC is broad and large proportion TIA. Confounding measurement and account –Y Analysis – N No odds ratios reported. Back calculated by reviewer. No sample size calculation. 4/6 met = LOW RISK OF BIAS

1 **Table 57**

Bibliographic reference	**Tleyjeh, IM et al (2007) The impact of valve surgery on 6 month mortality in left-sided infective endocarditis. Circulation. 115:1721-1728.**
Study type	Cohort (retrospective/prospective)
Aim	To evaluate the role of valve surgery and all cause 6 month mortality among patients with L-sided IE
Patient characteristics	Consecutive patients 18yrs+ diagnosed and treated for Left-sided IE (modified Duke Criteria). 546 patients were included. (Of these 512 (93.8%) met the definite IE criteria). Exclusion criteria : pt refusal to consent to medical record review or if left hospital before a complete diagnosis/treatment plan.
Number of patients	546
Outcomes	Surgery All cause 6 month mortality after date of IE diagnosis.
Predictors/risk factors and effect estimates	**Characteristics by surgery or no surgery after IE.**

Characteristic	Total Cohort (N=546)	Non-surgical (n=417)	Surgical (n=129)	p-value
Age (y, mean (SD)	62.3 (16.31)	64.03 (15.58)	26.72 (17.4)	<0.0001
Male sex n(%)	359 (65.75)	273 (65.47)	86 (66.67)	0.80
Previous IE	59 (10.81)	43(10.31)	16(12.40)	0.50
Prosthetic valve ≤2 months after IE	23(4.21)	18(4.32)	5(3.88)	0.07
Prosthetic valve >2months after IE	167(30.59)	117(28.06)	50(38.76)	-

Bibliographic reference	**Tleyjeh, IM et al (2007) The impact of valve surgery on 6 month mortality in left-sided infective endocarditis. Circulation. 115:1721-1728.**
	No multivariate regression was carried out for predictors of surgery.
Analysis used	Surgical and non-surgical patients were compared with 2 sample t-tests (continuous variables) and either Chi-square or Fisher exact tests for nominal variables. Ordinal variables were compared with Wilcoxon rank-sum test. Adjustment for treatment selection and survivor biases with propensity score and time-dependent covariate analyses was carried out. Subgroup analyses was carried out using Cox proportional hazards regression models for mortality after surgery (not reported here).
Length of follow-up	1980-1998
Location	Minnesota, USA
Source of funding	Supported by grants from the Infectious Diseases Division Small Grants Program and the ENHANCE Award from the Department of Medicine, Mayo Clinic.
Comments	**Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))** Study Participation – N authors cite referral bias as a potential limitation (to limit the applicability of findings). Study attrition – Y Prognostic factor measurement – Y Outcome measurement – Y Confounding measurement and account – U authors cite potential for unmeasured confounders despite the statistical adjustments applied. Analysis – N No Calculation of odds ratios or multivariate analysis. Reviewer back calculated ORs. No sample size calculation. 3/6 met = HIGH RISK OF BIAS

1 **Table 58**

Bibliographic reference	**[CG64]** **Wang A, Athan E, Pappas PA et al. (2007) Contemporary clinical profile and outcome of prosthetic valve endocarditis 2926. JAMA: Journal of the American Medical Association 297: 1354-61**
Study type	Observational cohort
Aim	To describe the clinical characteristics and outcome of prosthetic valve endocarditis (PVE) and to determine prognostic factors associated with in-hospital mortality.

Bibliographic reference	**[CG64]** **Wang A, Athan E, Pappas PA et al. (2007) Contemporary clinical profile and outcome of prosthetic valve endocarditis 2926. JAMA: Journal of the American Medical Association 297: 1354-61**
Patient characteristics	Inclusion: patients with definite IE PVE defined by Duke criteria enrolled in the International Collaboration on Endocarditis-Prospective Cohort Study (61 medical centres in 28 countries) Data from the International Collaboration on endocarditis (ICE) were used for this study. n = 2670 with definite IE, n = 556 (20.1%) with PVE. Compared with NVE (n = 1895) those with PVE were significantly older; 65.0 (49.9 to 74.3) vs. 56.3 (41.1 to 69.9), p<0.001, less likely to use injection drugs; 10 (1.8) vs. 235 (12.4%), p<0.001, and more likely to have health care associated infection; 203 (36.5%) vs. 587 (31.0%), p=0.01 and previous IE; 112 (20.1%) vs. 91 (4.8%), p<0.001
Number of patients	n = 556
Predictors	Prosthetic valves
Outcomes	In-hospital mortality
Analysis used	Univariate comparisons of clinical characteristics were made with the Wilcoxon rank-sum test or the X^2 test as appropriate. Multivariate analysis was carried out (adjusting for 15 variables).
Length of follow-up	Study from June 2000 to August 2005
Location	Duke University – co-ordination. Participating sites USA (10), S.America (7), Northern/Central Europe (14), Southern Europe/Middle East/S.Africa (11 sites) and Australia/New Zealand/Asia (11).
Effect estimates	127 / 556 (22.8%) people with prosthetic valve endocarditis died vs. 310 / 1895 (16.4%) without prosthetic valves OR 1.51 (1.2-1.9) (Calculated by reviewer). 203 patients had a history of prior infective endocarditis. Of these, 112 had a subsequent diagnosis of PVIE vs. 91 who had a diagnosis of native valve IE. Of these 112 PVE patients, 21 patients died in hospital (18.8%) giving an unadjusted OR of **0.74 (0.49-1.12).** There was no significant difference in mortality after PV IE vs NVE in those with prior history of IE.
Source of funding	American Heart Association Grant-in-Aid
Comments	**Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))** Study Participation – Y Study attrition – Y no patients appeared to be lost to follow-up. Prognostic factor measurement - Y

Bibliographic reference	**[CG64]** **Wang A, Athan E, Pappas PA et al. (2007) Contemporary clinical profile and outcome of prosthetic valve endocarditis 2926. JAMA: Journal of the American Medical Association 297: 1354-61**
	Outcome measurement – Y Confounding measurement and account – U Authors cite that mortality rates were high in the study. Analysis – N odds ratio was not provided and was calculated by reviewer. 4/6 met = LOW RISK OF BIAS

1 **Table 59**

Bibliographic reference	**Wong, CW. Et al (2009). Outcome and prognostic factors on 57 cases of infective endocarditis in a single centre. Journal of the New Zealand Medical Association. 122:1304:54-62.**
Study type	Retrospective review
Aim	Evaluate the clinical characteristics and outcome of infective endocarditis and the prognostic significance of recurrent endocarditis.
Patient characteristics	57 episodes of IE in 47 patients. 41 (70%) were definite IE (modified Duke Criteria 2000) and 16 were possible. 41 cases of native valve IE and 15 cases of bioprosthetic/mechanical valve IE and 1 permanent pacemaker lead endocarditis. Demographic characteristics of patients were provided as numbers/percentages. Mean age 66 (range 16-93), male 36 (77%).
Number of patients	47 (57 episodes IE)
Outcomes	Recurrence of IE
Predictors/risk factors and effect estimates	Time to recurrence was from 3 weeks to 41 months (mean 8.9 months) 4 patients had a remote history of IE outside the study period. 17% of patients with underlying heart conditions had a recurrence. **Risk factors of recurrent endocarditis**

Parameters	**Total** **N=**47	**Recurrence** N=8	**No recurrence** N=39	**P-value**
Underlying heart conditions				
Prosthetic valve	13	1	12	0.41

Bibliographic reference	**Wong, CW. Et al (2009). Outcome and prognostic factors on 57 cases of infective endocarditis in a single centre. Journal of the New Zealand Medical Association. 122:1304:54-62.**
	Rheumatic heart disease: 9 / 1 / 8 / 1.0 Mitral valve prolapse: 8 / 1 / 7 / 1.0 Aortic stenosis: 4 / 2 / 2 / 0.12
Analysis used	Unpaired t-test on continuous data. Categorical risk factors were assessed using Fisher's exact test.
Length of follow-up	June 2002-June2007.
Location	Tauranga, New Zealand (Single centre)
Source of funding	Not mentioned
Comments	**Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))** Study Participation – N Retrospective from single centre. Study attrition – Y Prognostic factor measurement - Y Outcome measurement – P Results were not separated between definite and possible diagnoses. Confounding measurement and account – Y Analysis – N No odds ratios for univariate analysis for risk factors of interest. No multivariate analysis was carried out. Reviewer back calculated odds ratios. No Sample size calculation. 3/6 met = LOW RISK OF BIAS

1 **Table 60**

Bibliographic reference	**Yoshinaga, M et al. (2008) Risk factors for in-hospital mortality during infective endocarditis in patients with congenital heart disease. American Journal of Cardiology. 101:114-118.**
Study type	Retrospective observational cohort study.
Aim	To determine the risk factors for mortality in paediatric and adults with congenital heart disease (CHD).
Patient characteristics	Of 239 data sets of patients with CHD reviewed, 216 data sets of patients were complete. Of these 137 patients with IE (modified Duke's criteria) were included. Adults and Children - Age 1 month – 62 years (median 12 years).
Number of patients	137
Outcomes	In hospital mortality was 10% (14/137 patients).
Predictors/risk factors and	**Number of deceased patients with or without each risk factor, odds ratio and p-values by univariate**

Bibliographic reference	**Yoshinaga, M et al. (2008) Risk factors for in-hospital mortality during infective endocarditis in patients with congenital heart disease. American Journal of Cardiology. 101:114-118.**
effect estimates	**regression analysis**

Risk Factor	Present	Absent	Odds ratio (95% CI)	p-value
Male	8/75(11)	6/62(10)	1.11(0.365-3.40)	0.85
Age <18	11/98 (11)	3/39 (8)	1.52 (0.400-5.76)	0.54
Age<1 year	5/9	9/128(7)	16.5(3.77-72.5)	<0.001
Cyanotic CHD	9/40(23)	5/97(5)	5.34(1.66-17.2)	**0.005**
Previous surgery for CHD	11/65(17)	3/72(4)	4.69(1.25-17.6)	**0.02**
Previous IE	3/12(25)	11/125(9)	3.46(0.814-14.7)	0.09
Prosthetic heart valve	0/4	14/133(11)	0	0.99

Data expressed as number of deceased patients/total number of the group of the presence or absence of the risk factor and the (ratio of deceased patients).

After stepwise logistic regression analysis, previous cardiac conditions were not significantly associated with in hospital death. (Actual values not reported).

Age <1 year was an independent risk factor for in hospital mortality. Estimate 2.972, Estimate/SE 2.408, p-value 0.02, OR 19.5 (1.74-219)

Analysis used	Fisher's exact probability test was used for prevalence in children and adults. Univariate logistic regression was used to evaluate the association between each risk factor and in hospital death. Stepwise logistic regression analysis was further performed to account for confounders and included variables that were significant (p<0.1) after univariate analysis.
Length of follow-up	January 1997 – December 2001
Location	Japan
Source of funding	Not specified.
Comments	**Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))** Study Participation – N Retrospective design. Adults and children. Included those with complete data sets only. Study attrition – Y Prognostic factor measurement – Y Outcome measurement – U Authors cite that mortality was low (10%) which might be affected by the study

Bibliographic reference	Yoshinaga, M et al. (2008) Risk factors for in-hospital mortality during infective endocarditis in patients with congenital heart disease. American Journal of Cardiology. 101:114-118.
	population/geographical region. Confounding measurement and account – P authors cite potential for unmeasured confounders despite the statistical adjustments applied. Analysis – N adjusted ORs were not reported. No Sample size calculation. 2/6 met = HIGH RISK OF BIAS

1

G.3 Review question 3

Dental procedures

Table 61

Bibliographic reference	**Mohee (2014): A case-control study: are urological procedures risk factors for the development of infective endocarditis?** **ID:**
Study type	Case-control study
Aim	To evaluate the association between urological procedures and the development of infective endocarditis (IE).
Patient characteristics	• *Inclusion criteria:* Adult patients treated for IE between 1 January 2001 and 31 December 2010, at the Leeds Teaching Hospitals NHS Trust, using the Leeds endocarditis audit database. • IE was diagnosed according to the Duke criteria. Identified cases were split into 4 groups based on organisms: • (group 1) enterococci IE • (group 2) CoNS IE • (group 3) Streptococcus bovis-group IE • (group 4) oral streptococci IE *CoNS = coagulase-negative staphylococcal*
Number of patients	Total = 384 *Enterococci IE group* N = 111; Age >60 years = 79/111 (71.1%), male = 80/111 (72.1%) Lower GI procedures = 5/111 (4.5%); upper GI procedures = 5/111 (4.5%); urological procedures = 24/111 (21.6%) *CoNS IE group* N = 86; Age >60 years = 56/86 (65.1%), male = 56/86 (65.1%) Lower GI procedures = 3/86 (3.5%); upper GI procedures = 6/86 (7.0%); urological procedures = 4/86 (4.7%) *Streptococcus bovis-group IE group* N = 36; Age >60 years = 29/36 (80.6%), male = 21/36 (58.3%) Lower GI procedures = 1/36 (2.8%); upper GI procedures = 2/36 (5.6%); urological procedures = 2/36 (5.6%) *Oral streptococci IE group* N = 151; Age >60 years = 59/151 (39.1%), male = 122/151 (81.3%) Lower GI procedures = 5/151 (3.3%); upper GI procedures = 4/151 (2.6%); urological procedures = 4/151 (2.6%)

Bibliographic reference	**Mohee (2014): A case-control study: are urological procedures risk factors for the development of infective endocarditis?** **ID:**
Procedures	Upper and lower GI procedures, urological procedures (including transurethral endoscopic procedure, cystoscopy, endoscopic resection of the prostate and bladder tumour and ureterorenoscopy)
Outcomes and effect estimates	*Univariate ananlysis in patients with IE:* Enterococcal IE group (n=111) Upper GI procedures: OR = 0.95 (95%CI: 0.33 to 2.72) Lower GI procedures: OR = 1.25 (95%CI: 0.41 to 3.73) Urological procedures: OR = 7.28 (95%CI: 3.35 to 15.8) CoNS IE group (n=86) Upper GI procedures: OR = 1.19 (95%CI: 0.65 to 4.93) Lower GI procedures: OR = 0.86 (95%CI: 0.24 to 3.14) Urological procedures: OR = 0.44 (95%CI: 0.15 to 1.28) Streptococcus bovis group (n=36) Upper GI procedures: OR = 1.22 (95%CI: 0.27 to 5.55) Lower GI procedures: OR = 0.68 (95%CI: 0.09 to 5.36) Urological procedures: OR = 0.58 (95%CI: 0.13 to 2.54) Oral streptococcal IE group (n=151) Upper GI procedures: OR = 0.43 (95%CI: 0.14 to 1.33) Lower GI procedures: OR = 0.77 (95%CI: 0.26 to 2.29) Urological procedures: OR = 0.19 (95%CI: 0.06 to 0.54) *Multivariate analysis in patients with enterococcal IE:* Urological procedures: adj OR = 8.56 (95%CI: 3.69 to 19.85)
Analysis used	Details of urological, upper and lower GI procedures were collected, including any procedures undertaken ≤1 year before the development of IE. Univariate and multivariate analysis were performed. A logistic regression model was used for the multivariable analysis. Missing data patterns were identified and a multiple imputation method was used to complete the data set.
Length of follow-up	Not reported.
Location	Between 1 January 2001 and 31 December 2010, Leeds, UK.
Source of funding	Supported by the Leeds Charitable Trust.
Comments	

1 **Table 62**

Bibliographic reference	**Chen (2013): Dental Scaling and Risk Reduction in Infective Endocarditis: A Nationwide Population-Based Case-Control Study.** **ID:**
Study type	Case-control study
Aim	To investigate whether the improvement of oral hygiene through dental scaling could reduce the risk of IE.
Patient characteristics	*Inclusion criteria:* • Patients who were age 18 or older with newly diagnosed IE, from the National Health Insurance (NHI) Research Database (NHIRD), from January 1, 2000 to December 31, 2009. • On the same index date, 10 patients (without IE) with matched age, sex, and significant underlying diseases, were selected to be the control group for each study patient.
Number of patients	Total = 8096 Cases = 736 Mean age = 55.40 years old (SD: 21.10); male = 60.2%; female = 39.8%. Control = 7360 Mean age = 55.41 years old (SD: 21.08); male = 60.2%; female = 39.8%.
Procedures	Dental scaling
Outcomes and effect estimates	*Adjusted odds ratio of IE in patients receiving dental scaling:* 0 time in 2 years: adj OR = 1 (95%CI: n/a) 1 time in 2 years: adj OR = 0.845 (95%CI: 0.693 to 1.012) At least 1 time per year: adj OR = 0.696 (95%CI: 0.542 to 0.894)
Analysis used	The frequencies of dental scaling and other dental procedures, including tooth extractions, root therapy, endodontic treatment, mouth or gingival surgery, and treatment of tooth abscess, within 2 years before the index date were analyzed and compared between the study and the control groups. Also further divided patients into 3 groups based on the frequency of dental scaling and compared the risk of IE between groups. The risk of patients in developing IE was expressed as the odds ratio which was analyzed using logistic regression analysis.
Length of follow-up	Not reported.
Location	From January 1, 2000 to December 31, 2009, Taiwan.
Source of funding	Grants from the National Science Council (NSC98-2410-H-010-003-MY2), and Taipei Veterans General Hospital (V99C1-140, V99A-153, and V100D-002-3).
Comments	

2 **Table 63**

Bibliographic reference	**Ammar (2013); ID:** **Case – Control study of potential culprit procedures for infective endocarditis in an Egyptian tertiary care centre.**
Study type	Case control study
Aim	To test the hypothesis that underlying medical conditions, not culprit procedures, are the most important risk factor for development of IE.

Bibliographic reference	**Ammar (2013); ID:** **Case – Control study of potential culprit procedures for infective endocarditis in an Egyptian tertiary care centre.**
Patient characteristics	*Inclusion criteria:* • 175 patients with definite IE according to modified Duke Criteria for diagnosis of IE from the IE database of the Cardiology Department at Cairo University Hospital and 175 control cases without IE collected from the Cairo University Hospital and the National Heart Institute, Outpatient Clinic, and Family Medicine Clinic. • Control cases were matched to IE cases by age (±x years), sex, and medical comorbidities including underlying heart disease and prosthetic valves. • A consented questionnaire was used to collect the clinical data from the control. • The following history and clinical data were collected from both IE cases and controls including: ○ Age, sex, history of hospitalization (for at least 24 h) within the last 3 months for indication unrelated to a possible or definite diagnosis of IE, underlying valvular heart disease, congenital heart disease, prosthetic valves or intracardiac devices. ○ Co-morbid conditions: such as diabetes mellitus, renal impairment defined as GFR<60 ml/min/1.73 m2,11 renal dialysis, prior IE, hepatic disease, drug abuse and malignancy. ○ Potential culprit procedures including: upper respiratory tract procedures, upper and lower GI endoscopy, barium enema, gynecological surgery, urinary catheterization, cardiac catheterization, device implantation, peripheral and central intravenous lines and dental procedures (tooth extraction and any procedure involving manipulation of the gingiva). ○ The causative organism (if identified), in patients with confirmed IE.
Number of patients	Cases = 175 Gender: 102 males; 73 females; Mean age: 32.13 years old (SD: 13.76); known structural heart disease = 117/175 Control = 175 Gender: 103 males; 72 females; Mean age: 32.90 years old (SD: 12.12); known structural heart disease = 111/175
Procedures	Dental procedures, gynaecological procedures, urinary catheterization
Outcomes and effect estimates	*Procedure-related risk factors:* Dental procedures: Cases = 6 (3.4%); control = 8 (4.6%), P>0.05 Gynaecological procedures: Cases = 1 (0.6%); control = 4 (2.3%), P>0.05 Urinary catheterization: Cases = 2 (1.1%); control = 6 (3.4%), P>0.05
Analysis used	Unpaired student's t test for normally distributed, continuous variables and Pearson's chi-square test for categorical variables. Correlations between normally distributed variables were done using Pearson's correlation coefficient. A probability value (p value) less than 0.05 was considered significant. There was no correction for multiple testing.
Length of follow-up	Not reported

Bibliographic reference	**Ammar (2013); ID:** **Case – Control study of potential culprit procedures for infective endocarditis in an Egyptian tertiary care centre.**
Location	From March 2005 till June 2008, Cairo, Egypt.
Source of funding	Not reported
Comments	

1 **Table 64**

Bibliographic reference [from CG64]	**Duval X, Alla F, Hoen B, et al. (2006) Estimated risk of endocarditis in adults with predisposing cardiac conditions undergoing dental procedures with or without antibiotic prophylaxis. Clinical Infectious Diseases. 42: e102–07. Ref ID: 10629**
Study type	Epidemiological study (cross sectional study)
Aim	To estimate the risk of endocarditis in adults with predisposing cardiac conditions (PPC) undergoing dental procedures with or without antibiotic prophylaxis.
Patient characteristics	Included: 25-84 yrs from the French population
Number of patients	n = 2805 interviewed adults, n = 104 native valve PCC n = 24 prosthetic valve PCC
Procedures	Dental procedures
Outcomes and effect estimates	Effect size: **Prevalence of PCC and number of at-risk dental procedures** n = 104 native valve PCC, n = 15 of which had undergone an at-risk dental procedure, unprotected in n = 12 n = 24 prosthetic valve PCC, n = 4 of which had undergone an at-risk dental procedure, unprotected in n = 2 Applying these to the adult French population, in 1999, resulted in the following estimates: n = 1,287,296 (CI; 999,196 to 1,575,396) had a known PCC, corresponding to 3.3% (CI; 2.6 to 4%) of the 39 million adults In 1999, a total of 2,746,384 at-risk dental procedures (CI; 2,304,094 to 3,188,384) were performed in these adults, a rate of 2.1 procedures per subject per year n = 1,704,195 (62%) of these procedures were performed without antibiotic prophylaxis **Annual number of IE cases after at-risk dental procedures in adults with known PCC** n = 12/182 cases of IE that occurred in adults with PCC in the 1999 survey occurred after an at-risk dental procedure and were due to an oral micro-organism (n = 10 unprotected) With the estimated 1370 cases of IE, 714 would have occurred in adults with PCC, 44 attributable to dental procedures (37 without and 7 with antibiotic prophylaxis) **Risk of IE after at-risk dental procedures in adults with known PCC**

Bibliographic reference [from CG64]	**Duval X, Alla F, Hoen B, et al. (2006) Estimated risk of endocarditis in adults with predisposing cardiac conditions undergoing dental procedures with or without antibiotic prophylaxis. Clinical Infectious Diseases. 42: e102–07. Ref ID: 10629**
	The estimated risk of IE was: 1 case per 46,000 (CI; 36,236 to 63,103) unprotected at-risk dental procedures 1 case per 54,300 (CI; 41,717 to 77,725) unprotected at-risk dental procedures in adults with native valve PCC 1 case per 10,700 (CI; 6,000 to 25,149) unprotected at-risk dental procedures in adults with prosthetic valve PCC 1 case per 149,000 (88,988 to 347,509) protected dental procedures, a 70% reduction in the risk compared with unprotected procedures **Assessment of IE prophylaxis strategies intact** Using the annual number of procedures and the risk estimates if antibiotics have been administrated in 100% of at-risk dental procedures [a] , n = 41 cases (CI; 29 to 53) of IE would have been prevented in those with native valve PCC and 39 cases (CI; 11 to 72) in those with prosthetic valve PCC in France in 1999 **Estimated incidence of IE** Annual incidence 35 cases per million (CI; 32 to 39) in the entire 25-84yr French population 555 cases per million (CI; 520 to 588) in those with known PCC 980 cases per million (CI; 875 to 1090) in those with known prosthetic valve PCC 460 cases per million (CI; 415 to 500) in those with known native valve PCC 18 cases per million (CI; 16 to 21) in those without known PCC An estimate of the number of IE cases that would have been prevented during 1-yr if antibiotic prophylaxis had been administered in 100% of cases of at-risk dental procedures. (*Author's conclusion: antibiotic prophylaxis reduces the risk of IE after a dental procedure. However, because of the very limited risk of "spontaneous" IE after unprotected dental procedures in adults with known PCCs, a huge number of doses of prophylaxis must be prescribed to prevent a very low number of IE cases)*
Analysis used	Monte-Carlo simulation.
Length of follow-up	1-year study 1999
Location	France
Source of funding	Programme hospitalier de recherché clinique, the federation francaise de cardiologie, Aventis and SmithKilne Beecham Labs
Comments	To assess the risk of developing IE after an at-risk dental procedure using estimations of: the estimated annual number of IE cases that occur after at-risk dental procedures in adults with known predisposing cardiac conditions (PCC) [b] (numerator) [c] and the annual number of at-risk dental procedures performed in adults with known PCCs (denominator) [d]

(a) 2.7 administered antibiotic courses, corresponding to 2,228,545 for those with native valve PCC and 512,829 for those with prosthetic valve PCC
(b) PCC were defined according to the French recommendations for IE prophylaxis
(c) Data used was taken from a 1-yr French epidemiological study on IE in
(d) 1999Sample drawn from 2 studies ongoing in 1998, a structured and previously validated questionnaire was administered by phone interview to classify subjects as having a PCC or not

1 **Table 65**

Bibliographic reference [from CG64]	**Lacassin F, Hoen B, Leport C, Selton-Suty C, Delahaye F, Goulet V et al. Procedures associated with infective endocarditis in adults. A case control study.[see comment] 1013. European heart journal 1995;16:1968-74. Ref ID: 1013**
Study type	Case-control study
Aim	To investigate procedures associated with infective endocarditis in adults
Patient characteristics	Inclusion: cases: definite and probable IE defined according to revised Von Reyn's criteria with modifications; possible IE defined according to non revised Von Reyn's criteria Exclusion: cases: patients younger than 15yrs, valve replacement within the previous year, prematurely dead, intravenous drug users, those with Coxiella burnetti IE (unlikely to be related to any procedure) Cases: those without IE who satisfied the same exclusion criteria as the cases. Cases were recruited randomly from cardiology or medicinal wards either during a consultation for echocardiography or during hospitalisation in the same period of observations as cases. Cases and controls were distributed into 3 groups of underlying cardiac conditions: native valve disease, prosthetic valve or no known cardiac disease Each case was matched to one control as regards sex, age (±5yrs) and group of underlying cardiac conditions. The proportion of those with diabetes mellitus, or who consumed alcohol and tobacco did not differ between the 2 groups. Cases had significantly more often an infectious episode or a skin wound than controls (39% and 19% vs. 15% and 5% respectively)
Number of patients	Total = 171 pairs n = 171 cases were interviewed as soon as possible after the diagnosis of IE Following a pre-established list, they were requested to indicate all the procedures involving cutaneous and mucosal surfaces they had undergone within the 3mths prior to diagnosis In case of medical consultation or procedure, the information was checked by the cited practitioner [b] n = 171 controls were interviewed under the same conditions as cases using the same questionnaire form Following a pre-established list, they were requested to indicate all the procedures involving cutaneous and mucosal surfaces they had undergone within the 3mths prior to diagnosis In case of medical consultation or procedure, the information was checked by the cited practitioner
Procedures	Dental, urological, gastrointestinal procedures

Bibliographic reference [from CG64]	**Lacassin F, Hoen B, Leport C, Selton-Suty C, Delahaye F, Goulet V et al. Procedures associated with infective endocarditis in adults. A case control study.[see comment] 1013. European heart journal 1995;16:1968-74. Ref ID: 1013**
Outcomes and eefect estimates	The relative risk of IE for each procedure, causative organisms, antibiotic prophylaxis **Procedures** *Univariate adjusted for other procedures:* Any dental procedures: cases = 37 (22%); control = 33 (19%); OR = 1.2 (95%CI: 0.7 to 2.1) Any urological procedures: cases = 6 (3.5%); control = 2 (11%); OR = 3.1 (95%CI: 0.6 to 15.7) Any GI procedures: cases = 14 (8.2%); control = 8 (4.7%); OR = 1.2 (95%CI: 0.7 to 4.1) n = 88 (51.5%) of cases and n = 70 (41%) of controls had undergone at least one procedure, the adjusted OR for the risk of IE related to a procedure 1.6 (1.01 to 2.53, 95%CI), p<0.05 Taking the frequency of the procedures in the control group (40%) as an estimation of the frequency in the general population, the risk of IE attributable ≥1 procedure (attributable risk) was 20% Any dental procedure – no increased risk (cases n = 37 (22%), controls n = 33 (19%)); Dental extraction no higher risk of IE; scaling and root canal work showed a trend towards a higher risk (NS) Any urological procedure – no increased risk (cases n = 6 (3.5%), controls n = 2 (1%)) Any GI procedure – no increased risk (cases n = 14(8.2%), controls n = 8 (4.7%)) Any surgical procedure – cases n = 11 [a] (6%), controls n = 2 (1%); adjusted OR for the risk of IE 4.7 (1.02 to 2.53, 95%CI) All procedures, the mean number of procedures was significantly higher in cases than in controls (2.0 vs. 4.5, p<0.05) The risk of IE increased with the number of procedures per case, RR for one procedure 1.2; 1.7 for two procedures; 3.6 for three or more procedures (p=0.005) No control had had >1 dental procedure in the previous 3mths, n = 3 cases had undergone 2 procedures **Multivariate analysis:** Urological procedure: adj OR = 6.1 (95%CI: 0.9 to 39.7) Scaling: adj OR = 2.7 (95%CI: 0.8 to 9.0) Canal treatment: adj OR = 1.7 (95%CI: 0.5 to 5.2) **Causative organism** The only procedure associated with a risk for IE due to viridans streptococci was scaling (n = 9/50 in the cases; n = 2/50 in the controls, OR=5.25, p=0.025) The only procedure associated with the subsequent occurrence of IE was surgery for staphylococcal IE (n = 4/27 in the cases; n = 0/27 in the controls, p=0.03) In multivariate analysis, scaling was associated with a significant risk for IE due to viridans streptococci, independently of an infectious episode. Conversely, only infectious episodes contributed to the risk of staphylococcal infective endocarditis, the risk after skin wound and surgery being non-significant in this analysis

Bibliographic reference [from CG64]	**Lacassin F, Hoen B, Leport C, Selton-Suty C, Delahaye F, Goulet V et al. Procedures associated with infective endocarditis in adults. A case control study.[see comment] 1013. European heart journal 1995;16:1968-74. Ref ID: 1013**
	Antibiotic prophylaxis n = 8 cases of IE occurred in those who had received an appropriate antibiotic prophylaxis, (n = 4 PVE, n = 4 NVE). Procedures included multiple extractions within a single session (n = 3), scaling (n = 3), ENT procedure (n = 1) and urethrocystoscopy (n = 1) n = 6 controls had received appropriate antibiotic prophylaxis (n = 2 PV disease, n = 4 NV disease)
Analysis used	Univariate and multivariate analyses.
Length of follow-up	1st November 1990 to 31st October 1991, Public and private medical facilities in 3 regions in France
Location	France
Source of funding	Several grants from medical societies in France and from the following companies: Baxter, Dideco-Shiley, Eli-Lily, Medtronic, St Jude Medical Companies
Comments	

(a) Abdominal surgery N=3, soft tissue surgery N=6, gynaecological surgery N=2. Two of the 7 clean surgical procedures were done with antibiotic prophylaxis and five without antibiotic prophylaxis

(b) To adjust for factors which could potentially influence the risk of IE associated with procedures, the questionnaire requested items concerning general co-morbid conditions such as alcohol and tobacco consumption, and diabetes mellitus

Table 66

Bibliographic reference [from CG64]	**Strom BL, Abrutyn E, Berlin JA, Kinman JL, Feldman RS, Stolley PD et al. Risk factors for infective endocarditis: oral hygiene and nondental exposures. Circulation 2000;102:2842-8. Ref ID: 31**
Study type	Case-control study
Aim	To investigate risk factors for infective endocarditis
Patient characteristics	Information was abstracted from medical records and obtained from structural telephone interviews with controls and endocarditis cases (medical records were requested to validate individual diagnosis and procedures, agreement between interviews and medical records exceeded 90% Cases were more likely than controls to suffer from self-reported severe kidney disease, they were also more likely to report physician diagnosed diabetes. Cases did not differ from controls in history of living with pets, animal bites, smoking, menopausal status, history of rheumatoid arthritis, other autoimmune disease, thyroid disease, alcoholism, cancer, stroke, ischaemic heart disease, cardiomyopathy, arrhythmia, heart operation other than valve replacement, cardiac disease other than prior history of endocarditis, valvular heart disease, congenital heart disease, rheumatic fever, heart murmur Cases and controls were similar with respect to age and sex, race, education, occupation, and dental insurance Controls and case-patients were matched for age, sex, race, education, occupation and dental insurance

Bibliographic reference [from CG64]	**Strom BL, Abrutyn E, Berlin JA, Kinman JL, Feldman RS, Stolley PD et al. Risk factors for infective endocarditis: oral hygiene and nondental exposures. Circulation 2000;102:2842-8.** **Ref ID: 31**
	Cases were more likely to have self-reported prior kidney disease, to report physician diagnosed diabetes
Number of patients	n = 416 enrolled potential case-patients n = 287 community acquired IE not associated with IV drug use n = 273 interviewed case-patients
Procedures	Pulmonary, Barium enema, lower and upper GI endoscopy, urinary catheterization, other genitourinary procedures.
Outcomes and effect estimates	**Medical procedures and therapies** Multivariable adjusted OR (in previous 3 months): Pulmonary procedures (inc. lung biopsy & bronchoscopy): cases = 3 (1.1%); control = 3 (1.1%); adj OR = 0.27 (95%CI: 0.01 to 5.46) Barium enema: cases = 11 (4%); control = 1 (0.4%); adj OR = 11.9 (95%CI: 1.34 to 106) Lower GI endoscopy: cases = 14 (5.1%); control = 8 (2.9%); adj OR = 1.95 (95%CI: 0.58 to 6.53) Upper GI endoscopy: cases = 8 (2.9%); control = 4 (1.5%); adj OR = 1.36 (95%CI: 0.26 to 6.99) Urinary catheterization cases = 12 (4.4%); control = 4 (1.5%); adj OR = 0.58 (95%CI: 0.11 to 3.10) Gynecological surgery: cases =3 (1.1%); control = 0 (0.0%); adj OR = N/A Other genitourinary procedures (inc. cystoscopy, lithotripsy, vasectomy) cases = 4 (1.5%); control = 3 (1.1%); adj OR = 0.61 (95%CI: 0.06 to 5.80) Only barium enema remained significant after multivariate adjustment OR 11.9 (CI; 1.34 to 106), p=0.026 (review indicated that in some cases the procedure was performed as part of the workup for the illness finally diagnosed as IE, or for a comorbidity, accordingly this cannot be interpreted as indicating a causal relationship between the procedure and IE)(NS were pulmonary procedures, lower GI endoscopy, upper GI endoscopy, gynaecological surgery, urinary catheterisation, other genitourinary, cardiac procedure, other surgery, intravenous therapy, nasal-oxygen therapy) Overall IV fluid administration was not associated with IE, when analysis was restricted to those with infected skin flora and their controls the unadjusted OR increased from 1.8 to 5.0(CI: 1.1 to 23), p=0.04. Adjusted [b] OR was 6.7 (CI; 1.1 to 41), p=0.04 Tests of interaction between procedures and antibiotic use provided no evidence that anti biotic use modified the risk associated with those procedures **Prior infection as a risk factor** An association between endocarditis and skin infection was NS with multivariate analysis [a] The elevated OR for skin infection disappeared after the analysis was restricted to subjects with cardiac valvular abnormalities When restricted to cases who were infected with skin flora and their matched controls the OR for skin infections increased markedly to 6.0 (CI; 1.3 to 27), p=0.019.

Bibliographic reference [from CG64]	**Strom BL, Abrutyn E, Berlin JA, Kinman JL, Feldman RS, Stolley PD et al. Risk factors for infective endocarditis: oral hygiene and nondental exposures. Circulation 2000;102:2842-8.** **Ref ID: 31**
	UTIs were not associated with IE Initially pneumonia showed an increase among cases, but this occurred in the month before study dates and may be an early manifestation of endocarditis **Oral hygiene** No association was found between IE and the frequency of routine dental care within the previous year, tooth brushing, or use of a toothpick, Water Pik or gum stimulator, there was no association between IE and complete denture prosthesis for edentulous mouths There was no evidence that of a risk in having teeth vs. being edentulous, when this was repeated considering only cases affected with dental flora (n = 106 and matched controls) there was an increased risk associated with having teeth, adjusted OR 7.02 (CI; 1.25 to 2.14), p=0.03. Edentulousness was associated with decreased risk compare with having teeth and not flossing, OR 0.11 (CI; 0.02 to 0.71), p=0.02
Analysis used	Multivariable analysis
Length of follow-up	From August 1988 – November 1990 surveillance for IE in 54 hospitals
Location	Philadelphia
Source of funding	NIH grant
Comments	

(a) The elevated OR for skin infection disappeared after the analysis was restricted to subjects with cardiac valvular abnormalities
(b) Adjusted for cardiac valvular abnormality and diabetes

G.4 Review question 4

Dental procedures

Table 67

Bibliographic reference	**Tuna (2012), ID: 165** **Do antibacterial mouthrinses affect bacteraemia in third molar surgery? A pilot study.**
Study type	RCT
Aim	To evaluate the effects of mouthrinses containing 7.5% povidone iodine and 0.2% chlorhexidine on bacteraemia following impacted third molar surgery.
Patient characteristics	*Inclusion criteria:* • Aged over 18 years requiring surgical removal of a third molar

Bibliographic reference	**Tuna (2012), ID: 165** **Do antibacterial mouthrinses affect bacteraemia in third molar surgery? A pilot study.**
	• No systemic disorder nor any signs or symptoms of pericoronitis at the time of surgery nor during the previous month • No known risk factor for bacterial endocarditis • No antibiotic treatment during the previous 30 days • Not using routine oral antiseptic mouthrinse nor suffering any type of congenital or acquired immunodeficiency • Had no other disease or condition which could predispose to infections or bleeding. *Exclusion criteria:* • Patients with an oral hygiene index and gingival bleeding index (GBI) higher than 10%.
Number of patients	Total number = 34; control group = 10 (group of interest) *[the other 24 patients had povidone iodine or chlorhexidine prophylaxis].* Gender: 5 males; 5 females Mean age: 26.8 years old (SD: 4.8)
Procedures	Third molar extraction. • Peripheral venous blood samples were collected from each patient at baseline (before the injection of local anaesthesia with articaine and adrenaline), 1 minute and 15 minutes after completion of the extraction.
Outcomes and effect estimates	Incidence of bacteraemia: Baseline= 5/10 (50%); 1st min = 4/10 (40%); 15th min = 3/10 (30%); McNemar's p = 0.810. Types of bacteria: 1st min = *3 Streptococcus anginosus; Streptococcus gordonii; Streptococcus oralis; Streptococcus salivarius; Streptococcus mitis* 15th min = *Streptococcus salivarius; 2 Streptococcus anginosus; Streptococcus oralis; Staphylococcus epidermis*
Analysis used	• Every blood sample comprised 20 ml of blood which was divided into two bottles with anaerobic culture medium (10 ml) and aerobic culture medium (10 ml). Altogether, 60 ml of blood was obtained from each patient by a researcher who was blind to details of the study. • After each sample was drawn, the angiocath needle and the line were flushed with 3 ml of saline. This procedure was repeated three times (baseline, 1 minute and 15 minutes postoperatively). All the blood culture bottles were processed in the BACTEC 9120 system (Becton Dickinson, NJ, USA) in the microbiology laboratory.
Length of follow-up	7 days incubation of the blood samples.
Location	Yeditepe University, Faculty of Dentistry, Istanbul, Turkey.
Source of funding	Not reported.
Comments	

1 **Table 68**

Bibliographic reference	**DuVall (2013), ID: 80** **The comparative efficacy of 0.12% chlorhexidine and amoxicillin to reduce the incidence and magnitude of bacteraemia during third molar extractions. Oral surgery, oral medicine and oral pathology.**
Study type	RCT
Aim	To compare the incidence and magnitude of bacteraemia of a 0.12% chlorhexidine pre-procedure rinse to the AHA and the ADA/AAOS recommended 2g amoxicillin antibiotic prophylaxis during third molar extractions.
Patient characteristics	*Inclusion criteria:* • ASA I or II: healthy, no systemic disease • Diagnosed/planned extraction #1, 16, 17, 32 under conscious sedation • #17 and 32 required a mucogingival flap for extraction • 18 years of age or older • Previously received penicillin and/or amoxicillin without a hypersensitivity or allergic reaction *Exclusion criteria:* • ASA III or IV: poorly controlled systemic disease • Known penicillin, amoxicillin or cephalosporin drug allergy • Pregnant women • Current immunosuppressed status • Active viral disease • Cardiac anomalies or another condition/situation requiring pre- or intra-operative use of antibiotics • Antibiotic use within the previous two months • Steroid therapy within the previous two months • Chlorhexidine use or other oral antimicrobial rinses within the previous 2 months • The routine use of an oral antiseptic at home • Gingival tissue manipulation within 2 hours of the procedure • 7 of the original 37 eligible subjects were excluded due to technical reasons (complications during blood draws and/or unavailable microbiological lab support).
Number of patients	Total number = 30; control group = 10 (group of interest) *[the other 20 patients had amoxicilin or chlorhexidine prophylaxis].* Gender (total): 23 males; 7 females Mean age (total): 21.8 years old (range: 18 to 29) *[no subgroups data]*
Procedures	Third molar extraction

Bibliographic reference	**DuVall (2013), ID: 80** **The comparative efficacy of 0.12% chlorhexidine and amoxicillin to reduce the incidence and magnitude of bacteraemia during third molar extractions. Oral surgery, oral medicine and oral pathology.**
	4 blood samples (BS) were obtained through IV access line for each patient in the following manner: • Baseline (before placebo tablet) • 1.5 min following initiation of the mucogingival flap #32 • 1.5 min following initiation of the mucogingival flap #17 • 10 min following initiation of the mucogingival flap #17
Outcomes and effect estimates	*Incidence of bacteraemia (defined as at least one positive culture of the 4 BS per patient):* 6/10 (60%) *Magnitude of bacteraemia (mean CFU/ml per BS with SD):* BS1 = 0.00 (SD:0.00); BS2 = 1.26 (SD: 3.67); BS3 = 1.90 (SD: 5.36); BS4 = 0.45 (SD: 0.83); Kruskal-Wallis P = 0.031
Analysis used	The Wampole ISOSTAT/ISOLATOR Microbial System was used for blodd culture. No irrigation/flush with 10ml sterile saline solution was completed prior to BS1, but was completed prior to BS2 to BS4. For each colony type the concentration/magnitude of the bacteria in the blodd was calculated in CFU/ml.
Length of follow-up	Aerobic: 2 days incubation; anaerobic: 4 days incubation.
Location	Patients presenting to the surgical centre, oral surgery clinic for third molar extractions under conscious sedation from June 2011 to December 2011
Source of funding	Funding provided by the 59th Clinical Research Training Division, Lackland, AFB, TX
Comments	

1 **Table 69**

Bibliographic reference	**Lockhart (2008), ID: 457** **Bacteremia Associated with Tooth Brushing and Dental Extraction.**
Study type	RCT
Aim	To compare the incidence, duration, nature and magnitude of endocarditis-related bacteraemia from single tooth extraction and tooth brushing, and to determine the impact of amoxicillin prophylaxis on single tooth extraction.
Patient characteristics	*Inclusion criteria:* • Patients presented to our urgent care service with the need for extraction of at least one erupted tooth. *Exclusion criteria:* • less than ten teeth • use of systemic antibiotics within the previous 2 weeks • need for antibiotic prophylaxis based on current practice guidelines

Bibliographic reference	**Lockhart (2008), ID: 457** **Bacteremia Associated with Tooth Brushing and Dental Extraction.**
	• active viral disease, immunocompromised, poorly controlled systemic disease • history of penicillin allergy • temperature greater than 100.5 degrees Fahrenheit • facial cellulitis and manipulation of the gingival tissues (e.g., chewing, tooth brushing) within 1 hr prior to the study.
Number of patients	Total number = 290; control group = 96 (group of interest) *[the other 194 patients either had amoxicilin prophylaxis or on brushing intervention].* Mean age = 40.5 years old (SD: 10.9) Gender = 51 males; 45 females. *No. of blood samples:* Baseline = 89 After surgery at 1.5 min = 84; 5 min = 84; 20 min = 83; 40 min = 83; 60 min = 82
Procedures	Tooth extraction. 6 blood samples (BS) were drawn as follow: The baseline blood sample (20 mL) was then drawn and 7-8 mL was inoculated directly into both aerobic and anaerobic BACTEC® bottles for bacterial culturing. Subsequent blood draws of 20 mL were taken at 1.5 min and at 5 min after the initiation of surgery. Additional blood samples (20 mL) were drawn 20, 40, and 60 min following the end of the procedure.
Outcomes and effect estimates	*Incidence and duration of bacteraemia:* Baseline = 0/89 (0%); 1.5 min = /84 (45%); 5 min = 42/84 (50%); 20 min = 8/83 (10%); 40 min = 4/83 (5%); 60 min = 4/82 (5%) *IE-related bacterial species identified:* Overall those with (viridans) streptococci = 106/151 (70%) *Individual IE-related species identified:* *Actinomyces meyeri/odontolyticus* *Capnocytophaga sp.* *Eikenella corrodens* *Fusobacterium nucleatum* *Granulicatella adiacens* *Haemophilus aphrophilus* *Lactobacillus salivarius* *Neisseria elongata*

Bibliographic reference	**Lockhart (2008), ID: 457** **Bacteremia Associated with Tooth Brushing and Dental Extraction.**
	Neisseria flavescens *Neisseria mucosa/sicca* *Peptostreptococcus micros* *Prevotella melaninogenica* *Prevotella oralis* *Propionibacterium acnes* *Staphylococcus epidermidis* *Streptococcus anginosus* *Streptococcus constellatus* *Streptococcus cristatus* *Streptococcus gordonii* *Streptococcus intermedius* *Streptococcus mitis* *Streptococcus mutans* *Streptococcus oralis* *Streptococcus salivarius* *Streptococcus sanguinis* *Veillonella parvula*
Analysis used	Blood samples were cultured in BACTEC Plus Aerobic/F and LYTIC/10 Anaerobic/F (Becton, Dickinson, Sparks, MD). Bacterial colonies were isolated on both selective and non-selective media such as blood agar, Chocolate agar and MacConkey II agar for aerobes, and on anaerobic blood agar. All false-positive bottles (i.e., bottles that were signaled positive but the subculture was negative) were further incubated for the total of 2 weeks. Bottles with positive cultures were also kept for two weeks and subcultured periodically to ensure recovery of additional species.
Length of follow-up	2 weeks incubation.
Location	USA
Source of funding	This study was supported by NIDCR/NIH Grant # R01 DE13559-01.
Comments	

1 **Table 70**

Bibliographic reference	**Assaf (2007), ID: 687** **Effect of the Diode Laser on Bacteremia Associated with Dental Ultrasonic Scaling: A Clinical and Microbiological Study.**
Study type	Split-mouth trial

Bibliographic reference	**Assaf (2007), ID: 687** **Effect of the Diode Laser on Bacteremia Associated with Dental Ultrasonic Scaling: A Clinical and Microbiological Study.**
Aim	To evaluate the potential use of diode lasers (DLs) to reduce bacteraemia associated with ultrasonic scaling (US).
Patient characteristics	*Inclusion criteria:* • adults who presented for treatment to the clinics with the diagnostic criteria of plaque-induced generalized chronic gingivitis. • systemically healthy and required to have at least 20 teeth and no history of periodontal therapy. *Exclusion criteria:* • Those who were smoking, had antibiotic therapy within the previous 3 months, subgingival restorations, use of antiseptic mouthwash, history of infective endocarditis, congenital or acquired cardiac defects, cardiac prosthesis, haematological disorders, immune defects, corticosteroid or immunosuppressive medication, or any systemic conditions that might affect the periodontium and the treatment protocol.
Number of patients	Total number = 22 Gender: 14 females; 8 males Age range: from 21 years to 50 years Mean age: 31.8 years for females; 33 years for males.
Procedures	Ultrasonic scaling (US) with or without diode lasers (DL) (on all patients, split-mouth design) On treatment day, a blood sample of 10 mL was drawn just before and 3 min after initiation of US on the control side. Following the completion of US on the control side, laser energy was applied to the gingival crevices of the teeth present on the experimental side (DL+US). Thirty minutes later,blood was drawn again just before and 3 min after initiation of US in the previously lased teeth. Clinical assessment was repeated 4 weeks after treatment.
Outcomes and effect estimates	*Incidence of bacteraemia (those with positive culture):* US: Baseline = 0/22 (0%); 3 min = 15/22 (68%) US+DL: Baseline = 0/22 (0%); 3 min = 8/22 (36%); RR = 1.87 (95%CI: 1.01 to 3.49) *Individual bacterial identified:* *Streptococcus mitis* *Streptococcus salivarius* *Streptococcus sanguis* *Prevotella intermedia and P. nigrescens* *Prevotella melaninogenica* *Capnocytophaga spp.* *Haemophilus spp.* *Bacteroides spp.*

Bibliographic reference	**Assaf (2007), ID: 687** **Effect of the Diode Laser on Bacteremia Associated with Dental Ultrasonic Scaling: A Clinical and Microbiological Study.**
	Fusobacterium spp.
Analysis used	Blood samples of 10 mL were drawn from the patient through an antecubital vein using strict aseptic technique via a 22-gauge sterile plastic cannula. Samples were then incubated at 37°C for 14 days. Results were considered positive when the blood–broth mixture in the bottles had risen above the sleeve of the growth indicator device.
Length of follow-up	14 days incubation.
Location	Faculty of Dentistry of Yeditepe University, Turkey.
Source of funding	Not reported.
Comments	

1 **Table 71**

Bibliographic reference	**Cherry (2007), ID: 1075** **Effect of rinsing with povidone–iodine on bacteraemia due to scaling: a randomized-controlled trial.**
Study type	RCT
Aim	To investigate rinsing with povidone–iodine on bacteraemia caused by ultrasonic scaling.
Patient characteristics	*Inclusion criteria:* • adults to have plaque induced gingivitis, as defined by the American Academy of Periodontology, involving five adjacent teeth (FDI teeth 31–35). *Exclusion criteria:* • allergy to iodine, significant medical problems (e.g. diabetes), known infection with the human immunodeficiency virus, cardiac defects or other conditions requiring prophylactic antibiotic cover • pregnancy • having taken antibiotics in the last 3 months or currently taking corticosteroid or immunosuppressive medications or having received periodontal treatment within the previous 6 months. Patients were instructed not to brush for at least 30 min before their appointment to avoid the possibility of any tooth brushing-induced bacteraemia.
Number of patients	Total = 60; control group = 30 (group of interest) *[the other 30 patients had povidone–iodine wash prophylaxis].* Mean age: 43.9 years old (SD: 20.8) Gender: 7 males; 23 females
Procedures	Ultrasonic scaling.

Bibliographic reference	**Cherry (2007), ID: 1075** **Effect of rinsing with povidone–iodine on bacteraemia due to scaling: a randomized-controlled trial.**
	10 ml of blood was sampled as a baseline measurement immediately following rinsing with either NaCl or POV–I and before scaling commenced, to ensure the absence of a pre-existing bacteraemia. 10 ml of blood was sampled 30 s after scaling was commenced and a further 10 ml of blood was sampled at the completion of 2 min of scaling.
Outcomes and effect estimates	Overall, a positive bacteraemia of oral origin was found in 33% of the patients in the group. *Incidence of bacteraemia:* Baseline = 0/30 (0%); 30s = 4/30 (13%); 2 min = 9/30 (30%) 4 of the 9 bacteraemic patients were al bacteraemic at 30s. 24 isolates were identified, with 11 of these were Viridans group streptococci (42%).
Analysis used	A lysocentrifugation tube was inoculated with each blood sample immediately following collection and then centrifuged at room temperature for 10 min at 5000 g. The CHBA plates were incubated for 7 days at 351C, 5% CO_2 in a CO_2 incubator; the Chromogenic agar plates were incubated for 7 days in ambient atmosphere at 37C; and the BHV plates were incubated for 7 days in an anaerobic cabinet at 37C, 10% CO_2, 80% N_2, 10% H_2.
Length of follow-up	7 dyas incubation.
Location	Westmead Centre for Oral Health, Australia.
Source of funding	Not reported.
Comments	

1 **Table 72**

Bibliographic reference	**Morozumi (2010), ID: 381** **Effects of irrigation with an antiseptic and oral administration of azithromycin on bacteraemia caused by scaling and root planning.**
Study type	RCT
Aim	To investigate the effects of irrigation with an essential oil-containing antiseptic (EO) and oral administration of azithromycin (AZM) on bacteraemia caused by scaling and root planing.
Patient characteristics	*Inclusion criteria:* • Adults who had >20 teeth, moderate to severe chronic periodontitis *Exclusion criteria:* • Had congenital valve defects or other risk factors for IE; low level of haematocrit; high risk of cardiovascular disease and diabetes; allergy to macrolides

Bibliographic reference	**Morozumi (2010), ID: 381** **Effects of irrigation with an antiseptic and oral administration of azithromycin on bacteraemia caused by scaling and root planning.**
	• Had taken systemic antibiotics, anti-inflammatory drugs, immunosuppressive drugs within 3 months before the study • Had received periodontal treatment within the previous 6 months, regularly used an oral irrigation device or mouthrinse, had an incompatible dentition.
Number of patients	Total = 30; Control group = 10 (group of interest) Gender: 8 males; 2 females Mean age: 55.4 years old (SD:9.3)
Procedures	Scaling and root planing At baseline, peripheral blood and subgingival plague were collected. The second sample of peripheral blood was taken 6 min after the initiation of SRP.
Outcomes and effect estimates	*Prevalence of bacteraemia:* Baseline = 0/10 (0%); 6 min = 9/10 (90%) *Individual bacteria identified:* alpha-*Streptococcus* beta-*Streptococcus* *Streptococcus constellatus* *Streptococcus mutans*
Analysis used	Blood was obtained by venepuncture in the antecubital fossa. Each sample comprised 10 ml of blood, which was obtained using a 22-gauge butterfly and safety lock blood collection set and 30 ml syringe. The collected blood samples were inoculated into an anaerobic culture bottle that could cover both anaerobic and aerovic bacteria. Bottles were incubated and continuously monitored over 6 days.
Length of follow-up	6 days incubation.
Location	Between Jan 2006 and Oct 2008, Niigata University Medical & Dental Hospital, Japan.
Source of funding	Not reported.
Comments	

1 **Table 73**

Bibliographic reference	**Pineiro (2010), ID: 395** **Bacteraemia following dental implants' placement.**
Study type	RCT

Bibliographic reference	**Pineiro (2010), ID: 395** **Bacteraemia following dental implants' placement.**
Aim	To investigate the prevalence, duration and aetiology of bacteraemias following the placement of implants as well as the prophylactic efficacy of a chlorhexidine digluconate mouthrinse.
Patient characteristics	*Inclusion criteria:* • Adults suitable for oral rehabilitation using osseointegrated implants. *Exclusion criteria:* • Less than18 years of age, use of antibiotics in the previous 3 months, routine use of oral antiseptics, immunodeficiency and any other disease that could predispose them to infections or bleeding complications.
Number of patients	Total = 50; control group = 30 (group of interest) *[the other 20 patients had chlorhexidine prophylaxis].* Mean age: 55 years old (SD: 13.5) Gender: 8 males; 22 females
Procedures	Dental implant placement All patients received intravenous sedation with midazolam and propofol, together with infiltrative local anaesthesia by injection of an average of four cartridges (1.8ml per cartridge) of 2% lidocaine with epinephrine. A peripheral venous blood sample (10 ml) was collected from each patient before the start of the surgical procedure to determine the prevalence of bacteraemia before intervention (baseline). Further peripheral blood samples (10 ml) were taken 30 s after insertion of the last implant and at 15 min after the completion of suturing of themucoperiosteal flap to determine the prevalence and duration of bacteraemia secondary to implant placement.
Outcomes and effect estimates	*Incidence of bacteraemia:* Baseline = 1/30 (3.3%); 30 s = 2/30 (6.6%); 15 min = 1/30 (3.3%) *Individual bacterial identified:* *Streptococcus viridans (anginosus group)* *Streptococcus viridans (mitis group)* *Neisseria cinerea* *Streptococcus viridans (mitis group)*
Analysis used	After disinfection with alcohol and povidone iodine, an intravenous catheter was inserted into the antecubital fossa or on the dorsumof the hand. Each sample was inoculated in equal measure into containers with aerobic and anaerobic culture media (Bactec plus, Becton Dickinson) and immediately transported to the laboratory. The blood samples were processed using the Bactec 9240. A Gram stain was performed on each positive blood culture. Positive

Bibliographic reference	**Pineiro (2010), ID: 395** **Bacteraemia following dental implants' placement.**
	aerobic blood cultures were subcultured on blood agar, on chocolate agar in an atmosphere with 5–10% CO_2 and on MacConkey agar in an aerobic atmosphere. The same protocol was used for positive anaerobic blood cultures, although also including subculture on Schaedler agar incubated in an anaerobic atmosphere.
Length of follow-up	Incubation period not reported.
Location	Spain.
Source of funding	This work was supported by the Xunta de Galicia (grant PGIDT 08CSA010208PR and grant RH 107/05, Research Intensification), Spain.
Comments	

1 **Table 74**

Bibliographic reference	**Yagci (2013), ID: 112** **Relationship between odontogenic bacteremia and orthodontic stripping.**
Study type	Before-and after study.
Aim	To evaluate the prevalence of bacteraemia associated with an orthodontic stripping procedure.
Patient characteristics	*Inclusion criteria:* • Adults and children with a Class I molar relationship with minimal anterior crowding and in the permanent dentition • with adequate oral hygiene • with plaque scores of 0 or 1. *Exclusion criteria:* • with a history of congenital heart disease, rheumatic fever, hypertrophic cardiomyopathy, subacute bacterial endocarditis, aortic or mitral stenosis, prosthetic heart valves, bleeding disorders, or diabetes mellitus; immune suppressed or pregnant patients and patients who had used an antiseptic mouthwash or antibiotics within the last 3 months.
Number of patients	Total = 29 Gender: 22 female, 7 male Mean age: 18.2 years old (SD: 3.4, range, 14.7-24.3)
Procedures	Orthodontic stripping. Patients were instructed not to eat anything or brush their teeth during the 2 hours preceding the stripping. All blood samples were collected from the patients under sterile conditions at 2 time points: before and soon after stripping.
Outcomes and effect estimates	*Prevalence of bacteraemia:* Baseline = 0/29 (0%) Post stripping = 1/29 (3.4%) [*Streptococcus sanguis*]

Bibliographic reference	**Yagci (2013), ID: 112** **Relationship between odontogenic bacteremia and orthodontic stripping.**
Analysis used	A sterile plastic cannula of 20 g and a sterile syringe were used, and an initial blood sample of 10 cm^3 was collected before treatment. Soon after completing the stripping procedure, the valve of the cannula was reopened, and a second blood sample of 10 cm^3 was taken with a new syringe. The blood samples were injected into aseptic culture flasks containing 50 cm^3 of brain-heart infusion broth and incubated at 37C for 5 days.
Length of follow-up	5 days incubation.
Location	The Department of Orthodontics, Erciyes University, Turkey.
Source of funding	Not reported.
Comments	

1 **Table 75**

Bibliographic reference	**Sonbol (2009), ID: 545** **Prevalence, intensity and identity of bacteraemia following conservative dental procedures in children.**
Study type	RCT
Aim	To investigate the prevalence, intensity and microbial identity of bacteraemia following conservative dental procedures.
Patient characteristics	*Inclusion criteria:* • children and adolescents heavier than 17.5 kg undergoing general anaesthesia for dental treatment. *Exclusion criteria:* • with chronic medical disorders, predisposing cardiac lesions, known viral carriage, haemorrhagic disorders and difficult veins
Number of patients	Total = 205 (at randomisation) Gender: 102 boys; 103 girls Mean age: 10.8 years old (SD: 3.67), range 4.00–17.5 years old. 43 were withdrawn with final total number of 162 children. Rubber dam and clamp: N=41 Fast drill: N=40 Slow drill: N=40 Matrix band and wedge: N=41
Procedures	1. Rubber dam and clamp: a clamp was placed on either a single, fully erupted maxillary or mandibular primary or permanent molar. 2. Fast drill: either a carious primary or permanent molar tooth was drilled for 1 min using a high-speed handpiece and a diamond bur with water irrigation.

Bibliographic reference	**Sonbol (2009), ID: 545** **Prevalence, intensity and identity of bacteraemia following conservative dental procedures in children.**
	3. Slow drill: either a carious primary or permanent molar tooth was drilled for 1 min using a slow-speed handpiece and a number 4 rosehead bur. 4. Matrix band and wedge: a matrix band was placed on either a mandibular or maxillary primary or permanent molar. A wooden wedge was pushed between the matrix band and the adjacent tooth. Blood samples of 6 ml pre-procedure and then another 6 ml 30 s after the procedure were drawn.
Outcomes and effect estimates	*Prevalence of bacteraemia:* Rubber dam and clamp: Baseline = 12/41 (29%); post-procedure = 22/41 (54%); p=0.01 Fast drill: Baseline = 6/40 (15%); post-procedure = 9/40 (22%); p=0.5 Slow drill: Baseline = 4/40 (10%); post-procedure = 9/40 (22%); p=0.2 Matrix band and wedge: Baseline = 13/41 (32%); post-procedure = 27/41 (66%); p=0.001 *Intensity of bacteraemia (detectable ≥0.33 CFU/ml):* *Anaerobic:* Rubber dam and clamp: Baseline = 7/41 (17%); post-procedure = 17/41 (41%); p=0.005 Fast drill: Baseline = 4/40 (10%); post-procedure = 7/40 (18%); p=0.6 Slow drill: Baseline = 2/40 (5%); post-procedure = 9/40 (23%); p=0.02 Matrix band and wedge: Baseline = 9/40 (23%); post-procedure = 18/40 (45%); p=0.002 *Aerobic:* Rubber dam and clamp: Baseline = 6/41 (15%); post-procedure = 16/41 (39%); p=0.001 Fast drill: Baseline = 4/40 (10%); post-procedure = 5/40 (13%); p=0.4 Slow drill: Baseline = 2/40 (5%); post-procedure = 1/40 (3%); p=1.0 Matrix band and wedge: 6/40 (15%); post-procedure = 21/40 (53%); p=0.0001 A total of 628 bacterial isolates were recovered from the membrane filters of which 53 were from baseline blood samples and 575 from postprocedure samples. *Streptococcus* spp.: baseline = 3.8%; post-procedure = 52% *Staphylococcus* spp.: baseline = 49%; post-procedure = 18.3%
Analysis used	• Following attainment of general anaesthesia, a 21-gauge Y-cannula was placed in a vein in either the right or left antecubital fossa using aseptic technique. Using a separate sterile syringe, 6 ml blood was withdrawn and placed immediately into a sterile universal bottle containing 1.23 ml 0.35% of sodium polyanetholesulfonate solution to prevent clotting and to inactivate the natural antibacterial action of the blood. • Thirty seconds after the procedure, a further 6 ml blood was withdrawn and placed into a second sterile universal bottle containing 1.23 ml 0.35% SPS solution.

Bibliographic reference	**Sonbol (2009), ID: 545** **Prevalence, intensity and identity of bacteraemia following conservative dental procedures in children.**
	• Two equal volumes of the solution were poured into a disposable, sterile filtration unit. One filter was incubated aerobically and the other filter was incubated in an anaerobic chamber, for 10 days.
Length of follow-up	10 days incubation.
Location	UK
Source of funding	Not reported.
Comments	

1 **Table 76**

Bibliographic reference	**Zhang (2013), ID: 155** **Effects of irrigation with an antiseptic and oral administration of azithromycin on bacteraemia caused by scaling and root planning.**
Study type	Before-and-after study
Aim	To investigate incidence, magnitude and bacterial diversity of bacteraemia due to flossing compared with scaling and root planing (SRP)
Patient characteristics	*Inclusion criteria:* • had radiographic evidence of inter-proximal bone loss viewed on an orthopantomogram • required to be >21 years old, with a diagnosis of chronic periodontitis • have a palpable vein in an antecubital fossa • at least one quadrant (qualified quadrant) with a minimum of five teeth with two or more inter-proximal sites with probing depths ≥5 mm, not at the same tooth. *Exclusion criteria:* • had significant medical conditions (e.g. diabetes), immune deficiency, congenital or acquired cardiac defects or other conditions requiring antibiotic cover, haematological disorders, pregnancy, infection, history of taking antibiotics in the past 3 months, or taking immunosuppressive or corticosteroid medication.
Number of patients	Total = 30 Gender: 12 males and 18 females Mean age: 47 years old (SD: 9.5)
Procedures	Scaling and root planning (SRP) Patients were instructed not to brush or floss their teeth, chew any food or perform any intraoral manipulations for at least 1 h before the experimental visits. A 20 ml blood sample was obtained as a baseline at the beginning of prior to SRP. Another 20 ml of blood was sampled at 5 min after the initiation of SRP, and at 30 s and 10 min after the completion of SRP.

Bibliographic reference	**Zhang (2013), ID: 155** **Effects of irrigation with an antiseptic and oral administration of azithromycin on bacteraemia caused by scaling and root planning.**
Outcomes and effect estimates	The term total bacteraemia (TB) is used to describe positive bacteraemia samples comprising any genus of oral bacteria, whilst VSB describes positive bacteraemia samples in which any bacteria of the genus viridans streptococci was present, either in combination with other oral bacteria or as the only bacteria in the blood sample. *Prevalence of bacteraemia:* Baseline TB = 3/30 (10%); 5 min after initiation = 10/30 (33.3%); 30 s post = 5/30 (16.7%); 10min post = 2/30 (6.7%) Baseline VSB = 0/30 (0%); 5 min after initiation = 6/30 (20%); 30 s post = 2/30 (6.7%); 10min post = 0/30 (0%) *Magnitude of bacteraemia (mean CFU/ml):* TB: 5 min after initiation = 2.2 (SD: 3.2); 30 s post = 2.1 (SD: 3.8); 10min post = 1.0 (SD: 1.1) VSB: 5 min after initiation = 0.4 (SD: 0.2); 30 s post = 0.3 (SD: 0.1); 10min post = 0.0
Analysis used	Blood samples was obtained from each patient via a vein in the antecubital fossa using a 25 mm/22 gauge cannula which was left in place during each experimental visit to avoid multiple insertions of a needle. Two lysocentrifugation tubes (10 ml each) were inoculated with each 20 ml blood sample immediately following collection and were transferred to the laboratory immediately. Inoculation of cultures was performed in a Class II biosafety laminar flow cabinet to reduce the risk of contamination. The plates were incubated for 7 days.
Length of follow-up	7 days incubation.
Location	Westmead Centre for Oral Health, Sydney, Australia.
Source of funding	Not reported.
Comments	

1 **Table 77**

Bibliographic reference [from CG64]	**Lucas VS, Omar J, Vieira A, Roberts GJ. The relationship between odontogenic bacteraemia and orthodontic treatment procedures 9668. European Journal of Orthodontics 2002;24:-301. Ref ID: 9668**
Study type	RCT
Aim	To investigate the relationship between odontogenic bacteraemia and orthodontic treatment procedures
Patient characteristics	Inclusion: mean age 13.5yrs (range 9.2 to 17.9), n = 64 males, n = 78 females Indices were recorded for bacterial dental plaque and gingival inflammation. A separate score was recorded for the teeth involved in the orthodontic procedure

Bibliographic reference [from CG64]	**Lucas VS, Omar J, Vieira A, Roberts GJ. The relationship between odontogenic bacteraemia and orthodontic treatment procedures 9668. European Journal of Orthodontics 2002;24:-301. Ref ID: 9668**
Number of patients	Total = 142 (n = 81 undergoing GA, n = 61 receiving treatment in the O/P department) n = 39 upper alginate impression n = 42 separator n = 25 fit/placement of band n = 36 archwire adjustment
Procedures	Upper alginate impression, separator, fit/placement of band, archwire adjustment. Blood samples: baseline sample and 30 second sample taken after the orthodontic procedure
Outcomes and effect estimates	Prevalence and intensity of bacteraemia following 4 orthodontic procedures. **Prevalence of bacteraemia** Upper alginate impression: Baseline = 9/39 (23%); post-procedure = 12/39 (31%) Separator: Baseline = 12/42 (27%); post-procedure = 15/42 (36%) Fit/placement of band: Baseline = 9/25 (36%); post-procedure = 11/25 (44%) Archwire adjustment: Baseline = 12/36 (23%); post-procedure = 7/36 (31%) There was NS difference in the number of positive blood cultures between baseline and the dentogingival manipulations There was NS association between the mean plaque and gingivitis scores and the number of positive blood cultures for any of the procedures **Intensity of bacteraemia (mean and SD cfu per ml of blood)** Upper alginate impression: Baseline = 0.2 (0.7); post-procedure = 0.3 (0.6), p>0.05 Separator: Baseline = 0.9 (0.2); post-procedure = 2.2 (9.1), p<0.02 Fit/placement of band: Baseline = 0.1 (0.2); post-procedure = 0.3 (0.6), p>0.05 Archwire adjustment: Baseline = 0.2 (0.7); post-procedure = 0.04 (0.1), p>0.05 The mean total number of aerobic and anaerobic bacteria isolated from the blood samples (cfu of bacteria per ml of blood) was significantly greater following the placement of a separator (p<0.02) There was NS difference in the mean number of aerobic or anaerobic, or the combined total bacteria isolated from the blood samples between baseline and an upper alginate impression or placement of a band or archwire adjustment **Identity of bacteria** The identity of bacteria isolated from blood cultures were similar to those following dental operative procedures, these included S. gordonii, S. sanguis, S. salivarius, S. vestibularis and coagulase negative staphylococci

Bibliographic reference [from CG64]	**Lucas VS, Omar J, Vieira A, Roberts GJ. The relationship between odontogenic bacteraemia and orthodontic treatment procedures 9668. European Journal of Orthodontics 2002;24:-301. Ref ID: 9668**
Analysis used	Microbiology: 6ml per sample, inoculated into sodium polyanethol sulphonate and added to the lysing solution and 3ml of a proprietary streptokinase-streptodornase compound and incubated at 37˚C for 10mins. One plate was incubated aerobically and the other anaerobically for 10days, from day3 they were checked daily for bacterial growth
Length of follow-up	Not reported.
Location	London
Source of funding	Not stated
Comments	

1 **Table 78**

Bibliographic reference [from CG64]	**Roberts GJ, Gardner P, Longhurst P, Black AE, Lucas VS. Intensity of bacteraemia associated with conservative dental procedures in children.[see comment]. British Dental Journal 2000;188:95-8.** **Ref ID: 460**
Study type	RCT [a]
Aim	To explore the intensity of bacteraemia.
Patient characteristics	Inclusion: healthy children receiving dental treatment under general anaesthetic, Exclusion: those who had taken antibiotics within the previous month, known viral carriage and haemorrhagic disorders
Number of patients	Total = 257 children n = 141 male, n = 116 female, mean age 9yrs 1mth (range 2yrs to 19yrs 6mths) n = 54 baseline (no procedure) n = 51 rubber bam placement n = 49 slow drill n = 47 fast drill n = 56 matrix band and wedge
Procedures	Rubber dam placement Matrix band Slow drill Fast drill Blood samples: before procedure, 30 s after procedure.

Bibliographic reference [from CG64]	**Roberts GJ, Gardner P, Longhurst P, Black AE, Lucas VS. Intensity of bacteraemia associated with conservative dental procedures in children.[see comment]. British Dental Journal 2000;188:95-8.** **Ref ID: 460**
Outcomes and effect estimates	*Prevalence of bacteraemia:* Positive blood cultures: baseline n = 5/54 (9.3%); rubber dam placement n = 16/51 (31.4%); slow drill n=6/49 (12.2%); fast drill n = 2/47 (4.3%; matrix band and wedge n = 18/56 (32.1%) Significant differences in the number of positive cultures for: - baseline vs. rubber dam placement (p<0.005) - baseline vs. matrix band (p<0.003) - rubber dam placement vs. slow drill (p<0.02) - rubber dam placement vs. fast drill (p<0.001) - slow drill vs. matrix band (p<0.02) - fast drill vs. matrix band (p<0.0001) NS difference: - baseline vs. slow drill; baseline vs. fast drill; rubber dam placement vs. matrix band; slow drill vs. fast drill Intensity of bacteraemia There was NS differences between any of the groups in the cfu (colony forming units per/ml of blood) Micro-organisms The organisms isolated are typical of those associated with bacteraemia of dental origin Exploration by each group of samples did not reveal showed NS relation between plaque accumulation, gingival inflammation, gingival bleeding and the presence or absence of bacteraemia
Analysis used	Blood cultures Microbiology: Two commercial blood culture systems were used; the Bactec radiometric system and the Bactec 760, a 3ml volume of blood was inoculated into each of the aerobic and anaerobic bottles. Bacteria were speciated using standard methods, streptococci were speciated using API Strep 20. A further 1.5ml was inoculated into the Isolator system vial
Length of follow-up	Not reported
Location	GOSH and Guy's and St Thomas' Hospital Trust, London.
Source of funding	Not stated

Bibliographic reference [from CG64]	**Roberts GJ, Gardner P, Longhurst P, Black AE, Lucas VS. Intensity of bacteraemia associated with conservative dental procedures in children.[see comment]. British Dental Journal 2000;188:95-8.** **Ref ID: 460**
Comments	

1 *(a) randomisation by random number table*

2 **Table 79**

Bibliographic reference [from CG64]	**Roberts GJ, Jaffray EC, Spratt DA, Petrie A, Greville C, Wilson M et al. Duration, prevalence and intensity of bacteraemia after dental extractions in children. Heart (British Cardiac Society) 2006;92:1274-7.** **Ref ID: 2375**
Study type	RCT
Aim	To investigate the duration, prevalence and intensity of bacteraemia after dental extractions.
Patient characteristics	Inclusion: children attending Eastman Dental Hospital for treatment under general anaesthetic, Exclusion: antibiotic usage within the previous month, viral carriage, haemorrhagic disorders and body weight less than 17.5kg An orodontic examination was carried out according to the WHO criteria for dental caries, plaque and gingivitis were assessed Age, plaque index, gingivitis index, number of teeth present at the start of the operation and number of teeth extracted were all similar between the various groups
Number of patients	Total = 500 Mean age of the children was 7.6yrs (range 3.4 to 18.9) Children were allocated to one of the time groups in random permuted blocks; 10sec, 30sec, 1min, 2min, 4min, 7.5min, 15min, 30min, 45min, 1hr
Procedures	Dental extraction
Outcomes and effect estimates	*Intensity of bacteraemia (cfu/6ml sample):* 10sec; before extraction median 2.9 (range 0 to 46); after extraction median 9.8 (range 0 to 149), p=0.001 30sec; before extraction median 0.5 (range 0 to 4); after extraction median 2.6 (range 0 to 17), p=0.001 1min; before extraction median 0.4 (range 0 to 4); after extraction median 16.4 (range 0 to 247), p=0.003 2min; before extraction median 1.2 (range 0 to 23); after extraction median 8.1 (range 0 to 162), p=0.009 4min; before extraction median 0.4 (range 0 to 4); after extraction median 1.7 (range 0 to 15), p=0.002 7.5min; before extraction median 0.4 (range 0 to 4); after extraction median 1.2 (range 0 to 14), p=0.002 15min; before extraction median 1.7 (range 0 to 53); after extraction median 1.9 (range 0 to 33), NS 30min; before extraction median 0.3 (range 0 to 6); after extraction median 0.6 (range 0 to 8), not determined

Bibliographic reference [from CG64]	**Roberts GJ, Jaffray EC, Spratt DA, Petrie A, Greville C, Wilson M et al. Duration, prevalence and intensity of bacteraemia after dental extractions in children. Heart (British Cardiac Society) 2006;92:1274-7.** **Ref ID: 2375**
	45min; before extraction median 0.7 (range 0 to 3); after extraction median 2.4 (range 0 to 46), NS 1hr; before extraction median 1.0 (range 0 to 28); after extraction median 2.1 (range 0 to 49), NS The intensity was significantly greater at the post-extraction time than at the pre-extraction time up to and including 7.5min; however by 15min and beyond, the difference was NS The odds of having a positive culture were significantly greater in the post-extraction time than in the pre-extraction time (OR>1) at each time point up to an including a post-procedure time of 7.5min but not beyond this time The genera most often detected were Streptococcus, Actinomyces and Staphylococcus [a] (it is appropriate to estimate that dental bacteraemia is quenched within about 12min of completing dental extractions)
Analysis used	Percentage prevalence of positive cultures, intensity of bacteraemia, speciation of the organism isolated Microbiology: The samples were processed automatically in the Bactec 9480, for the lysis filtration samples the blood was processed by a well-established method, positive cultures from both broth culture and lysis filtration were isolated and identified. Negative controls were processed with every 10th run of broth culture and each run of lysis filtration and identify contamination
Length of follow-up	Not reported.
Location	UK.
Source of funding	British heart foundation grant
Comments	

(a) Some of the staphylococci may be contaminants, it is not possible to identify the skin as a source of contamination without carrying out DNA typing of the isolates and matching them to skin swabs taken at the time of the blood sample

Table 80

Bibliographic reference [from CG64]	**Roberts GJ, Simmons NB, Longhurst P, Hewitt PB. Bacteraemia following local anaesthetic injections in children. British Dental Journal 1998;185:295-8.** **Ref ID: 2440**
Study type	RCT

Bibliographic reference [from CG64]	**Roberts GJ, Simmons NB, Longhurst P, Hewitt PB. Bacteraemia following local anaesthetic injections in children. British Dental Journal 1998;185:295-8.** **Ref ID: 2440**
Aim	To estimate odontogenic bacteraemia.
Patient characteristics	Inclusion: healthy children attending for dental extractions under general anaesthetic, average age 8yrs 7mths (differences between the baseline and test groups was NS) Exclusion: children who had had antibiotics within the previous month, those with a history of Hepatitis B or HIV
Number of patients	Total = 143 children n = 50 baseline, blood taken before any dento-gingival manipulation n = 32 buccal infiltration n = 32 modified intraligamental n = 29 conventional intraligamental
Procedures	Local anaesthetic injections (buccal infiltration, modified intraligamental, conventional intraligamental) Blood samples: taken 30sec after injection
Outcomes and effect estimates	*Prevalence of bacteraemia:* Positive blood cultures: - baseline n = 4/50 (8.0%; 0.5 to 15.5% 95% CI) - buccal infiltration n = 5/32 (15.6%; 2.8 to 28.5%, 95% CI) - modified intraligamental n = 16/32 (50.0%; 29.2 to 64.5% 95% CI) - conventional intraligamental n = 28/29 (96.6%; 75.2 to 99.2%, 95% CI) Significant differences: - baseline vs. modified intraligamental (p<0.0001) - baseline vs. conventional intraligamental (p<0.0001) - buccal infiltration vs. modified intraligamental (p<0.003) - buccal infiltration vs. conventional intraligamental (p<0.0001) - modified intraligamental vs. conventional intraligamental (p<0.0001) NS differences: - baseline vs. buccal infiltration

Bibliographic reference [from CG64]	**Roberts GJ, Simmons NB, Longhurst P, Hewitt PB. Bacteraemia following local anaesthetic injections in children. British Dental Journal 1998;185:295-8.** **Ref ID: 2440**
	Colony forming units (cfu): The results for infiltration, modified intraligamental and the baseline were always zero. Positive cultures were only obtained in those who had had a conventional intraligamental injection, mean value 252cfu/ml, with a range of 0 to 3018cfu/ml Micro-organisms isolated The organisms isolated are typical of those associated with bacteraemia of dental or oral origin Peridontal indices and bacteraemia There was no positive association between the presence of plaque on the tooth surface adjacent to the conventional intraligamental injection, similarly there was no association with gingivitis
Analysis used	Blood cultures Microbiology: Two commercial blood culture systems were used; the Bactec radiometric system and the Bactec 760, a 3ml volume of blood was inoculated into each of the aerobic and anaerobic bottles. Bacteria were speciated using standard methods, streptococci were speciated using API Strep 20. A further 1.5ml was inoculated into the Isolator system vial
Length of follow-up	
Location	Guy's Dental Hospital, London
Source of funding	Not stated
Comments	

1 **Table 81**

Bibliographic reference [from CG64]	**Tomas I, Alvarez M, Limeres J, Potel C, Medina J, Diz P. Prevalence, duration and aetiology of bacteraemia following dental extractions. ORAL DIS 2007;13:56-62.** **Ref ID: 27**
Study type	RCT
Aim	To investigate the prevalence, duration and aetiology of bacteraemia following dental extractions.
Patient characteristics	Inclusion: patients, who for behavioural reasons, underwent dental extractions under general anaesthesia; n = 29(55%) male and n = 24(45%) female, mean age 26.1±12.3yrs (range 8 to 52yrs) Exclusion: patients who had taken antibiotics in the 3mths prior to the study (including antibiotic prophylaxis for the surgical procedure in the present series), routine use of oral antiseptics, patients suffering from any type of congenital or acquired

Bibliographic reference [from CG64]	**Tomas I, Alvarez M, Limeres J, Potel C, Medina J, Diz P. Prevalence, duration and aetiology of bacteraemia following dental extractions. ORAL DIS 2007;13:56-62.** **Ref ID: 27**
	immunodeficiency
Number of patients	Total = 106 (Control group = 53, group of interest) Oral health scale n = 10 (19%) were grades 0-1, n = 21(40%) were grade 2 and n = 22(41%) were grade 3
Procedure	Dental extractions Blood samples: baseline (after nasotracheal intubation and before local anaesthetic injection), 30sec after final dental extraction, 15min and 1hr after finishing the surgical procedure
Outcomes	Bacteraemia, factors related to the development of bacteraemia *Bacteraemia* At baseline, 5/53 (9.4%) had positive blood cultures, at 30sec 51/53 (96.2%), at 15min 34/53 (64.2%) and at 1hr 11/53 (20%) Of the 209 pairs of blood culture bottles were used, n = 100 were positive, a single bacterium was identified in n = 71 of the positive blood cultures, two bacteria in n = 26, three bacteria to n = 2 and four in the remaining blood culture n = 133 bacterial strains were isolated of which n = 10(7.5%) were aerobes, n = 110(82.7%) were facultative and n = 13(9.8%) were obligate anaerobes The most frequent were Streptococcus spp. (63.8%), particularly S. viridans, followed by Staphylococcus spp. (11.25) and Neisseria spp. (7.5%) Factors related to the development of bacteraemia Analysis of the factors potentially contributing to bacteraemia at 30sec was not performed as there were only n = 2 patients with negative blood cultures Female gender and gingival inflammation <3 were significantly related to bacteraemia at 15min, the risk of bacteraemia was x5 higher in females than in males (OR 5.385; 1.356 to 21.378, 95%CI), and x5 higher in patients with gingival inflammation <3 compared with those with grade 3 (OR 0.186; 0.047 to 0.737, 95%CI) At 15min the following were NS related to bacteraemia; age, levels of plaque and calculus, presence of periodontal pockets, dental mobility, number of decayed teeth, presence of submucous abscesses and/or periapical lesions and number of teeth extracted None of the variables showed significant association with bacteraemia at the 1ht time point
Analysis used	Microbiology: Bottles with aerobic and anaerobic culture media were processed in Bactec 9240, each positive culture was gram stained,

Bibliographic reference [from CG64]	**Tomas I, Alvarez M, Limeres J, Potel C, Medina J, Diz P. Prevalence, duration and aetiology of bacteraemia following dental extractions. ORAL DIS 2007;13:56-62.** **Ref ID: 27**
	Bacteria isolated were identified using biochemical tests provided by the Vitek system
Length of follow-up	Not reported.
Location	Santiago de Compostela University Hospital, Spain
Source of funding	Grant from Xunta de Galicia
Comments	

1

2 **Upper and lower respiratory tract procedures**

3 **Table 82**

Bibliographic reference	**Sharif-Kashani (2010), ID: 368** **Incidence of Fever and Bacteraemia Following Flexible Fiberoptic Bronchoscopy: A Prospective Study**
Study type	Before-and-after study
Aim	To determine the incidence of bacteraemia and fever following FB.
Patient characteristics	*Inclusion criteria:* • adults who were scheduled for FB with different indications were enrolled in the study. *Exclusion criteria:* • had immunosuppressant states including diabetes mellitus and low white blood cell count; receiving antibiotic therapy within a week prior to the FB; current active infection; fever >38°C during 48 hours prior to the FB and concurrent treatment with a systemic steroids.
Number of patients	Total = 85 Gender: 69 males (81%); 16 females (19%) Mean age: 57 years old (SD: 28); range: 34-90 years old.
Procedures	Flexible fiberoptic bronchoscopy Three aerobic and anaerobic cultures for venous blood and lavage fluid were drawn just prior, immediately following and 20 min after bronchoscopy using 10 cc of venous blood samples and bronchoalveolar lavage (BAL) specimens.
Outcomes and effect estimates	*Prevalence and duration of bacteraemia:* Baseline: 0/85 (0%); Immediately after FB: 7/85 (8%); 20 min after FB: 1/85 (1%)

Bibliographic reference	**Sharif-Kashani (2010), ID: 368** **Incidence of Fever and Bacteraemia Following Flexible Fiberoptic Bronchoscopy: A Prospective Study**
	Individual bacteria identified: *Staphylococcus coagulase negative* *Staphylococcus coagulase positive* *Citrobacter freundii* *Streptococcus viridans*
Analysis used	Blood specimens were injected in a dual culture (aerobic and anaerobic) medium bottle and bottles were incubated in a BabT-Alert incubator for 7 days at temperature of 35-37 °C. Positive cultures were considered if one bacteria growth concentration was more than 10 4 cfu/mL and also visual examination of blood cultures indicated bacterial growth by rapid development of turbidity in the medium within up to 7 days after inoculation and incubation.
Length of follow-up	7 days incubation.
Location	Between October 2006 and March 2007, National Research Institute of Tuberculosis and Lung Disease, Tehran, Iran.
Source of funding	Not reported.
Comments	

1 **Table 83**

Bibliographic reference	**El Batrawy (2014), ID: 776** **Bacteraemia associated with bronchoscopy.**
Study type	Before-and-after study
Aim	To assess the incidence of bacteraemia following bronchoscopy to determine whether the use of prophylactic antibiotics is warranted in patients at risk of endocarditis.
Patient characteristics	*Inclusion criteria:* • adults and children who underwent bronchoscopy during the study period *Exclusion criteria:* • Patients with current respiratory tract infection or febrile illnesses and those receiving antibiotic therapy within a week prior to the bronchoscopy
Number of patients	Total = 45 Overall mean range: 8 to 65 years old. Adults: gender: 29 males; 7 females (total = 36) Adults mean age: 48 years old (SD: 13.75) Children: gender: 4 males; 5 females (total = 9) Children mean age: 12.3 years old (SD: 2.8)

Bibliographic reference	**El Batrawy (2014), ID: 776** **Bacteraemia associated with bronchoscopy.**
Procedures	Bronchoscopy (rigid or flexible). Blood sampling: three 10 mL blood samples were taken from the anti-cubical fossa one immediately before and two after bronchoscopy 10 min apart under complete aseptic conditions. True bacteraemia was defined as episodes in which two post bronchoscopy positive blood cultures yielded the same organisms.
Outcomes and effect estimates	*Prevalence of bacteraemia:* Baseline = 0/45; 10 min after = 0/45; 20 min after = 0/45
Analysis used	The 10 mL venous blood samples were inoculated, at bed side, onto the BACTECTM PLUS Aerobic/F blood culture medium which usually contains nutritive elements for microorganisms, anticoagulant, and resins for the adsorption of antibiotics. Bottles were then transported immediately to the Microbiology Laboratory for further processing. After 18–24 h incubation, plates were examined for the presence of any relevant growth. If no growth appeared after 18–24 h incubation, plates were re-incubated for additional 48 h and re-examined thereafter. If no evidence of microbial growth exists bottles were discarded and reports were discharged as no growth after 5 days incubation.
Length of follow-up	5 days incubation.
Location	Chest Department, Thoracic Surgery Department and Microbiology Laboratory of Ain Shams University Hospitals, Cairo, Egypt.
Source of funding	Not reported.
Comments	

1 **Table 84**

Bibliographic reference	**Saayman (2009), ID: 505** **Bacteraemia following single-stage percutaneous dilatational tracheostomy.**
Study type	Before-and-after study
Aim	The aim of the current study is to establish the incidence of bacteraemia in consecutive ICU patients undergoing PDT with a single dilator technique.
Patient characteristics	*Inclusion criteria:* • ventilated adult ICU patients requiring PDT were included. *Exclusion criteria:* • if the patient's advocate refused assent, survival was expected to be less than 24-h, patients were under age 18 years of age or immunosuppressed.
Number of patients	Total = 118; Non-antibiotics group = 57 (group of interest)

Bibliographic reference	**Saayman (2009), ID: 505** **Bacteraemia following single-stage percutaneous dilatational tracheostomy.**
	Overall gender: 43 females and 75 males (subgroup not available) Overall age range: 19–88 years of age (median 61) (subgroup not available)
Procedures	Single-stage percutaneous dilatational tracheostomy. Peripheral venous blood cultures were performed using full aseptic conditions immediately prior to the procedure (pre-tracheostomy). A second set of peripheral venous blood cultures were taken immediately after securing the tracheostomy tube (post-tracheostomy). The time between the insertion of the tracheostomy tube and sampling was no more than 15 min.
Outcomes and effect estimates	*Prevalence of bacteraemia:* Baseline = 0/57 (0%); post PDT = 5/57 (8.7%) *Individual bacteria identified:* *Coagulase Negative Staphylococcus* *S. milleri* *H. influenza* *Candida spp.* *Enterobacter*
Analysis used	Povidone-iodine solution (10% w/v) was applied to the skin and 20 ml of blood withdrawn from a peripheral vein and 10 ml inserted into aerobic and anaerobic blood culture bottles respectively. Incubation of pre- and post-cultures was performed using the BACTEC system until positive or for up to 5 days. Blood cultures were recorded as positive if growth of one or more significant organisms were identified.
Length of follow-up	5 days incubation.
Location	Adult Critical Care, University Hospital of Wales, Cardiff, UK.
Source of funding	Not reported.
Comments	

1 **Table 85**

Bibliographic reference	**Yokoyama (2014), ID: 74** **Randomized clinical trial of the effect of perioperative synbiotics versus no synbiotics on bacterial translocation after oesophagectomy.**
Study type	RCT
Aim	To investigate the effect of perioperative symbiotic administration on the incidence of bacterial translocation to mesenteric lymph nodes (MLNs) and the occurrence of postoperative bacteraemia.

Bibliographic reference	**Yokoyama (2014), ID: 74** **Randomized clinical trial of the effect of perioperative synbiotics versus no synbiotics on bacterial translocation after oesophagectomy.**
Patient characteristics	*Inclusion criteria:* • adult patients with oesophageal cancer scheduled to undergo oesophagectomy. *Exclusion criteria:* • oesophagectomy without a planned MLN dissection (no thoracotomy or median sternotomy), cancers that needed a two-step procedure, and age over 80 years.
Number of patients	Total number = 42; control group = 21 (group of interest) Gender: 18 males; 8 females Mean age: 66 years old (range: 25 to 77 years old)
Procedures	Oesophagectomy. Blood samples (1ml) were collected into a test tube on the morning of the operation after induction of anaesthesia and just before laparotomy (baseline), and on post-operative day 1. Patients in the control group consumed an ordinary diet without synbiotics before surgery.
Outcomes and effect estimates	*Prevalence of bacteraemia:* Baseline = 5/21 (24%); post-operative day 1 = 12/21 (57%)
Analysis used	The samples were held at room temperature for 5min until storage at −80◦C. Bacterial detection in blood samples collected on post-operative day 1 was correlated with bacterial detection in the MLN-2 samples.
Length of follow-up	Not reported.
Location	Between January 2008 and August 2011, Nagoya University Hospital, Japan.
Source of funding	Not reported.
Comments	

1 **Table 86**

Bibliographic reference [from CG64]	**Ho H, Zuckerman MJ, Wassem C. A prospective controlled study of the risk of bacteremia in emergency sclerotherapy of esophageal varices. [Review] [44 refs]. Gastroenterology 1991;101:1642-8.** **Ref ID: 829**
Study type	Before-and-after study
Aim	To determine the frequency of bacteraemia after endoscopy.
Patient characteristics	Inclusion: patients admitted for upper GI bleeding or elective oesophageal variceal sclerotherapy (EVS) Exclusion: had received any antibiotics in the last 2 weeks before admission

Bibliographic reference [from CG64]	**Ho H, Zuckerman MJ, Wassem C. A prospective controlled study of the risk of bacteremia in emergency sclerotherapy of esophageal varices. [Review] [44 refs]. Gastroenterology 1991;101:1642-8.** **Ref ID: 829**
	The emergency endoscopy and sclerotherapy groups were comparable in age and sex distribution
Number of patients	Total = 72 (n = 126 endoscopies) n = 36 (n = 37 sessions) emergency endoscopy group n = 36 sclerotherapy groups (n = 14 the emergency EVS group, n = 33 sessions) (n = 36 the elective EVS group, n = 56 sessions)
Procedures	Emergency endoscopy, elective EVS, emergency EVS Blood samples: Before endoscopy, at 5min and 30min after the procedure
Outcomes and effect estimates	Blood cultures Positive blood cultures were found in n = 30/378 cultures (7.9%), of these n = 11 were considered to be potentially significant *Prevalence of bacteraemia:* Emergency endoscopy group blood cultures: Baseline = 0/37 (0%); 5 min = 2/37 (5%); 30 min = 3/37 (8%) Total n = 5 positive , the incidence of endoscopy-related bacteraemia was considered to be 11% (n = 4) with a predominance of skin flora Elective EVS sclerotherapy: Baseline = 3/33 (9%); 5 min = 1/33 (3%); 30 min = 4/33 (12%) Total n = 8 positive blood cultures (n = 3 drawn before endoscopy), no significant bacteraemia was noted and no patients had signs or symptoms of infection Emergency EVS sclerotherapy; Baseline = 7/56 (13%); 5 min = 5/56 (9%); 30 min = 5/56 (9%) Total n = 17 positive blood cultures (n = 7 drawn before endoscopy), n = 4 (7.1%) sessions had significant pre-endoscopic blood cultures and n = 5 (8.9%) sessions had six significant post-endoscopic blood cultures n = 8/17 (47%) testing positive for E coli, Campylobacter coli, Pseudomonas fluorescens, Bacteroides fragilis, or they were polymicrobial with Clostridium. The other n = 9/17 (53%) positive blood culture results were with oral and skin flora

Bibliographic reference [from CG64]	**Ho H, Zuckerman MJ, Wassem C. A prospective controlled study of the risk of bacteremia in emergency sclerotherapy of esophageal varices. [Review] [44 refs]. Gastroenterology 1991;101:1642-8.** **Ref ID: 829**
	In this group there were positive blood cultures in n = 8/56 (14%) of sessions, excluding those with the same organisms identified pre and post procedure, bacteraemia was n = 6/56 (11%), this was significant bacteraemia in n = 3/56 (5.4%) <u>Differences in bacteraemia between groups</u> There were NS differences in the positive blood culture results in: - the post endoscopy groups between: emergency EVS vs. emergency endoscopy; emergency EVS vs. elective EVS; elective EVS vs. emergency endoscopy - within groups (post endoscopic vs preendoscopic); elective EVS; emergency EVS The difference within groups (post endoscopic vs preendoscopic) in the emergency group was significant p=0.03 There was no difference in postendoscopic bacteraemia compared with preendoscopic bacteraemia in emergency alone, or for elective ECS or emergency EVS <u>Analysis of significant bacteraemia:</u> There was NS differences in the significant bacteraemia in the postendoscopy groups; emergency EVS vs. emergency endoscopy; emergency EVS vs. elective EVS; elective EVS vs. emergency endoscopy
Analysis used	Microbiology: 5ml per sample inoculated into each Trypiticase Soy Broth for both aerobic and anaerobic, bacterial growth was monitored for 7days with Bactec 360 Microscan system
Length of follow-up	Not reported.
Location	Texas, US.
Source of funding	Not stated
Comments	

1 **Table 87**

Bibliographic reference [from CG64]	**Melendez LJ, Chan KL, Cheung PK, Sochowski RA, Wong S, Austin TW. Incidence of bacteremia in transesophageal echocardiography - a prospective-study of 140 consecutive patients. J AM COLL CARDIOL 1991;18:1650-4. Ref ID: 9109**
Study type	Before-and-after study
Aim	To investigate the incidence of bacteraemia in transesophageal echocardiography
Patient characteristics	Inclusion: consecutive ambulatory patients scheduled for transoesophageal echocardiography (TOE) at 2 tertiary hospitals

Bibliographic reference [from CG64]	**Melendez LJ, Chan KL, Cheung PK, Sochowski RA, Wong S, Austin TW. Incidence of bacteremia in transesophageal echocardiography - a prospective-study of 140 consecutive patients. J AM COLL CARDIOL 1991;18:1650-4. Ref ID: 9109**
	Age 53±15yrs (range 19 to 84yrs), n = 69 male, n = 71 female, n = 34 patients with a valve prosthesis Exclusion: those with a potential source of bacteraemia (known or suspected bacterial infection, indwelling urinary catheter, multiple venipuncture sites, recent surgery or trauma) None of the patients received prophylactic antibiotic agents before or after transoesophageal echocardiography
Number of patients	Total = 140
Procedure	Transoesophageal echocardiography (TOE) Blood samples: immediately before the procedure, within 5mins after termination of the procedure, 1hr after the procedure
Outcomes and effect estimates	*Prevalence of bacteraemia:* Baseline = 4/140 (2.9%); 5 min = 2/140 (1.4%); 1 hour = 2/140 (1.4%) Blood cultures were positive in n = 4 patients before TOE, in n = 2 in immediately after (bacteria species, coagulase negative staphylococci) and in n = 2 late samples (bacteria species, coagulase negative staphylococci, Propionibacterium), both these organisms were considered to be likely contaminants There was no correlation between difficulty in intubation and a positive blood culture, or between a positive culture and the presence of an indwelling intravenous line The relative risks of bacteraemia immediately after and 1hr after TOE were NS different from baseline All patients were contacted 12 weeks after transoesophageal echocardiography, none had developed bacterial endocarditis or other infections requiring the administration of antimicrobial therapy
Analysis used	Blood cultures Microbiology: 10ml per sample, 5ml were inoculated into aerobic and anaerobic culture, cultures were assessed for bacterial growth with use of a semiautomated instrument (Bactec 460) that detects carbon dioxide generated by bacterial metabolism, cultures were considered negative if no bacterial growth was observed after 7days.
Length of follow-up	12 weeks
Location	2 tertiary hospitals, Canada
Source of funding	Not stated
Comments	

1 **Table 88**

Bibliographic reference [from CG64]	**Roudaut R, Lartigue CM, Texier-Maugein J, Dallocchio M. Incidence of bacteraemia or fever during transoesophageal echocardiography: A prospective study of 82 patients. European Heart Journal 1993;14:936-40.Ref ID: 3797**
Study type	Before-and-after study
Aim	To investigate the incidence of bacteraemia or fever during transoesophageal echocardiography
Patient characteristics	Inclusion: patients referred from transoesophageal echocardiography Exclusion: had received antibiotics before the procedure, was febrile, had any suspicion of infective endocarditis The mean procedure duration was 19min and no complications occurred There was NS differences in the clinical characteristics of the two groups, n = 8 patients had prosthetic heart valves
Number of patients	Total = 82 n = 44 (group I) n = 38 (group II)
Procedures	Transoesophageal echocardiography Blood samples: - group I blood cultures taken before procedure, immediately after the procedure, 15min after procedure - group II blood cultures taken before procedure, during procedure (10min after the first attempt to introduce the endoscope), immediately after procedure [c] Rectal temperature of the n = 62 hospitalised patients was measured twice a day for a mean of 6 days after the procedure.
Outcomes and effect estimates	Incidence of bacteraemia: Group I: Baseline = 0/44 (0%); immediately after = 1/44 (2.3%); 15 min after = 0/44 (0%) Group II: Baseline = 0/38 (0%); 10 min into the procedure = 1/38 (2.6%); immediately after = 0/38 (0%) n = 2/82 (2.4%) patients had a single positive blood culture (Corynebacteria from a group I patient at the end of the procedure, Staphylococcus epidermis from a group II patient during the procedure from the second patient) [a] Incidence of fever: The rectal temperate rose above 37.5Cin n = 9 patients within the first 24hr after examination but returned to normal within the subsequent 24hr (maximum temperature observed was 38.4C) Follow-up: A third (34%) of the patients were seen within the first months after the procedure, average follow-up 4mths No sign of endocarditis was detected in these patients [b]

Bibliographic reference [from CG64]	Roudaut R, Lartigue CM, Texier-Maugein J, Dallocchio M. Incidence of bacteraemia or fever during transoesophageal echocardiography: A prospective study of 82 patients. European Heart Journal 1993;14:936-40.Ref ID: 3797
Analysis used	Microbiology: Aerobic and anaerobic blood culture bottles (BCB system roche) were inoculated and incubated for 10days at 37˚C
Length of follow-up	A third (34%) were examined a few months later to evaluate any occurrence of endocarditis
Location	France
Source of funding	Not stated
Comments	

(a) the smear samples from the surface of the endoscope after the procedure were positive in N=29/38 (79%), the organisms were essentially haemolytic Streptococcus or Neisseria

(b) for those who were lost to follow-up the authors assumed that patients would have been referred back to them in the event of an episode of endocarditis

(c) in addition in group II cotton swabs were used to take smear samples from the surface of the endoscope after the procedure

Table 89

Bibliographic reference [from CG64]	Shyu K-G, Hwang J-J, Lin S-C, Tzou S-S, Cheng J-J, Kuan P et al. Prospective study of blood culture during transesophageal echocardiography. American Heart Journal 1992;124:1541-4. Ref ID: 3820
Study type	Before-and-after study
Aim	To ascertain the incidence and significance of bacteraemia associated with transesophageal echocardiography.
Patient characteristics	Inclusion: patients undergoing transoesophageal echocardiography, n = 66 male, n = 66 women, ranging in age from 17 to 73yrs (mean age 44.6yrs) Exclusion: absence of fever (<37.5C) within 3days of the procedure, no leukocytosis (total white cell count <10000/mm3), no use of antibiotics for 3days before the procedure, other evidence of infection from clinical record review No procedure related complications were noted in any of the n = 132 patients
Number of patients	n = 132 (n = 135 procedures)
Procedures	Transesophageal echocardiography Blood samples: 30 to 60mins before the procedure, immediately after, 180 to 240mins after the procedure[b]
Outcomes and effect estimates	The mean time (±SD) of introducing the endoscope into the oesophagus was 50.1(±64.8)secs, the insertion time was less than 30sec in n = 61 procedures, 30 to 60sec in n = 52 procedures, and >60sec in n = 22 procedures The mean procedure time was 10.2(±4.3)mins *Prevalence of bacteraemia:* Baseline (pre-): 3/270 (1.1%); immediately after = 0/270 (0%); 180 to 240 min after = 1/270 (0.4%)

Bibliographic reference [from CG64]	Shyu K-G, Hwang J-J, Lin S-C, Tzou S-S, Cheng J-J, Kuan P et al. Prospective study of blood culture during transesophageal echocardiography. American Heart Journal 1992;124:1541-4. Ref ID: 3820
	Blood cultures [a] n = 3/270 pre-echocardiographic cultures were positive, the n = 3 patients were asymptomatic and subsequent cultures were negative None of the blood samples obtained immediately after the procedure was positive n = 2/270 cultures from n = 1 patient 4hrs after the procedure were positive No evidence of endocarditis was subsequently found in these patients and the positive cultures were considered to be transient bacteraemia, no positive blood samples were obtained in n = 21 patients with prosthetic valves Throat swabs n = 135 throat swabs, the majority of isolated microorganisms were Neisseria species and Streptococcus viridans, these are normal flora of the oral cavity. The microorganisms isolated from blood cultures were different to those isolated from the throat swab (post procedure, Staphylococcus epidermidis)
Analysis used	Microbiology: blood cultures were incubated at 35˚C for 7days, aerobic culture vials were tested twice on days 1 and 2 and once on days 3 through 7, anaerobic culture vials were tested once on days 1 through 7. Positive vials were subcultured on appropriate media and gram staining was performed
Length of follow-up	Not reported.
Location	October 1990 to August 1991, National Taiwan University Hospital
Source of funding	Not stated
Comments	

(a) The threshold of the growth value indicating a positive result was set at 25 to 30, a change in growth value of >10 to 15 between two consecutive readings was also indicative of a positive result
(b) A cotton swab took smear samples from the throat 30 to 60mins before the procedure

Table 90

Bibliographic reference [from CG64]	Yildirim I, Okur E, Ciragil P, Aral M, Kilic MA, Gul M. Bacteraemia during tonsillectomy. Journal of Laryngology & Otology 2003;117:619-23. Ref ID: 238
Study type	Before-and-after study
Aim	To investigate bacteraemia during tonsillectomy

Bibliographic reference [from CG64]	Yildirim I, Okur E, Ciragil P, Aral M, Kilic MA, Gul M. Bacteraemia during tonsillectomy. Journal of Laryngology & Otology 2003;117:619-23. Ref ID: 238
Patient characteristics	Inclusion: patients with a history of recurrent episodes of acute tonsillitis or obstructive symptoms due to tonsillar hypertrophy who had been admitted for elective tonsillectomy, randomly classified into two groups, n = 28 male, n = 36 female Exclusion: any cardiovascular risk factors, had received antibiotic therapy for at least 20days before the operation
Number of patients	Total = 64 n = 33, group I Blood samples: pre-operative (after intubation), early post-operative (within 2mins after tonsillectomy) and post-operative (60mins after tonsillectomy) Tonsillar surface and deep tissue cultures were taken n = 31, group II Blood samples: pre-operative (after intubation), post-operative (15 and 60mins after tonsillectomy) Tonsillar surface and deep tissue cultures were taken
Procedures	Tonsillectomy Blood samples: Group I: pre-operative (after intubation), early post-operative (within 2mins after tonsillectomy) and post-operative (60mins after tonsillectomy) Group II: pre-operative (after intubation), post-operative (15 and 60mins after tonsillectomy)
Outcomes and effect estimates	Blood cultures Group I: Baseline = 0/33 (0%); 2 min = 9/33 (27.3%); 60 min = 0/33 (0%) Group II: Baseline = 0/31 (0%); 15 min = 2/31 (6.5%); 60 min = 0/31 (0%) All of the pre-operative blood cultures were negative Group I, bacterial growth was observed in n = 9/33 (27.3%) blood cultures taken within 2mins of tonsillectomy Group II, bacterial growth was observed in n = 2/31 (6.5%) blood cultures taken within 15mins after tonsillectomy, the difference between the two groups was significant, p=0.027 (organisms identified both groups; E. coli, Staph sureus, H. influenzae, unclassified streptococci, GABHS , Streph viridans, Strep pneumoniae The organisms isolated from the tonsillar surface did not always correspond with the organisms isolated from the deep tissue specimens. Staphylococcus aureus was the most commonly grown organism in the core of the tonsillar tissue and/or surface culture (n = 18), followed by GABHS (n = 14), Haemophilus influenzae (n = 11) and Streptococcus pneumoniae (n = 10) The patients with bacteraemia did not have any clinical signs and/or symptoms of a serious infection and were discharged

Bibliographic reference [from CG64]	**Yildirim I, Okur E, Ciragil P, Aral M, Kilic MA, Gul M. Bacteraemia during tonsillectomy. Journal of Laryngology & Otology 2003;117:619-23. Ref ID: 238**
	without hospitals.
Analysis used	Microbiology: 6ml (those under 10yrs), 16-18ml)those >10yrs), half of the samples inoculated into an aerobic culture bottle, half into an anaerobic culture bottle, blood culture bottles were incubated within the Bactec 9050 automatic blood culture system, routine bacteriological inoculations were performed from the bottles in which bacterial growth took place, aerobic microorganisms were identified by standard lab methods, anaerobic were identified by using OXOID An-identdiscs
Length of follow-up	Not reported
Location	Turkey
Source of funding	Kahramanmaras Sutcu University Research Fund
Comments	

1 **Table 91**

Bibliographic reference [from CG64]	**Zuccaro G, Jr., Richter JE, Rice TW, Achkar E, Easley K, Lewis J et al. Viridans streptococcal bacteremia after esophageal stricture dilation.[see comment]. Gastrointestinal Endoscopy 1998;48:568-73.** **Ref ID: 5981**
Study type	Cohort study
Aim	To determine the frequency and duration of bacteraemia associated with esophageal stricture dilation.
Patient characteristics	Inclusion: consecutive patients with dysphagia presenting for upper endoscopy and stricture dilation, without valvular[a] disease . Patients, n = 73 male, n = 30 female; controls, n = 32 male, n = 18 female Exclusion: <18yrs old, received antibiotics within 2wks before the procedure, anaemic
Number of patients	Total = 153 patients n = 103 with dysphagia having upper endoscopy and stricture dilation n = 50 control, without dysphagia or oesophageal disease undergoing upper endoscopy for reasons unrelated to swallowing disorders
Procedures	Esophageal stricture dilation Blood samples: pre-procedure, 5, 20 and 30mins after the procedure
Outcomes and effect estimates	*Prevalence of bacteraemia (viridans streptococcus):* Baseline (before) = 0/103 (0%); 1 min = 19/81 (23%); 5 min = 16/96 (17%); 20-30 min = 3/63 (5%)

Bibliographic reference [from CG64]	**Zuccaro G, Jr., Richter JE, Rice TW, Achkar E, Easley K, Lewis J et al. Viridans streptococcal bacteremia after esophageal stricture dilation.[see comment]. Gastrointestinal Endoscopy 1998;48:568-73.** **Ref ID: 5981**
	All blood cultures performed before the procedure were negative. Viridans streptococcal bacteraemia occurred in n = 22/103 (21.4%; 13.4 to 29.3%, 95%CI) after stricture dilation, compared with n = 1/50 (2%; 0.06 to 10.7%, 95%CI) control patients, p=0.001 n = 19/81 (23%) blood cultures obtained 1min after stricture dilation were positive for viridans streptococcus, compared with n = 16/96 (17%) obtained 5min after dilation, and n = 3/63 (5%) obtained 20 to 30min after dilation Of the n = 19 bacteraemic patients at 1min, n = 14/19 (74%) were still bacteraemic at 5min and n = 2/19 were still bacteraemic at 20 to 30mins Benign strictures were dilated in n = 80 and malignant in n = 15, of the n = 103 patients n = 96 underwent endoscopy immediately before dilation Time after dilation: 1min; n = 81 blood cultures obtained; n = 24 positive cultures; organisms cultured, viridans streptococcus (n = 19), coagulase negative staph (n = 3), neisseria species (n = 3), diptheroids (n = 2), other (n = 3) 5min; n = 96 blood cultures obtained; n = 17 positive cultures; organisms cultured, viridans streptococcus (n = 16), coagulase negative staph (n = 3), neisseria species (n = 1), diptheroids (n = 1) 20to30min; n = 63 blood cultures obtained; n = 4 positive cultures; organisms cultured, viridans streptococcus (n = 3), coagulase negative staph (n = 1) Stricture diameter Stricture diameter before dilation appeared to be the single most predictive factor for viridans streptococcal bacteraemia, n = 13/96 had strictures which precluded passage of the endoscope before dilation of these bacteraemia occurred in N/13 (62%), the other n = 83/96 had strictures which allowed the passage of the endoscope before dilation of these n = 12/83 (14%); p=0.001, OR 9.5 (2.7 to 33.8, 95%CI) There was NS difference in the rate of viridans streptococcal bacteraemia among patients with benign versus malignant strictures, passage of single versus multiple dilators, presence or absence of oesophagitis, use of antisecretory therapy, or the presence or absence of periodontal disease No patients experienced fever, chills, or other symptoms/signs of clinically significant bacteraemia in the recovery room. All those with bacteraemia were follow-up by telephone and no adverse events related to transient bacteraemia were reported
Analysis used	Microbiology: 20ml sample, 10ml inoculated into commercially prepared blood culture bottles, the bottles were then incubated

Bibliographic reference [from CG64]	**Zuccaro G, Jr., Richter JE, Rice TW, Achkar E, Easley K, Lewis J et al. Viridans streptococcal bacteremia after esophageal stricture dilation.[see comment]. Gastrointestinal Endoscopy 1998;48:568-73.** **Ref ID: 5981**
	for 5days ion the BacT/Alert instrument, when a blood culture bottle became positive by the BacT/Alert signal or growth on the subculture plate it was removed from the BacT/Alert and a gram stain performed
Length of follow-up	9mth study period
Location	USA
Source of funding	Not stated
Comments	

1

2 **Upper and lower GI tract – colorectal procedures**

3 **Table 92**

Bibliographic reference	**Min (2008), ID: 617** **Low frequency of bacteraemia after an endoscopic resection for large colorectal tumours in spite of extensive submucosal exposure.**
Study type	Before-and-after study
Aim	To evaluate the frequency of bacteraemia associated with an EMR or ESD for colon lesions
Patient characteristics	*Inclusion criteria:* • adult patients admitted for endoscopic resection of colonic adenoma or adenocarcinoma. *Exclusion criteria:* • indications for antibiotic prophylaxis as determined by the American Society for Gastrointestinal Endoscopy or European Society for Gastrointestinal Endoscopy guidelines • antibiotic use within 1 week before the procedure • possible signs of any infection at the time of the procedure (body temperature >37C, heart rate >90 beats/min, or respiratory rate >20 breaths/min), and an inability to get informed consent.
Number of patients	Total = 40 (conventional EMR = 30; EMR-P = 3; ESD = 7) Gender: 28 males; 12 females Median age of 60.0 years old (range 44 to 80 years old)
Procedures	Endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) Blood cultures were obtained immediately before, 5 minutes after, and 30 minutes after the procedure.

Bibliographic reference	**Min (2008), ID: 617** **Low frequency of bacteraemia after an endoscopic resection for large colorectal tumours in spite of extensive submucosal exposure.**
Outcomes and effect estimates	*Prevalence of bacteraemia:* Baseline = 0/40 (0%); 5 min = 0/40 (0%); 30 min = 1/40 (2.5%) *Individual bacteria identified:* Coagulase-negative *Staphylococcus*.
Analysis used	To ensure accurate timing of the blood cultures, a 20-gauge angiocatheter was placed in a vein in the antecubital space before the procedure and was used for blood sampling. 20 ml of blood were collected through this catheter and then equally distributed into commercially available aerobic/anaerobic blood culture bottles. Before the second and the third blood cultures, the angiocatheter was flushed with sterile non-bacteristatic 0.9% sodium chloride solution. For the second and third blood cultures, an initial 5 ml of blood was collected and discarded. After that, another 20 ml was collected and then equally distributed into culture bottles. All samples were incubated for 5 days.
Length of follow-up	5 days incubation.
Location	Between October 2006 and March 2007, Samsung Medical Centre, Korea.
Source of funding	Study support by a grant from the In-Sung Foundation for Medical Research (CA68461).
Comments	

1 **Table 93**

Bibliographic reference	**Chun (2012), ID: 238** **Prospective Assessment of Risk of Bacteraemia Following Colorectal Stent Placement.**
Study type	Before-and-after study
Aim	To evaluate the risk of bacteraemia and infectious complications after stent insertion for colorectal obstruction.
Patient characteristics	*Inclusion criteria:* • adult patients with colorectal obstruction who needed stent insertion. *Exclusion criteria:* • those with conditions for which ASGE guidelines recommend antibiotic prophylaxis • antibiotic use within 1 week before the anticipated procedure • body temperature >38C • bleeding tendency, and declined participation or inability to give informed consent.
Number of patients	Total = 64 Gender: 35 males; 29 females

Bibliographic reference	**Chun (2012), ID: 238** **Prospective Assessment of Risk of Bacteraemia Following Colorectal Stent Placement.**
	Mean age: 68.8 years old (SD: 10.8)
Procedures	Colorectal stent placement. The first set of blood sample was taken immediately before the procedure, and the second set was taken 30 min after colorectal stent insertion.
Outcomes and effect estimates	*Prevalence of bacteraemia:* Baseline = 0/64 (0%); 30 min = 4/64 (6%) *Individual bacteria identified:* *Bacteroides fragilis* *Escherichia coli* *Klebsiella spp.*
Analysis used	The skin site was cleaned with 70% isopropyl alcohol solution and air-dried for 30 s. The area was then cleaned with 10% povidone-iodine solution for 60 s and allowed to air-dry for another 60 s. The 20-gauge angiocatheter then was inserted. Two sets of blood cultures were obtained. Before the second blood culture, the angiocatheter was flushed with sterile non-bacteriostatic 0.9% sodium chloride solution. 20 ml of blood was collected through the indwelling angiocatheter and then equally distributed into aerobic/anaerobic culture media sets. Cultures were observed for 5 days.
Length of follow-up	5 days incubation.
Location	Between May 2009 and April 2011, Seoul St. Mary's Hospital, Korea.
Source of funding	Not reported.
Comments	

1 **Table 94**

Bibliographic reference [from CG64]	**Weickert U, Vetter S, Burkhardt U, Eickhoff A, Buhl A, Riemann JF. Bacteremia after diagnostic conventional laparoscopy and minilaparoscopy: a prospective study in 100 patients. Journal of Clinical Gastroenterology 2006;40:701-4. Ref ID: 42**
Study type	Before-and-after study
Aim	To investigate bacteraemia rates caused by conventional diagnostic laparoscopy.
Patient characteristics	Inclusion: patients having undergone diagnostic laparoscopy, mean age 53.5yrs(range 19 to 81yrs), n = 59 male, n = 41 female Exclusion: <18yrs, fever or other signs of infection with 14days before laparoscopy, antibiotics within 14days before laparoscopy, conditions for which current guidelines recommend antibiotic prophylaxis, immunosuppressant therapy

Bibliographic reference [from CG64]	**Weickert U, Vetter S, Burkhardt U, Eickhoff A, Buhl A, Riemann JF. Bacteremia after diagnostic conventional laparoscopy and minilaparoscopy: a prospective study in 100 patients. Journal of Clinical Gastroenterology 2006;40:701-4. Ref ID: 42**
Number of patients	Total = 100 patients n = 50 (convention laparoscopy); n = 50 (mini-laparoscopy)
Procedures	Conventional laparoscopy and mimi-laparoscopy Blood samples: immediately before laproscopy and within 5mins after the procedure
Outcomes and effect estimates	*Prevalence of bacteraemia:* Baseline (before): 0/100 (0%); 5 min after = 4/100 (4%) There was no bacterial growth in 100 blood cultures drawn before laparoscopy, bacterial growth occurred in n = 4 blood cultures taken immediately after laparoscopy, all bacteria found were gram-positive No difference was found between patients with and without positive blood cultures, none of the patients developed fever or other signs of infection in the follow-up, n = 1 patient received oral antibiotics for 5 days
Analysis used	Microbiology: 20ml sample, kept in commercially available aerobic/anaerobic blood culture bottles (BD Bactec 9000 system), blood cultures were incubated at 35˚C for 7days
Length of follow-up	7 days incubation
Location	Germany
Source of funding	Not stated
Comments	

1 **Table 95**

Bibliographic reference [from CG64]	**Kullman E, Borch K, Lindstrom E, et al. (1992) Bacteremia following diagnostic and therapeutic ERCP. Gastrointestinal Endoscopy 38: 444–49. Ref ID: 10028**
Study type	Before-and-after study
Aim	To investigate the level of bacteraemia following diagnostic and therapeutic ERCP.
Patient characteristics	Inclusion: median age 66 yrs (range 26–92 yrs), n = 104 female, n = 76 male Exclusion: those with signs of localised or general infection, antibiotic treatment with the preceding 7 days, treatment with corticosteroids or other immunosuppressive drugs, history or signs of endocarditis or valvular heart disease

Bibliographic reference [from CG64]	**Kullman E, Borch K, Lindstrom E, et al. (1992) Bacteremia following diagnostic and therapeutic ERCP. Gastrointestinal Endoscopy 38: 444–49. Ref ID: 10028**
Number of patients	Total = 180 patients (n = 194 examinations) Diagnostic ERCP n = 115 participants (n = 126 procedures) Therapeutic ERCP n = 65 participants (n = 68 procedures)
Procedures	Diagnostic and therapeutic ERCP Blood samples: before the examination, 5min after cannulation and at 5 and 15 min after the end of examination.
Outcomes and effect estimates	*Prevalence of bacteraemia:* Diagnostic ERCP: Baseline (before) = 1/126 (0.8%); during = 10/126 (7.9%); after 5 min =12/126 (9.5%); after 15 min = 14/126 (11.1%) Therapeutic ERCP: Baseline (before) = 0/68 (0%); during = 10/68 (14.7%); after 5 min =10/68 (14.7%); after 15 min = 13/68 (19.1) Overall: n = 19/126 (15%) of diagnostic procedures and n = 18/68 (27%) of therapeutic procedures were associated with bacteraemia during and/or within 15min after the endoscopy, NS between the groups There was NS difference in the frequency of bacteraemia between diagnostic ERCP and biliary manometry or between endoscopic sphincterotomy and endoprosthesis Of the n = 37 bacteraemic patients, n = 9 had polymicrobial bacteraemia with 16 detected groups of microorganisms. Different Streptococci, mainly α-haemolytic, were the most common, they were identified in n = 14(38%) of the bacteraemic patients either alone or with other species There was no correlation between the occurrence of bacteraemia and the age of participants or the duration of the endoscopic procedure During follow-up for 4 to 26mths of bacteraemic patients none developed clinically overt endocarditis There was no correlation of bacteraemia with subsequent fever, pancreatitis, or sepsis in patients with partial or complete obstruction of the pancreaticobiliary system due to stones, strictures or cancer
Analysis used	Microbiology: A 2-phase blood culture system, one aerobic and one anaerobic flask was inoculated with 4ml of blood and each incubated at

Bibliographic reference [from CG64]	**Kullman E, Borch K, Lindstrom E, et al. (1992) Bacteremia following diagnostic and therapeutic ERCP. Gastrointestinal Endoscopy 38: 444–49. Ref ID: 10028**
	37˚C, the flasks were inspected for bacterial growth twice daily for 2 days and then once daily for an additional 8days. When growth was observed or suspected a gram stain was done. Subcultures were performed on blood-agar, hematin-agar and anaerobic blood-agar plates, which were incubated at 37˚C in air, carbon dioxide and in an anaerobic box
Length of follow-up	4 to 6 months
Location	University Hospital, Sweden
Source of funding	Not stated
Comments	

1 **Table 96**

Bibliographic reference [from CG64]	**London MT, Chapman BA, Faoagali JL, Cook HB. Colonoscopy and bacteraemia: an experience in 50 patients. New Zealand Medical Journal 1986;99:269-71. Ref ID: 952**
Study type	Before-and-after study
Aim	To investigate the incidence of bacteraemia during colonoscopy.
Patient characteristics	Inclusion: patients undergoing colonoscopy, n = 24 males, n = 26 females, mean age 58.8yrs (range 22 to 80yrs) Exclusion: patients with evidence of infection or who had taken antibiotics in the previous 2 weeks Biopsies, often multiple were taken from n = 26 patients, n = 19 had neither a biopsy or a polypectomy n = 45 were prepared for colonoscopy by a whole gut lavage usually 8 litres of an isotonic solution, n = 5 were prepared with soap and water enemas
Number of patients	Total = 50 (204 blood samples)
Procedure	Colonoscopy Blood sample: before insertion (baseline); 5 min after insertion; 5 min after removal
Outcomes and effects estimates	Blood cultures Baseline = n = 204 blood cultures from n = 50 patients, n = 6 positive blood cultures from n = 5 patients (n = 2 patients had samples positive prior to colonoscopy not from later samples) In n = 2 patients the positive culture was considered to be directly related to the colonoscopy, the blood samples were collected at the limit of insertion of the colonoscope and were for Bacteroides fragilis and Bacillus sp. (these n = 2 patients were from the n = 7 group with carcinoma of the colon)

Bibliographic reference [from CG64]	**London MT, Chapman BA, Faoagali JL, Cook HB. Colonoscopy and bacteraemia: an experience in 50 patients. New Zealand Medical Journal 1986;99:269-71. Ref ID: 952**
	Positive blood cultures were in n = 4/45 patients who had whole gut lavage and in n = 1/5 who had an enema
Analysis used	Blood cultures Microbiology: 7-10ml was inoculated into 40ml BBL(vacutainer) supplemented broth, cultures were incubated at 30˚C for 3wks and examined daily, aerobic and anaerobic subcultures were made at 24hrs, 6days, 14days and 21days and the cultures identified
Length of follow-up	Not reported
Location	New Zealand
Source of funding	Not stated
Comments	

1

G.52 Review question 5

3 **Table 97**

Bibliographic reference	**Lucas,VS., Gafan, G., Dewhurst, S., Roberts, GJ. (2008). Prevalence, intensity and nature of bacteraemia after toothbrushing. Journal of Dentistry. 36: 481-487**
Study type	RCT* *randomisation performed using random number table
Aim	To estimate the prevalence, intensity and microbial identity of bacteraemia associated with toothbrushing
Patient characteristics	<u>Inclusion criteria</u> - Children and adolescents aged between 3 and 17 years, having dental treatment (extractions only) under general anaesthesia at the Eastman Dental Hospital <u>Exclusion criteria</u> - Weight less than 17.5kg - The use of antibiotics within the preceding month because of changes in the oral flora - Medical condition requiring antibiotic prophylaxis eg: cardiac anomalies - Systemic disease eg: insulin dependent diabetes - Known cases of HIV and hepatitis because changes in the oral flora

<table>
<tr><td>Bibliographic reference</td><td>Lucas,VS., Gafan, G., Dewhurst, S., Roberts, GJ. (2008). Prevalence, intensity and nature of bacteraemia after toothbrushing. Journal of Dentistry. 36: 481-487</td></tr>
<tr><td></td><td>- Poor veins

<u>Other characteristics</u>
- Mean age (SD): 7.9 years (3.3), range: 3.2 to 17.3 years
- Gender: 85 boys (60%), 56 girls (40%)</td></tr>
<tr><td>Number of patients</td><td>N=141 included from a total sample of 183 (exclusion reasons included failed venepuncture, refusal to participate, change in treatment plan or unfit for general anaesthesia)

Subjects randomised to the following toothbrushing groups:

1. Manual Oral B 30: n=32
2. Braun electric (rotary movement): n=35
3. Sonicare (oscillating movement): n=33
4. Dental handpiece and rubber cup: n=41</td></tr>
<tr><td>Outcomes</td><td>3. Bacteraemia levels/intensity/bacterial counts per uni volume at one or more timepoints following the everyday activity – reported in study as intensity of bacteraemia, recorded as the number of colony forming units of bacteria per millilitre of blood (cfu/ml)
4. Duration of bacteraemia following everyday activity – not reported in study
5. Number/incidence/odds of having positive blood samples before and after everyday activity – reported in study as the prevalence of bacteraemia in each group, recorded as the number of positive blood cultures and expressed as the percentage prevalence</td></tr>
<tr><td>Predictors/risk factors and effect estimates</td><td><u>Predictor of interest to this question</u>
- Toothbrushing (for 1 minute)- carried out as an isolated procedure before any extractions, thus removing the potential for confounding bacteraemia from other procedures

<u>Effect estimates</u>
1. Bacteraemia levels/intensity at one or more timepoints following the procedure – reported in study as intensity of bacteraemia, recorded as the number of colony forming units of bacteria per millilitre of blood (cfu/ml)
<table>
<tr><th colspan="10">Aerobic intensity of detectable bacteraemia (cfu/ml blood)</th></tr>
<tr><th colspan="5">Baseline</th><th colspan="5">30 seconds after toothbrushing</th></tr>
<tr><th></th><th>Mean</th><th>SD</th><th>Median</th><th>Range</th><th>Mean</th><th>SD</th><th>Median</th><th>Range</th><th>Significance, p</th></tr>
<tr><td>Oral B 30</td><td>0.05</td><td>0.21</td><td>0</td><td>0 to 1.17</td><td>0.39</td><td>1.34</td><td>0</td><td>0 to 0.67</td><td>>0.05</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Lucas,VS., Gafan, G., Dewhurst, S., Roberts, GJ. (2008). Prevalence, intensity and nature of bacteraemia after toothbrushing. Journal of Dentistry. 36: 481-487

(n=32)									
Braun electric (n=35)	0.05	0.11	0	0 to 0.50	0.28	1.15	0	0 to 6.83	>0.05
Sonicare electric (n=33)	0.02	0.06	0	0 to 0.17	0.51	2.35	0	0 to 13.3	**0.03**
Dental handpiece and rubber cap (n=41)	0.02	0.07	0	0 to 0.3	1.00	3.10	0	0 to 15.2	**0.001**

Anaerobic intensity of detectable bacteraemia (cfu/ml blood)									
	Baseline				30 seconds after toothbrushing				
	Mean	SD	Median	Range	Mean	SD	Median	Range	Significance, p
Oral B 30 (n=32)	0.01	0.04	0	0 to 0.17	0.46	1.8	0	0 to 8.83	>0.05
Braun electric (n=35)	0.02	0.07	0	0 to 0.33	0.11	0.43	0	0 to 2.50	>0.05
Sonicare electric (n=33)	0.04	0.10	0	0 to 0.50	0.79	3.68	0	0 to 20.83	>0.05
Dental handpiece and rubber cap (n=41)	0.008	0.04	0	0 to 0.17	0.94	2.87	0	0 to 13.83	**0.005**

2. **Duration of bacteraemia following everyday activity** – not reported in study

<table>
<tr><td>Bibliographic reference</td><td>Lucas,VS., Gafan, G., Dewhurst, S., Roberts, GJ. (2008). Prevalence, intensity and nature of bacteraemia after toothbrushing. Journal of Dentistry. 36: 481-487</td></tr>
<tr><td></td><td>3. Number/incidence/odds of having positive blood samples before and after everyday activity – reported in study as the prevalence of bacteraemia in each group, recorded as the number of positive blood cultures and expressed as the percentage prevalence
<table>
<tr><th>Toothbrush</th><th>Baseline</th><th>30 seconds after brushing for 1 minute</th><th>Significance</th></tr>
<tr><td>Oral B 30</td><td>7 (22%)</td><td>6 (19%)</td><td>ns</td></tr>
<tr><td>Braun electric</td><td>9 (26%)</td><td>12 (34%)</td><td>ns</td></tr>
<tr><td>Sonicare electric</td><td>9 (27%)</td><td>11 (33%)</td><td>ns</td></tr>
<tr><td>Dental handpiece and rubber cap</td><td>6 (15%)</td><td>15 (37%)</td><td>p=0.02</td></tr>
</table></td></tr>
<tr><td>Analysis used</td><td>1. All data were tested for normality using the Shapiro-Wilk test and found to be not normally distributed
2. Categorical data were analysed using the McNemar test
Continuous variables were analysed using the Wilcoxon Rank Sum Test</td></tr>
<tr><td>Length of follow-up</td><td>Measurements taken at baseline and 30 seconds after toothbrushing</td></tr>
<tr><td>Location</td><td>UK (London)</td></tr>
<tr><td>Source of funding</td><td>Not reported</td></tr>
<tr><td>Comments</td><td><u>Clinical procedure and microbiological assessment of bacteraemia</u>
- Following induction of general anaesthesia, either a laryngeal mask (n=138) or nasotracheal intubation (n=3) was used
- The first 0.5ml of blood withdrawn through the cannula was discarded to void any skin contaminants
- 6ml of blood was taken before toothbrushing (baseline) for each group of subjects.
- A second 6ml sample was taken 30 seconds after toothbrushing
- All blood samples processed in a laminar flow cabinet within 1 hour of collection. Blood and sodium polyanethol sulphonate (SPS) added to lysing solution.
- Sample divided into two equal volumes –each inoculated onto Brain Heart Infusion Agar, one plate incubated aerobically and the other anaerobically for 10 days.
- From day 3, each filter checked daily for bacterial growth using a stereo microscope.
- For each batch of blood samples, two separate blank filters were placed onto infusion agar.
- Bacteria characterised initially by gram staining. Bacterial colonies were subjected to Catalase and Oxidase testing and presumptive Staphylococcus spp. and Streptococcus spp. to a coagulase test.
- Bacterial colonies further identified using commercial carbohydrate fermentation and enzyme hydrolysis tests.</td></tr>
</table>

Bibliographic reference	Lucas,VS., Gafan, G., Dewhurst, S., Roberts, GJ. (2008). Prevalence, intensity and nature of bacteraemia after toothbrushing. Journal of Dentistry. 36: 481-487
	Microbial identity of organisms identified in study - Oral Streptococcus spp. comprised 2 and 15% at baseline and 30 seconds after toothbrushing respectively. - Coagulase negative Staphylococcus spp. comprised 12 and 24% at baseline and after toothbrushing respectively - Other bacteria included Lactobacillus spp, Actinomyces spp, Neisseria spp. and Micrococcus spp - No obligate anaerobes were detected Study limitations: assessed using checklist for prognostic studies from Hayden et al., 2006 - Study participation: period of recruitment not reported, sample size calculation not reported, highly selected population with pre-existing dental disease - Study attrition: no major limitations - Prognostic factor measurement: details of toothbrushing intervention not reported eg: whether it was performed by one or more investigators and whether standardised procedures were used or not. - Outcome measurement: no major limitations, outcomes well defined, raw data not reported for all outcomes therefore no further analyses possible in some cases. - Confounding measurement and account: no major limitations, toothbrushing carried out as an isolated procedure before any extractions, thus removing potential for confounding bacteraemia from other procedures, blood samples processed within one hour of collection. - Analysis: no major limitations, methods described.

1 **Table 98**

Bibliographic reference	Lockhart, PB., Brennan, MT., Sasser, HC., Fox, PC., Paster, BJ., Bahrani-Mougeot, FK. (2008). Bacteremia associated with toothbrushing and dental extraction. Circulation. 117: 3118-3125
Study type	Double blind randomised* controlled trial *randomly assigned using computer-generated list with a block size of 12 to 1 of 3 interventions
Aim	To compare the incidence, duration, nature and magnitude of endocarditis-related bacteremia from single-tooth extraction and toothbrushing and to determine the impact of amoxicillin prophylaxis on single tooth extraction
Patient characteristics	Inclusion criteria - Patients presenting to urgent care service with the need for extraction of at least 1 erupted tooth Exclusion criteria - Fewer than 10 teeth - Use of systemic antibiotics within the previous 2 weeks - Need for antibiotic prophylaxis based on current practice guidelines

Bibliographic reference	Lockhart, PB., Brennan, MT., Sasser, HC., Fox, PC., Paster, BJ., Bahrani-Mougeot, FK. (2008). Bacteremia associated with toothbrushing and dental extraction. Circulation. 117: 3118-3125
	- Active viral disease - Immunocompromised - Poorly controlled systemic disease - History of penicillin allergy - Temperature >100.5F - Facial cellulitis - Manipulation of the gingival tissues (eg: chewing, toothbrushing) within one hour before the study <u>Other characteristics</u> 1. Age in years, mean (SD) Brushing group: 39.7 (11.7) Extraction-amoxicillin group: 39.7 (10.5) Extraction-placebo group: 40.5 (10.9) 2. Male, n (%) Brushing group: 55 (56) Extraction-amoxicillin group: 61 (64) Extraction-placebo group: 51 (53) 3. Ethnicity, n (%) Brushing group: white – 27 (28), black – 68 (69), Hispanic – 2 (2), Other – 1 (1) Extraction-amoxicillin group: white – 18 (19), black – 73 (76), Hispanic – 3 (3), Other – 2(2) Extraction-placebo group: white – 23 (24), black- 73 (76), Hispanic – 1 (1), Other – 0 (0) 4. Diabetes, n (%) Brushing group: 5 (5) Extraction-amoxicillin group: 9 (9) Extraction-placebo group: 8 (8) 5. Surgery type, n (%) Brushing group: - Extraction-amoxicillin group: simple – 83 (87), complex – 9 (9), missing – 4 (4) Extraction-placebo group: simple – 70 (73), complex – 18 (19), missing – 8 (8)

<table>
<tr><td>Bibliographic reference</td><td>Lockhart, PB., Brennan, MT., Sasser, HC., Fox, PC., Paster, BJ., Bahrani-Mougeot, FK. (2008). Bacteremia associated with toothbrushing and dental extraction. Circulation. 117: 3118-3125</td></tr>
<tr><td></td><td></td></tr>
<tr><td>Number of patients</td><td>N=290
Subjects randomised to the following groups:
1. Toothbrushing n=98
2. Single tooth extraction with amoxicillin prophylaxis n=96
3. Single tooth extraction with an identical placebo (placebo not defined) n=96

Power calculation: assuming a significance level of 0.05, 80 subjects per study arm would yield power of 90% to detect a difference in cumulative incidences of at least 20% (prior work suggested that the incidence of bacteraemia from single tooth extraction would range between 70% and 100%. No consenus available on incidence after toothbrushing).</td></tr>
<tr><td>Outcomes</td><td>1. Bacteraemia levels/intensity/bacterial counts per unit volume at one or more timepoints following the everyday activity – reported in study as magnitude of bacteraemia
2. Duration of bacteraemia following everyday activity – reported in study as a) overall duration of bacteraemia b) duration of bacteraemia from endocarditis-related bacterial species
3. Number/incidence/odds of having positive blood samples before and after everyday activity – reported in study as a) overall incidence of bacteraemia at any of the 6 draws b) overall incidence of bacteraemia at the time of the procedures and c) incidence of bacteraemia from endocarditis related bacterial species</td></tr>
<tr><td>Predictors/risk factors and effect estimates</td><td><u>Predictor of interest to this question</u>
- Toothbrushing: brushing arm subjects brushed all surfaces of the teeth adjacent to the gingiva with a new toothbrush without toothpaste for 2 minutes, timed as 30 seconds for each of the maxillary and mandibular quadrants of teeth. Subjects randomised to the brushing group had their dental extraction accomplished at the end of study period, after the last blood straw or on a subsequent visit (hence, no potential for confounding of bacteremia from other procedures)

<u>Effect estimates</u>
1. Bacteraemia levels/intensity/bacterial counts per unit volume at one or more timepoints following the everyday activity/procedure – reported in study as magnitude of bacteraemia – all analysed samples were below the detection threshold of 10^4 CFU per millilitre of blood
2. Duration of bacteraemia following everyday activity/procedure – reported in study as a) overall duration of bacteraemia b) duration of bacteraemia from endocarditis-related bacterial species

<table>
<tr><th colspan="3">f) overall duration of bacteraemia</th></tr>
<tr><td></td><td>Number of subjects (%) bacteraemic at 40 minutes after activity/procedure</td><td>Number of subjects (%) bacteraemic at 60 minutes after activity/procedure</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Lockhart, PB., Brennan, MT., Sasser, HC., Fox, PC., Paster, BJ., Bahrani-Mougeot, FK. (2008). Bacteremia associated with toothbrushing and dental extraction. Circulation. 117: 3118-3125

Toothbrushing group	-	9 (9)
Extraction-amoxicillin group	2 (2)	-
Extraction-placebo group	-	2 (2)

g) duration of bacteraemia from endocarditis-related bacterial species	
	Number of subjects (%) bacteraemic at 60 minutes after activity/procedure
Toothbrushing group	2 (2)
Extraction-amoxicillin group	-
Extraction-placebo group	5 (5)

3. Number/incidence/odds of having positive blood samples before and after everyday activity – reported in study as a) overall incidence of bacteraemia at any of the 6 draws b) overall incidence of bacteraemia at the time of the procedures and c) incidence of bacteraemia from endocarditis related bacterial species

c) overall incidence of bacteraemia* at any of the 6 draws	
Toothbrushing group	32%
Extraction-amoxicillin group	56%
Extraction-placebo group	80%
x^2	p<0.0001

d) overall incidence of bacteraemia* at the time of the procedures	
Toothbrushing group	28%
Extraction-amoxicillin group	56%
Extraction-placebo group	79%
x^2	Not reported

*'All baseline blood cultures were negative with the exception of 3 instances, likely from skin contamination eg: Staphylococcus epidermis'

h) cumulative incidence of bacteraemia from endocarditis related bacterial species from all 6 blood draws**

Bibliographic reference	**Lockhart, PB., Brennan, MT., Sasser, HC., Fox, PC., Paster, BJ., Bahrani-Mougeot, FK. (2008). Bacteremia associated with toothbrushing and dental extraction. Circulation. 117: 3118-3125**

Toothbrushing group	23%
Extraction-amoxicillin group	33%
Extraction-placebo group	60%
X^2	p<0.0001

i) incidence of positive cultures from endocarditis related bacterial species in the first 5 minutes of activity/procedure***	
Toothbrushing group	19%
Extraction-amoxicillin group	33%
Extraction-placebo group	58%
X^2	p=not reported

j) incidence of positive cultures from endocarditis related bacterial species at 20 minutes***	
Toothbrushing group	1%
Extraction-amoxicillin group	1%
Extraction-placebo group	10%
X^2	p=0.001

**All baseline blood cultures were negative, with the exception of one patients (with 2 species) in the brushing group
***The pattern observed at 20 minutes persisted to 40 minutes (numbers not reported).

Analysis used	- For analysis of incidence, each patient was assessed at each blood draw and coded as positive for any bacterium that was common to the list of 275 bacterial species reported to cause IE. Comparison by study arm at each blood draw and a summary comparison by study arm that combined all draws were made with Chi square tests. - Duration of bacteraemia was defined as the number of blood draws at which any target organism was cultured. - Intercurrent negative findings were rare (n=2), were judged to be spurious and were considered positive for analysis. - Duration of specific intervals by study arm was compared with x^2 tests. - Statistical significance of 0.05 was used in all cases.
Length of follow-up	60 minutes after completion of brushing or extraction
Location	USA
Source of funding	Supported by National Institute of Dental and Craniofacial Research/National Institutes of Health grant

Bibliographic reference	**Lockhart, PB., Brennan, MT., Sasser, HC., Fox, PC., Paster, BJ., Bahrani-Mougeot, FK. (2008). Bacteremia associated with toothbrushing and dental extraction. Circulation. 117: 3118-3125**
Comments	Clinical procedure and microbiological assessment of bacteraemia a) Procedures - Baseline blood samples drawn (20ml) and 7 to 8ml inoculated directly into both aerobic and anaerobic BACTEC bottles for bacterial culturing - Extraction began one hour after ingestion of amoxicillin or placebo - Brushing arm subjects brushed all surfaces of the teeth adjacent to the gingiva with a new toothbrush without toothpaste for 2 minutes, timed as 30 seconds for each of the maxillary and mandibular quadrants of teeth. - Subsequent blood draws of 20ml were taken at 1.5 minutes and at 5 minutes after the initiation of surgery or brushing. - Additional blood samples (20ml) were drawn at 20, 40 and 60 minutes after the end of the procedure. 2mls of blood was drawn into a new syringe and discarded before each of the 6 blood draws and the catheter was flushed with 2ml of saline from a new syringe after each blood draw. b) Bacterial isolation and identification - Blood samples were cultured in BACTEC Plus Aerobic/F and LYTIC/10 Anaerobic/F. All false-positive bottles were further incubated for a total of 2 weeks. - Bottles with positive cultures were kept for 2 weeks and subcultured periodically to ensure recover of additional species. - The 16S ribosomal RNA sequencing method was used for bacterial identification. - Bacterial lysates were used as templates in PCR with 16S rRNA universal primers according to standard protocols. - Identification of strains was based on comparisons of the first 500 bases with Database Project and GenBank by BLAST. - For those strains that were potentially new species, full 1500-base pair sequences were obtained. - Investigators involved in bacterial culturing and identification were blinded as to subject randomisation. c) Quantification of bacteria in blood - Sensitive, real time quantitative PCR was used to quantify bacteria - Bacterial DNA was isolated from patient blood draws and from blood seeded with known quantities of several common oral pathogens. - For real time quantitative PCR, TaqMan technology and probes and universal 16S rRNA primers conserved among oral pathogens were used with the Smart Cycler system. Standard curves were established for the seeded pathogens and calculated the levels of bacteria in subject blood cultures. - The sensitivity of the method was 25 CFU per PCR, which corresponds to 10^3 to 10^4 CFU per millilitre of blood. Microbial identity of organisms identified in study a) overall nature of bacteraemia

Bibliographic reference	Lockhart, PB., Brennan, MT., Sasser, HC., Fox, PC., Paster, BJ., Bahrani-Mougeot, FK. (2008). Bacteremia associated with toothbrushing and dental extraction. Circulation. 117: 3118-3125
	98 different bacterial species, the most common which belonged to Streptococcus (49%), Prevotella (9%), Actinomyces (5%) and Fusobacterium (5%) b) nature of bacteraemia from endocarditis related bacterial species 10 (31%) of the 32 IE associated oral bacterial species were viridans streptococci. 13 (48%) of 27 positive cultures in the brushing group were viridans streptococci compared with 23 (49%) of 47 in the extraction-amoxicillin group and 106 (70%) of 151 in the extraction-placebo group. With the exception of one subject in the placebo group, polymicrobial blood cultures occurred within the first 5 minutes of the procedure – 2%, 6% and 29% in the brushing, extraction-amoxicillin and extraction-placebo group respectively. Study limitations: assessed using checklist for prognostic studies from Hayden et al., 2006 - Study participation: highly selected population with pre-existing dental disease - Study attrition: no major limitations - Prognostic factor measurement: no major limitations - Outcome measurement: although the incidence and duration of bacteraemia at various other time points are reported, this is in graphical form without accompanying numbers and therefore could not be extracted. For magnitude of bacteraemia, study seems to have pre-set a threshold for detection. - Confounding measurement and account: no major limitations, toothbrushing carried out as an isolated procedure before any extractions, thus removing potential for confounding bacteraemia from other procedures, unclear if blood samples processed immediately. - Analysis: no major limitations

1

2 **Table 99**

Bibliographic reference	Jones, DJ., Munro, CL., Grap, MJ., Kitten, T., Edmond, M. (2010). Oral care and bacteraemia risk in mechanically ventilated adults. Heart Lung. 39 (60): S57 –S65
Study type	Prospective pre- and post-test design (without a control group)
Aim	To determine 1) the incidence of transient bacteraemia related to toothbrushing in mechanically ventilated critically ill adults 2) the relationship of oral microbial cultures and dental plaque scores to the incidence of transient bacteraemia, clinical outcomes and indicators of infection and 3) the relationships among patient characteristics and clinical outcomes
Patient characteristics	Inclusion criteria - Subjects from the surgical trauma, medical respiratory and neuroscience intensive care units - Mechanical ventilation - Age greater than 18 years

Bibliographic reference	**Jones, DJ., Munro, CL., Grap, MJ., Kitten, T., Edmond, M. (2010). Oral care and bacteraemia risk in mechanically ventilated adults. Heart Lung. 39 (60): S57 –S65**
	- Intubated less than 24 hours - Invasive catheter in place less than 24 hours to decrease the likelihood of organisms already present in the line - No documented evidence of clinical bloodstream infection prior to enrolment - Having at least one tooth - Haemoglobin greater than 7g/dl Exclusion criteria - Edentulous patients were excluded because dental plaque assessments could not be assessed in patients with no teeth - Patients with haemoglobin level less than 7g/dl (to reduce risks of repeated blood sample collection) Other characteristics 1. Gender, % Male: 63, Female: 37 2. Age in years, mean (SD) 46 (17) 3. ICU, % Surgical trauma – 37 Medical respiratory – 33 Neuroscience – 30 4. Ethnicity, % Hispanic - 3, Non-Hispanic – 97%
Number of patients	A sample of 30 subjects were enrolled
Outcomes	1. **Bacteraemia levels/intensity/bacterial counts per unit volume at one or more timepoints following the everyday activity –** not reported in study 2. **Duration of bacteraemia following everyday activity** – not reported in study 3. **Number/incidence/odds of having positive blood samples before and after everyday activity –** reported in study as incidence of transient bacteremia by positive blood cultures before and after toothbrushing (1 minute and 30 minutes post intervention)
Predictors/risk factors and effect estimates	**Predictor of interest to this question** Toothbrushing – all subjects received a toothbrushing intervention twice daily. Performed using standardized protocol. Mouth divided into 4 quadrants, every tooth in each quadrant brushed for 5 strokes on lingual, buccal and biting surfaces using a soft pediatric toothbrush and toothpaste (Biotene toothpaste). Palate and tongue were also brushed. Each quadrant,

Bibliographic reference	Jones, DJ., Munro, CL., Grap, MJ., Kitten, T., Edmond, M. (2010). Oral care and bacteraemia risk in mechanically ventilated adults. Heart Lung. 39 (60): S57 –S65
	palate and tongue were rinsed with a total of 15ml mouthwash (Biotene) and a moisturising gel (Oral Balance) was applied to all soft surfaces of the oral cavity and lips. Toothbrushing was for 2 minutes twice a day over 48 hours performed by the principal investigator. **Effect estimate** None of the subjects had evidence of transient bacteremia before or after toothbrushing
Analysis used	n/a (no data found for outcome of interest in study)
Length of follow-up	48 hours or until extubation if extubated prior to 48 hours
Location	USA
Source of funding	Supported by National Institutes of NIH/NINR
Comments	Clinical procedure and microbiological assessment of bacteraemia - Bacteremia measured by quantitiative blood cultures with specific surveillance for the following bacteria: viridans Streptococci, S.aureus, P aeruginosa, Enterococcus spp, Klebsiella pneumoniae, and Candida spp. - Blood cultures obtained for all subjects immediately preceding the first intervention, 1 minute post intervention and 30 minutes post intervention at both the first intervention and the last scheduled toothbrushing intervention (48 hours after first intervention). - Blood samples plated on three plates and incubated for 7 days. Microbial identity of organisms identified in study None identified from blood cultures (all 30 subjects had one set of useable blood culture data, 80% were extubated prior to day 3 and so a second set of blood cultures not obtained. 6 subjects remained intubated for greater than 48 hours and so second set of blood cultures was obtained at the last intervention. Study limitations: assessed using checklist for prognostic studies from Hayden et al., 2006 - Study participation: study dates not reported, no comparison group so not possible to determine relative levels of bacteremia associated with different activities (and therefore which groups may need prophylaxis) as opposed to just toothbrushing, no sample size calculation - Study attrition: no major limitations - Prognostic factor measurement: no major limitations - Outcome measurement: no major limitations - Confounding measurement and account: subjects also given Biotene mouthwash which could contain active ingredients and therefore have reduced bacteremia levels. - Analysis: no major limitations

1 **Table 100**

Bibliographic reference	**Lucas V, Roberts GJ, Lucas V, Roberts GJ. Odontogenic bacteremia following tooth cleaning procedures in children 891. Pediatric dentistry 2000;22:96-100. *[included in CG64]***
Study type	RCT* (Not blinded, 1991 to 1994) *randomisation using random number tables
Aim	To investigate the prevalence and intensity of odontogenic bacteraemia from tooth cleaning procedures in children and adolescents
Patient characteristics	Inclusion criteria - Children referred for dental treatment (Guy's Dental Hospital or Great Ormond Street Hospital) under general anaesthetic (GA) Exclusion criteria - Antibiotics within the previous month - Haemorrhagic disorders - Known viral carriage Other characteristics n = 79 male, n = 76 female, aged 21mths to 16yrs, 11mths
Number of patients	N = 155 recruited and randomised to following groups: 1. Toothbrushing: n= 52 2. Professional cleaning with a rubber cup: n= 53 3. Scaling: n=50 4. Control group (no cleaning procedures): n= 50 subjects for reference from study by Roberts et al., 1998a
Outcomes	Study reports on prevalence of bacteraemia following activity, intensity of bacteraemia following activity and incidence of positive blood cultures (see effect estimates section for details)
Predictors/risk factors and effect estimates	**Predictor of interest to this question** Home care toothbrushing (no further details) **Effect size** **Positive blood cultures** There was NS difference in the number of positive blood samples in the groups studied [toothbrushing – 20/52 (39%), dental flossing (data from De Leo et al., 1974) – 6/7 (86%), dental polishing – 13/53 (25%), dental scaling – 20/50 (40%), dental extractions (data from Roberts et al., 1998b) – 17/44 (39%)]. Chi square= 3.623, p=0.305 (excluding dental flossing), Chi square= 3.623, p=0.305 (excluding dental flossing and extractions) **Intensity of bacteraemia** There was NS difference in the intensity of bacteraemia (colony forming units per millilitre of blood, mean (SD), range) in

Bibliographic reference	**Lucas V, Roberts GJ, Lucas V, Roberts GJ. Odontogenic bacteremia following tooth cleaning procedures in children 891. Pediatric dentistry 2000;22:96-100. *[included in CG64]***
	any of the 3 cleaning groups [toothbrushing – 32.2 (231), 0 to 1666, dental flossing – no data, dental polishing – 15.9 (83.5), 0 to 557, dental scaling – 2.2 (13.2), 0 to 93, dental extractions (from Roberts et al., 1998) – 0.23 (0.8), 0 to 4]
Analysis used	- Data tested for orality using the Shapiro-Wilk test and found not to be normally distributed - Comparisons between the procedure group were made using the Kruskall-Wallis test
Length of follow-up	Measurement up to 30 seconds after intervention
Location	London
Source of funding	Not reported
Comments	Microbiology A single 8ml blood sample was taken from each patient 30 seconds after the procedure. 3ml volume of blood was inoculated into each of the aerobic and anaerobic bottles, two commercial broth culture systems were used: the Bactec 460 radiometric system and the Bactec 760, bacteria were identified using standard laboratory methods and the oral streptococci were further identified using API Strep20. A further 1.5ml was inoculated into the Isolator system vial which estimates the intensity of bacteraemia by lysis centrifugation and gives cfu/ml of blood. Bacteria isolated There were similar to bacteria isolated from blood cultures following dental operative procedures, these included S. mitis, S. sanguis and coagulase negative staphylococci (the bacteria isolated from the baseline group included S. sanguis, coagulase negative staphylococci and Oerskovia species) (authors conclude that even the professional cleaning procedures with a rubber cap and scaling should be carried out with benefit of pre-procedure antibiotic prophylaxis) Study limitations: assessed using checklist for prognostic studies by Hayden et al., 2006 - Study participation: sample size calculation not reported, highly selected population with pre-existing dental disease - Study attrition: no major limitations - Prognostic factor measurement: home based toothbrushing, unclear if standardised procedures were advised or not and for how long intervention was carried out. - Outcome measurement: no major limitations - Confounding measurement and account: no major limitations - Analysis: no major limitations

1 **Table 101**

Bibliographic reference	**Bhanji S, Williams B, Sheller B, et al. (2002) Transient bacteremia induced by toothbrushing: a comparison of the Sonicare toothbrush with a conventional toothbrush. Pediatric Dentistry 24: 295–99. *[included in CG64]***

Bibliographic reference	**Bhanji S, Williams B, Sheller B, et al. (2002) Transient bacteremia induced by toothbrushing: a comparison of the Sonicare toothbrush with a conventional toothbrush. Pediatric Dentistry 24: 295–99.** ***[included in CG64]***
Study type	RCT* (Not blinded) *Randomisation method not reported
Aim	To compare the incidence of bacteraemia resulting from the use of the Sonicare brush and manual brushing
Patient characteristics	Inclusion criteria - children receiving dental care under general anaesthesia at Children's Hospital and Regional Medical Centre - between the ages of 2 and 6 yrs - had no medical conditions requiring antibiotic prophylaxis for dental treatment - had not received antibiotic therapy within the past 30 days - had no sinus tracts associated with dental abscesses - had no conditions altering alveolar ridge or gingival anatomy Exclusion criteria - positive blood cultures before toothbrushing Other characteristics Not reported
Number of patients	N = 50 children Subjects randomised to the following groups: 1. Sonicare electric toothbrushing: n= 25 2. Manual toothbrushing: n=25
Outcomes	The following outcome was reported in the study: positive blood cultures after brushing (see effect estimates section for details)
Predictors/risk factors and effect estimates	**Predictor of interest to this question** Toothbrushing: teeth brushed for a timed one-minute interval with the Sonicare electric toothbrush (high frequency brushing, 31,000 brush strokes per minute) or manually. **Effect estimates** Incidence of positive blood cultures after* brushing, n (%, 95%CI) Manual group (n=24): 11/24 (46, 26 to 66) Sonicare group (n=23): 18/23 (78, 62 to 95) p=0.022

Bibliographic reference	**Bhanji S, Williams B, Sheller B, et al. (2002) Transient bacteremia induced by toothbrushing: a comparison of the Sonicare toothbrush with a conventional toothbrush. Pediatric Dentistry 24: 295–99.** ***[included in CG64]***
	*3 patients had positive blood cultures before toothbrushing and were excluded
Analysis used	- Proportion of subjects with positive cultures after toothbrushing in the two groups was compared using Chi-Square test and logistic regression
Length of follow-up	Measurement 30 seconds after brushing
Location	USA
Source of funding	Washington Dental Service Foundation, Phillips Oral Healthcare Corporation
Comments	Study limitations: assessed using checklist for prognostic studies by Hayden et al., 2006 - Study participation: study dates not reported, baseline characteristics (eg: gender, mean age etc) not reported, highly selected population with pre-existing dental disease - Study attrition: no major limitations - Prognostic factor measurement: no major limitations - Outcome measurement: no major limitations - Confounding measurement and account: no major limitations - Analysis: no major limitations Microbiology methods - 30 seconds after toothbrushing, 1ml of blood was drawn and discarded. A second samples was collected and distributed to culture vials. - 10 ml drawn per sample, divided into 3ml into an aerobic vial and 7 ml into an anaerobic vial, vials were incubated for 5 days using BacTec9240, positive vials were gram stained, isolated on agar media and analysed Microbial identity of positive cultures - Gram stain results of positive cultures were mainly gram positive cocci in chains (n=23). - Gram negative cocci: n=5 - Gram positive rods: n=3 - Gram negative rods: n=1

1 **Table 102**

Bibliographic reference	**Roberts GJ, Holzel HS, Sury MR, Simmons NA, Gardner P, Longhurst P. Dental bacteremia in children. SO: Pediatric cardiology 1997;18:24-7.** ***[included in CG64]***
Study type	RCT* (1991 to 1993) *randomisation was using random number tables, there were three exceptions, extractions which could only be performed if clinically needed, mucoperiosteal flap because of its relative infrequency was studied each time it was needed for treatment

Bibliographic reference	**Roberts GJ, Holzel HS, Sury MR, Simmons NA, Gardner P, Longhurst P. Dental bacteremia in children. SO: Pediatric cardiology 1997;18:24-7. *[included in CG64]***
	of the patient, the third was the cardiac group all of whom had antibiotic prophylaxis and therefore formed a separate group of patients
Aim	To investigate the frequency of odontogenic bacteremia following common dental procedures in children
Patient characteristics	Inclusion - children referred to Guy's Dental Hospital or GOSH for dental treatment under general anaesthetic, Exclusion - there were no exclusion criteria Other characteristics - n = 383 male, n = 352 female, mean age: 9yrs 3mths
Number of patients	n = 735 Group A – nonmanipulation group; baseline and dental examination Group B – cleaning procedures; toothbrushing, polishing and scaling Group C – minimal manipulation group; intraligamental injection and nasotracheal tube Group D – conservative dentistry procedures; rubber dam placement, slow drill, fast drill, and matrix band placement Group E – oral surgery group; single extractions, multiple extractions, and mucoperisoteal flaps Group F – groups having antibiotic prophylaxis; cardiac patients (Number for each of the above groups not reported however results for each of the above interventions has been reported separately – see effect estimates section)
Outcomes	Study reports on percentage of positive blood culture after procedure (see effect estimates section)
Predictors/risk factors and effect estimates	**Predictor of interest to this question** Toothbrushing: the dentist brushed the teeth with a new toothbrush for one minute with normal vigor. Blood samples taken 30 seconds after. **Effect size** **Positive blood cultures, n/N (%):** - baseline n = 5/53 (9.4%) - dental examination n = 9/53 (17.0%) - toothbrushing n = 20/52 (38.5%) - polishing teeth n = 13/53 (24.5%) - scaling teeth n = 20/50 (40.0%)

Bibliographic reference	Roberts GJ, Holzel HS, Sury MR, Simmons NA, Gardner P, Longhurst P. Dental bacteremia in children. SO: Pediatric cardiology 1997;18:24-7. *[included in CG64]*
	- intraligamental injection n = 28/29 (96.6%) - nasotracheal tube n = 3/31 (9.7%) - rubber dam placement n = 15/51 (29.4%) - slow drill n = 6/47 (12.8%) - fast drill n = 2/47 (4.3%) - matrix band placement n = 18/56 (32.1%) - single extraction n = 17/44 (38.7%) - multiple extractions n = 30/59 (50.9%) - mucoperiosteal flap n = 20/51 (39.2%) - cardiac patients n = 6/59 (10.2%) **Comparison of proportions compared to baseline (95% CI):** - dental examination -5.3 to 20.49% - toothbrushing 12.8 to 45.4% - polishing teeth 0.7 to 29.4% - scaling teeth 14.0 to 47.2% - intraligamental injection 76.9 to 97.3% - nasotracheal tube -6.5 to 13.2% - rubber dam placement 4.8 to 35.1% - slow drill -8.9 to 15.6% - fast drill -5.2 to 4.8% - matrix band placement 7.4 to 38.0% - single extraction 12.5 to 45.9% - multiple extractions 24.2 to 58.6% - mucoperiosteal flap 13.4 to 46.2% NS; dental examination, nasotracheal tube, slow drill, fast drill,
Analysis used	Results are expressed as the percentage of samples that yielded bacteria. Statistical calculations were made using Stata.
Length of follow-up	Measurement 30 seconds after procedure
Location	UK
Source of funding	Not stated
Comments	Study limitations: assessed using checklist list for prognostic studies from Hayden et al., 2006

Bibliographic reference	Roberts GJ, Holzel HS, Sury MR, Simmons NA, Gardner P, Longhurst P. Dental bacteremia in children. SO: Pediatric cardiology 1997;18:24-7. *[included in CG64]*
	- Study participation: highly selected population with pre-existing dental disease - Study attrition: no major limitations - Prognostic factor measurement: no major limitations - Outcome measurement: no major limitations - Confounding measurement and account: no major limitations - Analysis: no major limitations Microbiology methods Blood samples: one sample taken 30sec after each procedure Two commercial blood culture systems were used; the Bactec radiometric system and the Bactec 760, a 3ml volume of blood was inoculated into each of the aerobic and anaerobic bottles. Bacteria were speciated using standard methods, streptococci were speciated using API Strep 20 Microbial identity of organisms identified A total of 365 organisms were isolated (across all procedures), 212 (58%) were viridans streptococci

G.6 Review question 6a

Table 103

Bibliographic reference	Horstkotte D, Rosin H, Friedrichs W, Loogen F (1987) Contribution for choosing the optimal prophylaxis of bacterial endocarditis. Eur Heart J. 8: 379–81.
Study type	Retrospective cohort study
Aim	To compare the benefit of antibiotic prophylaxis with the results of a patient group in which retrospective questioning showed that invasive procedures had been performed without any prophylaxis
Patient characteristics	Both patient groups showed a nearly similar distribution in the site of implantation and the type of prosthesis including a similar relationship between mechanical (84%) and biological (16%) valves Exclusion: other procedures that could have caused bacteraemia of febrile conditions during a 6-month period before the procedure in question and before the onset of symptoms of endocarditis
Number of Patients	n = 533
Intervention	Group A, 229 patients with prosthetic heart valves in whom 287 diagnostic and therapeutic procedures were performed using

Bibliographic reference	Horstkotte D, Rosin H, Friedrichs W, Loogen F (1987) Contribution for choosing the optimal prophylaxis of bacterial endocarditis. Eur Heart J. 8: 379–81.
	a prophylactic antibiotic regime as follows; For patients with prosthetic heart valves without penicillin allergy - expected bacteraemia caused by cocci (dental procedures, diagnostic and therapeutic procedures involving oropharynx and respiratory tract): 2 mega units penicillin G i.v. + 1g streptomycin i.m* 30 to 60 mins before procedure (*no i.m injection in patients receiving anticoagulant therapy) and 1 mega unit penicillin V p.o. after 6 and 12 hours. - expected bacteraemia caused by enterobacteria (abdominal surgery, gastrointestinal interventions, diagnostic and therapeutic interventions involving the urogenital tract): 1g ampicillin i.v + 80mg gentamicin i.v. 30 to 60 mins before procedure and repeated injection after 6 and 8 hours. For patients with prosthetic heart valves with penicillin allergy - expected bacteraemia caused by cocci (dental procedures, diagnostic and therapeutic procedures involving oropharynx and respiratory tract): 1.0 to 1.5g erythromycin p.o 60 to 90 mins before procedure and 0.5g erythromycin p.o after 6 and 12 hours - expected bacteraemia caused by enterobacteria (abdominal surgery, gastrointestinal interventions, diagnostic and therapeutic interventions involving the urogenital tract): ca 1.0g cephalosporin i.m* + 80mg gentamicin i.v. 60 mins before (no i.m injection in patients receiving anticoagulant therapy) and repeated injection after 8 hours.
Comparison	Group B, 304 (out of n = 1898 patients questioned) subjects with prosthetic heart valves in whom 390 procedures were performed who gave reliable information that they had undergone one of the procedures regarded as requiring endocarditis prophylaxis without having received any antibiotic regimen
Length of follow up	Not reported
Location	Germany
Outcomes measures and effect size	Incidence of prosthetic valve endocarditis* - In group A no PVE was observed (0/287, 0%). - In group B, 6 cases of PVE (6/390, 1.5%) occurred within 14 days after the intervention which corresponds to an incidence of 1.5 cases per 100 procedures. - The highest incidence of PVE (n = 2/39 procedures, 5.1%) occurred after urological procedures, followed by oropharyngeal surgery (2.6%) and gynaecological (2.2%). Streptococci and enterococci were identified as causative organisms for PVE after oral, urological or gynaecological procedures. - 2 cases of PVE occurred in 117 dental procedures, both of which occurred after tooth extraction. - A further case of enterococcal PVE occurred after spontaneous passage of a renal calculus without having undergone any invasive intervention. *Two more patients in group B developed prosthetic valve endocarditis 8 and 13 weeks respectively after the initial intervention however PVE was considered related to the diagnostic or therapeutic procedure only if symptoms of endocarditis occurred within 2 weeks.
Source of funding	Not reported
Comments	**Study limitations**

Bibliographic reference	**Horstkotte D, Rosin H, Friedrichs W, Loogen F (1987) Contribution for choosing the optimal prophylaxis of bacterial endocarditis. Eur Heart J. 8: 379–81.**
	- Retrospective nature; reliant on patient's memory for data regarding interventional procedures undergone and whether prophylaxis was received or not – no indication that data provided by subject was verified in any way. - Unclear how similar the interventional procedures the 2 groups underwent were; numbers not reported - Unclear whether confounding factors were taken into account - Baseline characteristics: age, gender not reported - Power calculation not reported

1 **Table 104**

Bibliographic reference	**Lacassin F, Hoen B, Leport C, Selton-Suty C, Delahaye F, Goulet V et al. Procedures associated with infective endocarditis in adults. A case control study. European heart journal 1995;16:1968-74.**
Study type	Case-control
Aim	To assess the relative risk of infective endocarditis associated with various procedures (medical, surgical and dental) and the protective efficacy of antibiotic prophylaxis by a case-control study
Patient characteristics	**Inclusion** - cases: definite, probable or possible cases of IE identified from a prospective epidemiological survey conducted in all private and public medical facilities of three regions in France. Definite and probable IE defined according to revised Von Reyn's criteria with modifications to include echocardiographic and macroscopic findings for definite and probable cases. Definite endocarditis was defined on macroscopic or microbiological findings at operation or necropsy. Probable endocarditis was defined as 1) persistently positive blood cultures (at least two cultures obtained with 2 of 2 positive, 3 of 3 positive or at least 70% of cultures positive if 4 or more cultures obtained) with underlying heart disease plus echocardiographic vegetation or with vascular phenomena plus echocardiographic vegetation. Possible IE defined according to non-revised Von Reyn's criteria. Controls: those without IE who satisfied the same exclusion criteria as the cases. Controls were recruited randomly from cardiology or medicinal wards either during a consultation for echocardiography or during hospitalisation in the same period of observations as cases. **Exclusion:** cases: patients younger than 15yrs, valve replacement within the previous year, prematurely dead, intravenous drug users, those with Coxiella burnetti IE (unlikely to be related to any procedure) **Characteristics:** Cases and controls were distributed into 3 groups of underlying cardiac conditions: native valve disease, prosthetic valve or no known cardiac disease. Each case was matched to one control as regards sex, age (±5yrs) and group of underlying cardiac conditions. The proportion of those with diabetes mellitus, or who consumed alcohol and tobacco did not differ between the 2 groups. Cases had significantly more often an infectious episode or a skin wound than controls (39% and 19%

Bibliographic reference	Lacassin F, Hoen B, Leport C, Selton-Suty C, Delahaye F, Goulet V et al. Procedures associated with infective endocarditis in adults. A case control study. European heart journal 1995;16:1968-74.
	vs. 15% and 5% respectively) Age in years, mean (SD) Cases: 58 (15) Controls: 58 (15) Male/female, n Cases: 113/58 Controls: 113/58 Native valve disease, n (%) Cases: 66 (38.5) Controls: 66 (38.5) Prosthetic valve, n (%) Cases: 41 (24) Controls: 41 (24) No known cardiac disease, n (%) Cases: 64 (37.5) Controls: 64 (37.5) Duration of previous cardiac disease in months, mean (SD) Cases: 12.5 (13) Controls: 13 (15)
Number of Patients	n = 171 pairs
Intervention	Cases of definite, probable or possible IE that were requested to indicate all procedures (medical, surgical or dental) they had undergone within the 3 months prior to their diagnosis of IE. In the case of medical consultation or procedure, the information was checked by the cited practitioner. The use of antibiotics* was documented for the type, dosage, duration and administration schedule. Antibiotics* *regimen not described. To check whether the antibiotic regimen was appropriate for prophylaxis of IE, two independent investigators reviewed the use of antibiotics in each case and each control and compared it to the recommendations of the

Bibliographic reference	**Lacassin F, Hoen B, Leport C, Selton-Suty C, Delahaye F, Goulet V et al. Procedures associated with infective endocarditis in adults. A case control study. European heart journal 1995;16:1968-74.**
	European Society of Cardiology that at the time of this study, was used in France. Cases were interviewed as soon as possible after the diagnosis of IE.
Comparison	Controls without IE who were interviewed under the same conditions as cases using the same questionnaire form.
Length of follow up	1st November 1990 to 31st October 1991
Location	France
Outcomes measures and effect size	<u>Protective efficacy of antibiotic prophylaxis in subjects with underlying valvular disease (prosthetic or native) who had undergone a dental procedure</u> Among those with known heart disease who had a dental procedure (n = 48), 6/26 (23%) of the cases and 6/22 (27%) of the controls had received appropriate antibiotics. Therefore: - Number of patients with antibiotics who had IE = 6 - Number of patients with antibiotics who had no IE = 6 - Number of patients without antibiotics who had IE = 20 - Number of patients without antibiotics who had no IE = 16 Relative risk of developing endocarditis in those given prophylaxis compared to those without prophylaxis (95%CI): [6/12]/[20/36] = 0.9 (0.48 to 1.7)* *Calculated by reviewer
Source of funding	Several grants from medical societies in France and from the following companies: Baxter, Dideco-Shiley, Eli-Lily, Medtronic, St Jude Medical Companies
Comments	**Causative organism** The only procedure associated with a risk for IE due to viridans streptococci was scaling (n = 9/50 in the cases; n = 2/50 in the controls, OR=5.25, p=0.025) The only procedure associated with the subsequent occurrence of IE was surgery for staphylococcal IE (n = 4/27 in the cases; n = 0/27 in the controls, p=0.03) In multivariate analysis, scaling was associated with a significant risk for IE due to viridans streptococci, independently of an infectious episode. Conversely, only infectious episodes contributed to the risk of staphylococcal infective endocarditis, the risk after skin wound and surgery being non-significant in this analysis **Study limitations** - Retrospective nature of study; reliant on subjects memory for interventional procedures undergone and antibiotic use - Of the 171 cases, only 34% had definite infective endocarditis; 48% probable IE and 18% possible IE - In the case of medical consultation or procedure, information cited was checked by the cited practitioner; unclear whether what proportion of subjects this was possible for.

Bibliographic reference	**Lacassin F, Hoen B, Leport C, Selton-Suty C, Delahaye F, Goulet V et al. Procedures associated with infective endocarditis in adults. A case control study. European heart journal 1995;16:1968-74.**
	- Power calculation not reported

1 **Table 105**

Bibliographic reference	**van der Meer JT, van Wijk W, Thompson J, Vandenbroucke JP, Valkenburg HA, Michel MF. Efficacy of antibiotic prophylaxis for prevention of native-valve endocarditis. Lancet 1992;339:135-9.**
Study type	Case control
Aim	To assess the protective effect of antibiotic prophylaxis in subjects with native valve and cardiovascular anomalies.
Patient characteristics	Cases included: those with known cardiac disease (native valve and cardiovascular anomalies) in whom endocarditis developed within 180days of a medical or dental procedure for which prophylaxis was indicated. The diagnostic criteria for endocarditis described by Von Reyn et al was used. Cases excluded: those with prosthetic heart valves, those where a casual relation between the procedure and endocarditis was ruled out because it was unlikely that the agent isolated from the blood originated from the area of the procedure Controls included: with a cardiac lesion and increased risk of endocarditis, if they were in the same 5-yr age category as a case and had undergone a medical or dental procedure with an indication for prophylaxis within 180days of the interview Cases and potential controls were NS different in the number of procedures they had undergone in the previous 180 days, though there were more men among the cases (p=0.05). <u>Median age in years, range</u> Cases: 41 (5 to 78) Controls: 40 (5 to 80) <u>Gender, number male/female</u> Cases: 33/15 Controls: 109/91
Number of Patients	n = 48 cases, 200 controls Sample size and calculations of power were based on the assumption that a clinically important reduction in risk due to prophylaxis would have to be at least 75% and that 40% of the population at risk for endocarditis would be given prophylaxis. Based on significance level of 0.05, 31 cases and 4 controls per case would be needed.
Intervention	Cases with known cardiac disease in whom endocarditis developed within 180 days of a medical or dental procedure for which prophylaxis was indicated.

Bibliographic reference	**van der Meer JT, van Wijk W, Thompson J, Vandenbroucke JP, Valkenburg HA, Michel MF. Efficacy of antibiotic prophylaxis for prevention of native-valve endocarditis. Lancet 1992;339:135-9.**
	Subjects were interviewed using a structured questionnaire about recent medical or dental procedures and the use of prophylaxis. Data about previous diagnoses of heart disease, physical examination and lab results were obtained
Comparison	Controls selected from outpatients of the cardiology department of the university hospital and 4 regional hospitals, with same cardiac status in whom endocarditis did not develop within 180 days of a similar procedure.
Length of follow up	180 days
Location	Netherlands
Outcomes measures and effect size	Cases Total number of procedures was n = 48; 44 dental and 4 other, prophylaxis was definitely indicated in 28 of the 48 procedures. For the other 20, the indication for prophylaxis was not certain, all involved the removal of tartar. Antibiotics were given in n = 8/48 (17%) cases Prophylaxis was given more often to those who had previous IE than those who had not (n = 3/9 vs. n = 5/39) Controls n = 181/200 procedures were dental, prophylaxis was indicated in n = 96, for n = 104 the indication was possible because dental scaling had been done and it was unclear whether subgingival calculus had been removed. n = 26/200 (13%) of controls with a definite indication had received prophylaxis before a procedure, including 1/104 (1%) of those undergoing a procedure with a possible indication. First time epispdes OR (90%CI) for for first time episodes for procedures within 180 days of onset of symptoms: 1.04 (0.36 to 2.99)
Source of funding	Netherlands Heart foundation
Comments	**Study limitations** - Retrospective nature; data collected via structured questionnaire which although checked with medical and dental specialists, was highly reliant on patient's memory and reliability of medical records - Cases who were very ill or who died were included in the analysis via the use of proxy responders, however this did not occur for the 53/889 controls who died - Cases and controls did not undergo entirely the 'same' procedure however % undergoing dental procedures in both groups was comparable (92% and 91% cases and controls)

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G.7 Review question 7a

Table 106

Bibliographic reference	**Maharaj, B., Coovadia, Y., Vayej, AC. (2012). A comparative study of amoxicillin, clindamycin and chlorhexidine in the prevention of post-extraction bacteraemia. Cardiovascular journal of Africa. 23 (9): 491-494**
Study type	Randomised controlled trial
Aim	To assess and compare the effectiveness of amoxicillin, clindamycin, and the oral antiseptic chlorhexidine in eliminating post-extraction bacteraemia in black patients.
Patient characteristics	**Inclusion criteria** - Adult black patients attending the dental clinic - Healthy - No history of cardiovascular disease - Had not received antibiotics in the previous 2 weeks - Not allergic to penicillin **Exclusion criteria** - Any patient found to have a dental abscess or who required the extraction of more than one tooth **Other characteristics** Males, n/N (%): amoxicillin – 14/40 (35%), clindamycin – 16/40 (40%), control – 12/40 (30%) Females, n/N (%): amoxicillin – 26/40 (65%), clindamycin – 24/40 (60%), control – 28/40 (70%) Age in years, mean (range): amoxicillin – 29.9 (18 to 56), clindamycin – 28.1 (18 to 66), control – 32.1 (18 to 60)
Number of Patients	160 randomised to 4 groups (no therapy, chlorhexidine, amoxicillin or clindamycin) of 40 subjects each.
Intervention	Subjects were given 3g amoxicillin or 600mg clindamycin orally. Treatment was given one hour prior to dental extraction*. *dental extraction: only one tooth was extracted per patient. The same dental surgeon performed the procedure using dental forceps. No surgical procedures were used in any patient.
Comparison	No therapy prior to dental extraction
Length of follow up	Not reported, post-extraction bacteraemia assessed based on blood sample drawn 3 minutes after extraction.
Location	South Africa
Outcomes measures and effect size	**1.Bacteraemia levels/intensity:** not reported **2. Duration of bacteraemia:** not reported **3. Incidence of positive blood culture after* dental extraction, n (%)**

Bibliographic reference	**Maharaj, B., Coovadia, Y., Vayej, AC. (2012). A comparative study of amoxicillin, clindamycin and chlorhexidine in the prevention of post-extraction bacteraemia. Cardiovascular journal of Africa. 23 (9): 491-494**
	Amoxicillin group: 3 (7.5) Clindamycin group: 8 (20) Control group: 14 (35) *before data not reported, difference between amoxicillin and control group was statistically significant, p=0.003 (Adverse events not reported)
Source of funding	Not reported
Comments	**Statistical analysis** - Results in each group were arranged in a contingency table an analysed using Fisher's exact test - To analyse difference between control vs antibiotic groups and between antiseptic vs antibiotic group, the Chi Square test was used, employing Yates correction for continuity - Power calculation not reported **Assessment of bacteraemia** - The skin at the site of the venepuncture was prepared using 0.5% chlorhexidine in 70% alcohol - 8-10ml of blood was drawn 3 minutes after the extraction in each patient - 3 to 5ml blood was injected into BACTEC blood culture vials - Blood culture bottles transported to Microbiology Department within 2 hours of collection - The blood culture vials were tested on days 1, 3, 5 and 7 and positive vials were sub-cultured and Gram stained smears were prepared - The aerobic vials were sub-cultured onto chocolate, blood and MacConkey agar plates which were inoculated for 48 hours in air plus 10% carbon dioxide. - The anaerobic vials were sub-cultured onto 10% blood agar plates with and without amikacin and incubated for 48 to 72 hours in anaerobic gas pak. - The organisms isolated were identified using conventional laboratory methods and the identity of streptococcal isolates was confirmed using the API Strep 20 system. **Microbial identity** A range of microbes were identified including Streptococcus mitis, Streptococcus sanguis, Streptococcus anginosus, Viridans Streptococci, Streptococcus pneumonia, Staphylococcus epidermis, Enterococcus faecalis, Neisseria species, Corynebacterium species, Gram negative bacilli, Moraxella species, Peptostreptococcus species, Prevotella melaninogenica, Eikenella corrodens, Gemella haemolysins and mixed growth. **Study limitations: assessed using GRADE risk of bias checklist** - Allocation concealment not described

Bibliographic reference	**Maharaj, B., Coovadia, Y., Vayej, AC. (2012). A comparative study of amoxicillin, clindamycin and chlorhexidine in the prevention of post-extraction bacteraemia. Cardiovascular journal of Africa. 23 (9): 491-494**
	- Blinding not described - Number of positive blood cultures before prophylaxis not reported – unclear if subjects were tested for bacteraemia - Power calculation not reported

1 **Table 107**

Bibliographic reference	**Duvall, NB., Fisher, TD., Hensley, D. (2013). The comparative efficacy of 0.12% chlorhexidine and amoxicillin to reduce the incidence and magnitude of bacteraemia during third molar extractions. Oral surgery, oral medicine and oral pathology. 115 (6): 752-763**
Study type	RCT
Aim	To compare the incidence and magnitude of bacteraemia of a 0.12% chlorhexidine pre-procedure rinse to the AHA and the ADA/AAOS recommended 2g amoxicillin antibiotic prophylaxis during third molar extractions.
Patient characteristics	**Inclusion criteria** - Subjects presenting to the surgical centre, oral surgery clinic for third molar extractions under conscious sedation from June 2011 to December 2011 -ASA I or II: healthy, no systemic disease - Diagnosed/planned extraction #1, 16, 17, 32 under conscious sedation - #17 and 32 required a mucogingival flap for extraction - 18 years of age or older - Previously received penicillin and/or amoxicillin without a hypersensitivity or allergic reaction **Exclusion criteria** - ASA III or IV: poorly controlled systemic disease - Known penicillin, amoxicillin or cephalosporin drug allergy - Pregnant women - Current immunosuppressed status - Active viral disease - Cardiac anomalies or another condition/situation requiring pre- or intra-operative use of antibiotics - Antibiotic use within the previous two months - Steroid therapy within the previous two months - Chlorhexidine use or other oral antimicrobial rinses within the previous 2 months - The routine use of an oral antiseptic at home - Gingival tissue manipulation within 2 hours of the procedure

<table>
<tr><td>Bibliographic reference</td><td>Duvall, NB., Fisher, TD., Hensley, D. (2013). The comparative efficacy of 0.12% chlorhexidine and amoxicillin to reduce the incidence and magnitude of bacteraemia during third molar extractions. Oral surgery, oral medicine and oral pathology. 115 (6): 752-763</td></tr>
<tr><td></td><td>Other characteristics
Age in years, mean (range)
21.8 (18 to 29)
No significant difference among treatment arms, p=0.473

Gender, n
Male – 23
Female – 7
No significant difference among treatment arms, p=0.475

Surgical procedure length in minutes, mean (range)
42 (11 to 78)
No significant difference among treatment arms, p=0.632</td></tr>
<tr><td>Number of Patients</td><td>N=30
10 subjects per placebo, chlorhexidine and amoxicillin groups</td></tr>
<tr><td>Intervention</td><td>2g amoxicillin capsule and a placebo rinse.

The amoxicillin capsule (packaged and obtained from the 59th Pharmacy Squadron) was administered with a small amount of water 1 hour prior to procedure.
The placebo rinse was administered immediately prior to conscious sedation medication administration. The subjects rinsed with 15ml of the placebo rinse for one minute and expectorated.</td></tr>
<tr><td>Comparison</td><td>Placebo rinse and a placebo capsule.
The placebo rinse (1000ml sterile water for irrigation, [USP, Baxter Healthcare], where blue dye and mint extract was added until a similar appearance, taste and smell was obtained compared to the 0.12% chlorhexidine rinse). This was also administered immediately prior to conscious sedation medication administration. The subjects rinsed with 15ml of the placebo rinse for one minute and expectorated.</td></tr>
<tr><td>Length of follow up</td><td>Not reported</td></tr>
<tr><td>Location</td><td>USA</td></tr>
<tr><td>Outcomes measures and effect size</td><td>1) Bacteraemia levels/intensity

<table>
<tr><th colspan="3">Total mean magnitude of bacteraemia</th></tr>
<tr><td></td><td>Total bacteraemia in cfu/ml, mean (SD)</td><td>Total bacteraemia range</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Duvall, NB., Fisher, TD., Hensley, D. (2013). The comparative efficacy of 0.12% chlorhexidine and amoxicillin to reduce the incidence and magnitude of bacteraemia during third molar extractions. Oral surgery, oral medicine and oral pathology. 115 (6): 752-763**

Placebo	3.61 (7.09)	0.0 to 18.20
Amoxicillin	0.63 (1.33)	0.0 to 4.30

Mean magnitude of bacteraemia per blood draw					
	Blood draw 1, mean (SD)	Blood draw 2, mean (SD)	Blood draw 3, mean (SD)	Blood draw 4, mean (SD)	P value
Placebo	0 (0)	1.26 (3.67)	1.90 (5.36)	0.45 (0.83)	0.031
Amoxicillin	0.05 (0.16)	0.02 (0.06)	0.30 (0.73)	0.26 (0.60)	0.310

2) Duration of bacteraemia: not reported

3) Incidence of bacteraemia: defined as at least one positive culture of the four blood draws per subject and reported as n/N (%)

Placebo group: 5/10 (50)

Amoxicillin group: 4/10 (40)

*P value not reported for the above comparison but for the comparison between all 3 groups in the study (amoxicillin, placebo and chlorhexidine);0.670

Source of funding	Funding provided by the 59th Clinical Research Training Division, Lackland, AFB, TX
Comments	**Statistical analyses** Incidence of bacteraemia analysed via Chi-square tests Magnitude of bacteraemia analysed using the non-parametric Kruskal-Wallis test and the Friedman test with Bonferroni correction applied as there were multiple comparisons between the groups **Assessment of bacteraemia** - Once the IV access line was established, the first blood draw was completed at baseline - A second IV access line for the conscious sedation medications was obtained in the opposite arm in a similar manner after the blood draw IV access line was obtained, blood draw 1 was collected and the placebo or amoxicillin capsules were administered. - The third molar extractions was completed in the order of #1, 32, 16 and 17. - Blood draw 2 was completed 1.5 minutes following initiation of the mucogingival flap #32, blood draw 3 was completed 1.5 minutes following initiation of the mucogingival flap #17 and blood draw 4 was completed 10 minutes following initiation of the mucogingival flap #17 - The 4 blood samples per subject were transported to an on-site microbiology laboratory for immediate processing. All blood

Bibliographic reference	Duvall, NB., Fisher, TD., Hensley, D. (2013). The comparative efficacy of 0.12% chlorhexidine and amoxicillin to reduce the incidence and magnitude of bacteraemia during third molar extractions. Oral surgery, oral medicine and oral pathology. 115 (6): 752-763
	samples were processed within 4 hours of blood draw 1. - The bacterial concentrate was removed with an Isostat concentrate pipet and distributed equally onto 3 different agar plates: Trypticase soy agar with 5% sheep blood (incubated aerobically), chocolate agar (incubated aerobically) and Brucella blood agar (incubated anaerobically) - Colonies were counted and grouped by colonial morphology. Haemolytic reaction was recorded for colony types growing on Trypticase soy agar. - Following primary isolation, each colony type was subcultured to Trypticase soy agar or Brucella blood agar to obtain a pure culture and verify the required environmental growth conditions - A gram stain was performed on each pure culture with bacterial isolate identification accomplished using the VITEK 2 Compact bacterial identification system or the Biolog Microsation System **Microbial identity** - 33 different bacterial species were isolated among the placebo, chlorhexidine and amoxicillin groups - There were 24 different bacterial species isolated in the placebo group, 15 isolated in the chlorhexidine group and 10 isolated in the amoxicillin group - Of the 33 different bacterial species, 7 (21%) were alpha-hemolytic and also belonged to the viridans group streptococci. In the placebo group, 5 bacterial species isolated were alpha-hemolytic/viridans group streptococci, two isolated in the chlorhexidine group and one isolated in the amoxicillin group. **Study limitations: assessed using GRADE risk of bias checklist** - Blinding not described, insufficient information to judge whether subjects and/or assessors were blind - Incidence of positive blood cultures at baseline before prophylaxis not reported separately but together with incidence at any of the blood draws - Power calculation not reported

1 **Table 108**

Bibliographic reference	Sanchez-Carrion, S., Prim, MP., De Diego, JI., Sastre, N., Pena-Garcia, P. (2006). Utility of prophylactic antibiotics in pediatric adenoidectomy. International journal of pediatric otorhinolaryngology. 70 (7): 1275 -1281
Study type	RCT (double blind)
Aim	To determine the utility of prophylactic antibiotics in non-risk pediatric patients undergoing adenoidectomy
Patient characteristics	**Inclusion criteria** - Subjects under 14 years of age scheduled for adenoidectomy (without tonsillectomy)

Bibliographic reference	Sanchez-Carrion, S., Prim, MP., De Diego, JI., Sastre, N., Pena-Garcia, P. (2006). Utility of prophylactic antibiotics in pediatric adenoidectomy. International journal of pediatric otorhinolaryngology. 70 (7): 1275 -1281
	- Absence of immunosuppressive (medical and/or pharmacological) status - No risk of bacterial endocarditis - No antimicrobial therapy for at least 15 days prior to operation - No fever 1 week before surgery **Exclusion criteria** Not reported **Other characteristics** Age in months, mean With prophylaxis: 72.4 Without prophylaxis: 69.6 p=0.655 Gender, n (%) With prophylaxis: male – 29 (56.9), female – 22 (43.1) Without prophylaxis: male – 28 (56.0), female – 22 (44.0) P=1.000 Procedure, n (%) With prophylaxis: with ear tubes – 25 (49%), without ear tubes – 26 (51%) Without prophylaxis: with ear tubes – 27 (54%), without ear tubes – 23 (46%) p=0.692 Length of procedure in minutes, mean With prophylaxis: 28.1 Without prophylaxis: 30.2 p=0.662
Number of Patients	101 were randomised to: - prophylactic group n= 51 - no prophylaxis n=50
Intervention	Cefazolin 30 to 40mg/kg i.v given at induction of anaesthesia. Antibiotic prophylaxis was administered by the anaesthesiologist or the nurse before the entrance of the otolaryngologist into the operating room without his/her knowledge.

<table>
<tr><td>Bibliographic reference</td><td>Sanchez-Carrion, S., Prim, MP., De Diego, JI., Sastre, N., Pena-Garcia, P. (2006). Utility of prophylactic antibiotics in pediatric adenoidectomy. International journal of pediatric otorhinolaryngology. 70 (7): 1275 -1281</td></tr>
<tr><td></td><td>Adenoidectomy was performed by curettage of the nasopharynx (suction diathermy was not used after adenoidectomy in any case)</td></tr>
<tr><td>Comparison</td><td>No prophylaxis</td></tr>
<tr><td>Length of follow up</td><td>Not reported, blood samples taken up to 20 minutes after procedure</td></tr>
<tr><td>Location</td><td>Spain</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Outcomes measures and effect size
1) Bacteraemia levels/intensity
Not reported
2) Duration of bacteraemia
See 3) for number bacteraemia at different time points
3) Incidence of bacteraemia, n/N (%)
At 30 seconds
With prophylaxis – 2/51 (3.9), Without prophylaxis – 16/50 (32.7); p<0.001
At 20 minutes
With prophylaxis – 2/51 (3.9), Without prophylaxis – 7/50 (14.3) p=0.089
*In 4 cases from the without prophylaxis group, both samples were positive in the same subject
4) Complications (unclear whether these are complications of the procedures of effect of antibiotics)

<table>
<tr><td>Complication</td><td>With prophylaxis, n/N (%)</td><td>Without prophylaxis, n/N (%)</td><td>p value</td></tr>
<tr><td>Immediate bleeding</td><td>1/51 (2)</td><td>1/50 (2)</td><td>1.000</td></tr>
<tr><td>Airway compromise</td><td>0/51 (0)</td><td>0/50 (0)</td><td>Not analysed as cases =0</td></tr>
<tr><td>Fever in the inpatient</td><td>2/51 (3.9)</td><td>7/50 (14)</td><td>0.092</td></tr>
<tr><td>Delayed bleeding</td><td>0/51 (0)</td><td>0/50 (0)</td><td>Not analysed as cases =0</td></tr>
<tr><td>Fever during first week</td><td>3/51 (5.9)</td><td>7/50 (14)</td><td>0.200</td></tr>
<tr><td>Odinophagia</td><td>5/51 (9.8)</td><td>11/50 (22)</td><td>0.092</td></tr>
<tr><td>Acute otitis media</td><td>1/51 (2)</td><td>4/50 (8)</td><td>0.205</td></tr>
<tr><td>Otalgia</td><td>1/51 (2)</td><td>3/50 (6)</td><td>0.362</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Sanchez-Carrion, S., Prim, MP., De Diego, JI., Sastre, N., Pena-Garcia, P. (2006). Utility of prophylactic antibiotics in pediatric adenoidectomy. International journal of pediatric otorhinolaryngology. 70 (7): 1275 -1281**

Velopalatine insufficiency	0/51 (0)	1/50 (2)	0.495
Torticollis	0/51 (0)	0/50 (0)	Not analysed as cases =0

Source of funding	Not reported
Comments	**Statistical analyses** - All data collected were processed by one of the authors using SPSS statistical package, chi square test was used to compare variables. All tests received the same level of significance of 0.05. **Assessment of bacteraemia** - Venous blood samples were obtained under aseptic conditions at 30 seconds and 20 minutes after the removal of the adenoidal tissue - 10ml blood was taken from a peripheral vein district from the one used for intravenous anaesthetic induction - All samples taken to the microbiology lab within half an hour - Blood samples were treated in aerobic and anaerobic blood culture flasks and evaluated by means of a BacT/Alert blood culture system - All positive bottles were Gram stained and subcultured - Terminal subcultures were made 7 days after incubation - Bacteria from positive blood cultures were identified by standard laboratory methods **Microbial identity** - Organisms isolated from blood cultures in patients with prophylaxis included Haemophilus influenzae (n=1), Streptococcus viridans (n=2), Coagulase staphylococci (n=1) - Organisms isolated from blood cultures in patients without prophylaxis included Coagulase staphylococci (n=3), Neisseria flavescens (n=2), Neisseria subflava (n=3), Bacillus sp (n=1), Streptococcus salivarius (n=2), Neisseria cinerea (n=1), Streptococcus viridans (n=4), Streptococcus pneumoniae (n=1), Haemophilus influenzae (n=2), Neisseria eleongata (n=1), Neisseria sicca (n=1), Corynebacterium sp (n=1), Streptococcus agalactie (n=1) **Study limitations: assessed using GRADE risk of bias checklist** - Randomisation not described - Allocation concealment not described - Incidence of bacteraemia at baseline before prophylaxis not reported, subjects not tested - Power calculation not reported

1 **Table 109**

Bibliographic reference	**Diz DP, Tomas C, Limeres PJ, et al. (2006) Comparative efficacies of amoxicillin, clindamycin, and moxifloxacin in prevention of bacteremia following dental extractions. Antimicrobial Agents & Chemotherapy 50: 2996–3002.** ***[included in CG64]***
Study type	RCT
Aim	To investigate the efficacies of the prophylactic administration of amoxicillin, clindamycin and moxifloxacin for the prevention of bacteraemia following dental extractions
Patient characteristics	**Inclusion:** patients who for behavioural reasons (autism, learning disabilities, phobias, etc) underwent dental extractions under general anaesthesia. **Exclusion:** under 18yrs, antibiotics in the previous 3mths, routine use of oral antiseptics, history of allergy or intolerance to amoxicillin, clindamycin or moxifloxacin, any type of congenital or acquired immunodeficiency, any known risk factor for BE **Other characteristics** Age in years, mean (SD) Control group: 26.1 (7.3) Amoxicillin group: 23.8 (5.7) Clindamycin group: 24 (5.9) Moxifloxacin group: 22.4 (4.3) Gender, n (%) Control group: males – 29 (55), females – 24 (45) Amoxicillin group: males – 34 (61), females – 22 (39) Clindamycin group: males – 34 (63), females – 20 (37) Moxifloxacin group: males – 29 (50), females – 29 (50) There was NS difference in age, sex, oral health grade and number of dental extractions between the four groups
Number of Patients	N = 221 randomised Power calculation: calculated by comparing the prevalence of bacteraemia at 30 seconds after the dental extractions between a preliminary control group and antibiotic groups. Prevalence of bacteraemia in control group was 93%, amoxicillin group 58% (power 0.6, sample size 21), clindamycin group 87% (statistical power 0.08; sample size 392) and moxifloxacin group 42% (power 0.8, sample size 11)
Intervention	Amoxicillin group: 2g amoxicillin (Clamoxyl; Smith Kline Beecham) orally 1 to 2 hours before anaesthesia induction (n=56) Clindamycin group: 600 mg clindamycin (Dalacin) orally 1 to 2 hours before anaesthesia induction (n=54)

Bibliographic reference	**Diz DP, Tomas C, Limeres PJ, et al. (2006) Comparative efficacies of amoxicillin, clindamycin, and moxifloxacin in prevention of bacteremia following dental extractions. Antimicrobial Agents & Chemotherapy 50: 2996–3002.** ***[included in CG64]***
	Moxifloxacin group: 400 mg moxifloxacin (Actira) orally 1 to 2 hours before anaesthesia induction (n=58)
Comparison	No prophylaxis (n = 53)
Length of follow up	Study dates January 2003 to December 2004, blood samples up to an hour after extraction
Location	Spain
Outcomes measures and effect size	**1) Bacteraemia levels/intensity**: not reported **2) Duration of bacteraemia:** not reported **3) Incidence of bacteraemia** At baseline before dental manipulation but after nasotracheal intubation; control group (9.4%), amoxicillin (5%), clindamycin (12.5%), moxifloxacin (7.5%); n=40 in each group at baseline culture At 30sec; control group (96.2%) vs. amoxicillin (46.4%), p<0.001, vs. moxifloxacin (56.9%), p<0.001, vs. clindamycin (85.1%), NS. Amoxicillin vs. clindamycin (p<0.001) moxifloxacin vs. clindamycin (p≤0.001); n=50, 54 and 56 patients in control, amoxicillin and moxifloxacin groups respectively (due to technical reasons) At 15min; control group (64.2%) vs. amoxicillin (10.7%), p<0.001, vs. moxifloxacin (24.1%), p<0.001, vs. clindamycin (70.4%), NS. Amoxicillin vs. clindamycin (p<0.001) moxifloxacin vs. clindamycin (p<0.001); n=50, 54 and 56 patients in control, amoxicillin and moxifloxacin groups respectively (due to technical reasons) At 1hr; control group (20%) vs. amoxicillin (3.7%), p≤0.01, vs. moxifloxacin (7.1%), p<0.05, vs. clindamycin (22.2%), NS. Amoxicillin vs. clindamycin (p<0.01) moxifloxacin vs. clindamycin (p<0.05); n=50, 54 and 56 patients in control, amoxicillin and moxifloxacin groups respectively (due to technical reasons) Overall there were significant differences in the percentages of positive blood cultures between the control group (47.8%) vs. amoxicillin (17.5%) and vs. moxifloxacin (25.5%), p<0.001, but not vs. clindamycin (50%)
Source of funding	Xunta de Galicia of Spain
Comments	**Statistical analyses** - Results analysed using SPSS. Fisher's exact test used to compare the prevalence of bacteraemia at the different time points and the frequency of polymicrobial blood cultures between the study groups. P<0.05 was considered statistically significant. Power calculation reported in study. **Assessment of bacteraemia**

Bibliographic reference	**Diz DP, Tomas C, Limeres PJ, et al. (2006) Comparative efficacies of amoxicillin, clindamycin, and moxifloxacin in prevention of bacteremia following dental extractions. Antimicrobial Agents & Chemotherapy 50: 2996–3002.** ***[included in CG64]***
	Venous blood samples taken from subjcts at baseline, 30 seconds, 15 minutes and 1 hour after dental extraction and immediately transported to laboratory. 829 pairs of blood cultures were processed in a BACTEC 9240 instrument, a gram stain was performed on each positive blood culture, the positive blood cultures in the aerobic media were subcultured on blood agar and chocolate agar and on MacConkey agar, in the anaerobic media subcultured on Schaedler agar. **Microbial identity** There was a significant difference in the proportion of polymicrobial blood cultures in the control group (29%) vs. amoxicillin (0%) p<0.001, vs. moxifloxacin (14.8%) p<0.05, NS vs. clindamycin (31.7%). Most frequent in the positive blood cultures was streptococcus (63.1%), followed by staphylococcus (11.3%) and neisseria (7.5%). **Study limitations: assessed using GRADE risk of bias checklist** - Allocation concealment not described - 'Double blind'; details not described - Baseline blood samples only obtained from 40 subjects in each group (reason not given) - For postextraction blood cultures, n=50, 54 and 56 patients in control, amoxicillin and moxifloxacin groups respectively (due to technical reasons). However, these numbers don't fully match the percentages reported in study therefore missing data possible. - Unclear if the same subjects were bacteraemic at the different time points - Incidence of bacteraemia at baseline not comparable between groups

1 **Table 110**

Bibliographic reference	**Hall G, Hedstrom SA, Heimdahl A, Nord CE. Prophylactic administration of penicillins for endocarditis does not reduce the incidence of postextraction bacteremia.[see comment]. Clinical Infectious Diseases 1993;17:188-94** ***[included in CG64]***
Study type	RCT
Aim	To investigate with the use of a lysis filtration technique, the effects of prophylaxis with penicillin V and amoxicillin on the incidence, type and magnitude of bacteraemia in patients undergoing dental extraction.
Patient characteristics	**Inclusion:** otherwise healthy patients referred to the department of oral surgery for dental extraction, n = 42 male, mean age 47yrs (range 23 to 74yrs) **Exclusion:** allergy to penicillins, cardiovascular, renal, hepatic or GI diseases, pregnant women

Bibliographic reference	**Hall G, Hedstrom SA, Heimdahl A, Nord CE. Prophylactic administration of penicillins for endocarditis does not reduce the incidence of postextraction bacteremia.[see comment]. Clinical Infectious Diseases 1993;17:188-94** ***[included in CG64]***
	Other characteristics Age in years, mean (range) 47 (23 to 74 years) Gender, n Men – 42 Female – 18 None of the patients were receiving any medication except analgesics
Number of Patients	N = 60
Intervention	Penicillin V group: two 1g penicillin V tablets plus 4 tablets of amoxicillin placebo (n=20) Amoxicillin group: four 750mg amoxicillin tablets plus two tablets of penicllin V placebo (n=20) All interventions given orally 1hr before dental extraction* *Single tooth extraction all by the same surgeon because of dental caries or chronic periradicular osteitis.
Comparison	Placebo group: 2 tablets of penicillin V placebo and 4 tablets of amoxicillin placebo 1 hour before dental extraction (n=20)
Length of follow up	Blood samples taken up to 10 minutes after extraction
Location	Sweden
Outcomes measures and effect size	**1) Bacteraemia levels/intensity, reported as median cfu/ml in positive samples** Placebo: bacteraemia during surgery – 0.84, 10 minutes after surgery – 0.36 Penicillin V, 2g: bacteraemia during surgery – 0.66, 10 minutes after surgery – 0.36 Amoxicillin, 3g: bacteraemia during surgery – 1.08, 10 minutes after surgery – 0.24 **2) Duration of bacteraemia: not reported** **3) Incidence of bacteraemia (N=20 in each group)** No microorganisms were observed in any pre-treatment blood samples During dental extraction; placebo (90%), penicillin V (90%), amoxicillin (85%) 10mins after surgery; placebo (80%), penicillin V (70%), amoxicillin (60%) NS difference in the incidence or magnitude of bacteraemia, of bacteraemia due to viridans streptococci, or of bacteraemia due to anaerobic bacteria among the three patient groups at any of the sampling times

Bibliographic reference	**Hall G, Hedstrom SA, Heimdahl A, Nord CE. Prophylactic administration of penicillins for endocarditis does not reduce the incidence of postextraction bacteremia.[see comment]. Clinical Infectious Diseases 1993;17:188-94** ***[included in CG64]***
	10mins after dental extraction, the number of microorganisms had decreased in similar ways in all three patient groups from that found during extraction (p<0.01)
Source of funding	Supported by the Swedish National Association against Heart and Chest Diseases and the Swedish Dental Society
Comments	**Statistical analyses** Differences in the incidence of bacteraemia among the 3 patient groups were analysed with the use of Fisher's exact test. **Assessment of bacteraemia** - Blood samples were drawn before, during and 10 minutes after dental extraction and samples immediately processed to the laboratory. - The blood samples were injected into bottles with 0.193L of a lysin solution and vacuum filtration was performed. - Aerobic and anaerobic microorganisms were identified using the methods described in the Manual of Clinical Microbiology. Quantitative counts were estimated from the numbers of colonies visible on the filters. - Lysis filtration under anaerobic conditions Blood samples: before, during and 10mins after dental extraction. **Microbial identity** - Streptococcus intermedius was the most common species isolated and was also found to have the highest number of organisms per ml of blood in all 3 samples. - Other frequently isolated viridans streptococci were Streptococcus mitior, Streptococcus mutans and Streptococcus sanguis. - Aerobic species other than viridans streptococci were isolated in small numbers. **Study limitations assessed using GRADE risk of bias checklist** - Randomisation, allocation concealment and blinding not described - Unclear if subjects bacteraemic 10 minutes after surgery were those who were also bacteraemic during surgery - Power calculation not reported

1 **Table 111**

Bibliographic reference	**Roberts GJ, Radford P, Holt R. Prophylaxis of dental bacteraemia with oral amoxycillin in children. British Dental Journal 1987;162:179-82.** ***[included in CG64]***
Study type	RCT
Aim	To determine the incidence of bacteraemia from dental extractions, the levels of circulating amoxicillin following one dose equivalent to 3g in an adult, the feasibility of using this dose prior to a general anaesthetic and the efficacy of amoxicillin in

Bibliographic reference	**Roberts GJ, Radford P, Holt R. Prophylaxis of dental bacteraemia with oral amoxycillin in children. British Dental Journal 1987;162:179-82. *[included in CG64]***
	eliminating dental bacteraemia
Patient characteristics	**Inclusion:** under 16yrs and required admission for extensive conservative dental work as well as the extraction of at least one tooth. The presence of a peripheral vein suitable for cannulation was necessary. **Exclusion:** allergy to one of the penicillin group of drugs or a significant medical disorder **Other characteristics** Age, mean (SD) Controls: 9 years, 11 months (4 years, 1 month) Oral amoxicillin: 8 years, 4 months (2 years, 11 months) Gender, number female/male Controls: 19/28 Oral amoxicillin: 22/25 The randomised groups were comparable in age and sex
Number of Patients	n = 108 (47 control arm, 47 oral amoxicillin, 6 additional refusers and 8 additional cardiac patients)
Intervention	Oral amoxicillin 50mgs/kg 2hrs before the scheduled time for surgery (mean dose 50.4mg/kg) (n=47)
Comparison	No prophylaxis (n=47)
Length of follow up	Blood samples taken up to 5 minutes after extraction
Location	UK
Outcomes measures and effect size	**1) Bacteraemia levels/intensity: not reported** **2) Duration of bacteraemia: not reported** **3) Incidence of bacteraemia** - All samples taken at the pre-intubation sampling time were negative - 2mins after intubation n = 3/47 in the control group and n = 2/6 in the refusers had positive blood cultures (these were typical of those commonly colonising the upper respiratory tract). All other groups (amoxicillin and cardiac patients) were negative. - The post extraction samples (2 minutes post-extraction); n = 18/47 positive in the control group, n = 1/47 in the amoxicillin group and n = 2/6 in the refusers group, control vs. amoxicillin, p<0.001 (the organisms isolated were typical of those normally found in bacterial dental plaque) - All cardiac patients had sterile blood cultures pre and post extraction.
Source of funding	Not stated
Comments	**Statistical analyses**

Bibliographic reference	**Roberts GJ, Radford P, Holt R. Prophylaxis of dental bacteraemia with oral amoxycillin in children. British Dental Journal 1987;162:179-82. *[included in CG64]***
	Statistical tests used were the Chi Square and Student's t –test **Assessment of bacteraemia** - 4x1ml blood samples processed using differing broths, plates were incubated and positive results recorded as cfu, bacteria grown were identified by a described procedure (a broad spectrum penicillinase was added to all samples from those who had received amoxicillin, a pilot study confirmed that the addition did not alter culture results) - Blood samples: prior to nasotracheal intubation, 2mins after nasotracheal intubation, extensive conservative dental work was carried out before extraction; 2mins after extraction of the first tooth samples were taken. (supplementary studies; one had additional samples taken at 45secs post extraction, another 5mins post extraction) **Microbial identity** The organisms isolated were typical of those normally found in bacterial dental plaque. **Study limitations: assessed using GRADE risk of bias checklist** - Randomisation not described ('at random'), allocation concealment not described, blinding not described. - Patients 'satisfactorily' consume the oral amoxicillin - Unclear whether those positive post extraction were those positive post intubation - Power calculation not reported

1 **Table 112**

Bibliographic reference	**Hall G, Heimdahl A, Nord CE. Effects of prophylactic administration of cefaclor on transient bacteremia after dental extraction. European journal of clinical microbiology & infectious diseases 1996; 15: 646–49 *[included in CG64]***
Study type	RCT (Double-blind)
Aim	To investigate the effects of prophylaxis with ceflacor on the incidence, type and magnitude of bacteraemia in patients undergoing dental extraction
Patient characteristics	**Inclusion:** those undergoing dental extraction **Exclusion:** not reported **Other characteristics** Age in years, mean (range) Cefaclor group: 43 (26 to 66) Placebo group: 46 (21 to 61)

Bibliographic reference	**Hall G, Heimdahl A, Nord CE. Effects of prophylactic administration of cefaclor on transient bacteremia after dental extraction. European journal of clinical microbiology & infectious diseases 1996; 15: 646–49 *[included in CG64]***
	Gender, n Cefaclor group: 10 males, 10 females Placebo group: 10 males, 9 females
Number of Patients	N = 39 randomised
Intervention	Two 0.5g Cefaclor tablets (Eli Lilly, UK) 1g, 1 hr prior to dental extraction (n = 19)
Comparison	Two tablets of placebo 1 hr prior to dental extraction (n=20)
Length of follow up	Not reported, blood samples taken up to 10 mins following extraction
Location	Sweden
Outcomes measures and effect size	1) Bacteraemia levels/intensity The magnitude of bacteraemia (counts of cfu's) was reduced by 75% in the 10 minute blood sample in both patient groups (average in each group not reported) 2) Duration of bacteraemia Not reported 3) Incidence of bacteraemia - None of the patients were bacteraemic prior to dental extraction - During dental extraction positive blood cultures; 79% cefaclor group; 85% placebo group - 10mins after extraction positive blood cultures; 53% cefaclor group; 47% placebo group
Source of funding	Swedish Medical Research Council
Comments	**Statistical analyses** Difference in the incidence of bacteraemia between the 2 groups were analysed by use of a two sided chi-square test. The Wilcoxon rank sum test was used to compare the groups with respect to the counts of microorganisms isolated. **Assessment of bacteraemia** - 8.3ml blood samples were taken before, during and 10 minutes after dental extraction - The blood samples were processed immediately by lysis filtration - Aerobic and anaerobic microorganisms were identified using standard methods

Bibliographic reference	**Hall G, Heimdahl A, Nord CE. Effects of prophylactic administration of cefaclor on transient bacteremia after dental extraction. European journal of clinical microbiology & infectious diseases 1996; 15: 646–49 *[included in CG64]***
	Microbial identity Post-extraction bacteraemia had a dominance of gram-positive strains (>90%) in both groups Viridans streptococci during extraction; 79% cefaclor; 50% placebo group Viridans streptococci 10mins after extraction; 26% cefaclor; 30% placebo group Strains of streptococcus intermedius most frequently isolated, followed by streptococcus sanguis and streptococcus mitis in both patient groups Anaerobic bacteraemia during extraction; 74% cefaclor; 75% placebo group Anaerobic bacteraemia 10 minutes after extraction; 47% cefaclor; 35% placebo group Actinomyces spp. were most commonly identified strains (Veilloneela and Prevotella isolated from single patients) **Study limitations: assessed using GRADE risk of bias checklist** - Randomisation, concealment not described - 'Double blind', details not described - Unclear if those positive after extraction are those positive during extraction - Unclear if one subject lost from control group at 10 minutes - Power calculation not reported

1 **Table 113**

Bibliographic reference	**Shanson DC, Akash S, Harris M, Tadayon M. Erythromycin stearate, 1.5 g, for the oral prophylaxis of streptococcal bacteraemia in patients undergoing dental extraction: efficacy and tolerance. Journal of Antimicrobial Chemotherapy 1985;15:83-90 *[included in CG64]***
Study type	RCT
Aim	To determine the efficacy of 1.5g oral loading dose of erythromycin stearate given 1 hour before extraction for the prophylaxis of post-extraction streptococcal bacteraemia and to compare the incidence of gastrointestinal side effects associated with this dose of erythromycin with that of a placebo administered to a control group of dental patients.
Patient characteristics	**Inclusion** - Side effects study: adult patients aged 18 to 78 undergoing dental extractions in the out-patient department - Dental bacteraemia study: healthy non-fasting adults aged between 18 to 71 attending the outpatient department **Exclusion:** not reported **Other characteristics** Side effects study: age 18 to 78 years, male:female ratio 3:1

Bibliographic reference	**Shanson DC, Akash S, Harris M, Tadayon M. Erythromycin stearate, 1.5 g, for the oral prophylaxis of streptococcal bacteraemia in patients undergoing dental extraction: efficacy and tolerance. Journal of Antimicrobial Chemotherapy 1985;15:83-90 *[included in CG64]***
	Dental bacteraemia study: aged 18 to 71 years
Number of Patients	n = 109 side effects study n = 82 dental bacteraemia study
Intervention	1.5g erythromycin stearate orally 1hr before dental extraction (n=56 for side effects study, n=40 for dental bacteraemia study)
Comparison	Matched placebo (n=53 for side effects study and n= 42 for dental bacteraemia study)
Length of follow up	7days
Location	London
Outcomes measures and effect size	**1) Bacteraemia levels/intensity: not reported** **2) Duration of bacteraemia: not reported** **3) Incidence of bacteraemia** <u>Streptococcal bacteraemia post extraction</u> Streptococci were isolated from the nutrient broth cultures in n = 18/42 (43%) in the control group compared with n = 6/40 (15%) erythromycin group, p=0.01 **4) Side-effects** n = 29/56 (52%) receiving erythromycin reported GI side-effects compared with n = 10/53 (19%) placebo group. Side effects included mild or transient nausea, abdominal discomfort or flatulence usually occurring within a few hours of dental extraction. No patients vomited.
Source of funding	Abbott Laboratories
Comments	**Statistical analyses** Chi square test **Assessment of bacteraemia** - Blood samples were collected from patients 1 to 2 minutes after the dental procedure - Each blood sample was cultured by 3 different methods designed to reduce anti-streptococcal activity due to erythromycin using high dilution techniques after different time intervals (immediate 1 in 250 dilution blood culture broths, 6h 1 in 20 dilution blood culture broths and 24h 1 in 250 dilution blood culture broths) - All 1 litre blood culture bottles were subcultured after 24 hours, 48 hours and 5 days incubation. The plates were incubated aerobically for 48 hours in carbon dioxide incubator. -The identification of viridans streptococci was carried out using optochin tests and AP strep 20 tests. **Microbial identity**

Bibliographic reference	**Shanson DC, Akash S, Harris M, Tadayon M. Erythromycin stearate, 1.5 g, for the oral prophylaxis of streptococcal bacteraemia in patients undergoing dental extraction: efficacy and tolerance. Journal of Antimicrobial Chemotherapy 1985;15:83-90 *[included in CG64]***
	- Study specifically examined streptococci prevalence as summarised above **Study limitations: assessed using GRADE risk of bias checklist** - Number bacteraemic at baseline not reported (unclear if subjects were tested) - Power calculation not reported

1 **Table 114**

Bibliographic reference	**Wahlmann U, Al Nawas B, Jutte M, Wagner W. Clinical and microbiological efficacy of single dose cefuroxime prophylaxis for dental surgical procedures. International Journal of Antimicrobial Agents 1999;12:253-6 *[included in CG64]***
Study type	RCT
Aim	To study the effect of a single dose of cefuroxime before multiple tooth extractions on the clinical findings and occurrence of bacteraemia
Patient characteristics	**Inclusion:** patients with multiple tooth extraction in preparation for radiotherapy of oral cancer, **Exclusion:** those with allergy to cephalosporins, had received antibiotics in the past 3wks, those with an absolute indication for perioperative chemoprophylaxis **Other characteristics** Gender, n/N Male – 54/59 Age in years, mean (range) 48 (31 to 81)
Number of Patients	n = 59
Intervention	1.5g IV cefuroxime 10mins before multiple tooth extractions* (n=30) ***** A mean of 8.8 teeth were extracted in each patient
Comparison	Placebo - 0.9% NaCl (n=29)
Length of follow up	Not reported, blood drawn at upto 40 minutes after drug administration in intervention group, and upto 30 minutes after procedure in control group
Location	Germany
Outcomes measures and effect size	**1) Bacteraemia levels/intensity: not reported** **2) Duration of bacteraemia: not reported** **3) Incidence of bacteraemia** A significantly lower rate of bacteraemia was identified after cefuroxime administration at 10min (cefuroxime n = 7/30, 23% vs.

Bibliographic reference	**Wahlmann U, Al Nawas B, Jutte M, Wagner W. Clinical and microbiological efficacy of single dose cefuroxime prophylaxis for dental surgical procedures. International Journal of Antimicrobial Agents 1999;12:253-6 *[included in CG64]***
	control n = 23/29, 79%) and 30min (cefuroxime n = 6/30, 20% vs. control n = 20/29, 69%) after the start of surgery. This was also significant for 10 or 30min (n = 10/30, 33% vs. n = 25/30, 86%)
Source of funding	Not stated
Comments	**Statistical analyses** - Statistical analysis was performed using SAS - Fisher's exact test was used to test categorical variables for significant differences **Assessment of bacteraemia** - Blood cultures were drawn at the start of the surgical procedure and 30 minutes later. - Blood was inoculated into a Signal system and processed according to the manufacturer's recommendations - Susceptibility testing was carried out using he standard agar diffusion technique **Microbial identity** Gram positive cocci mostly streptococci were the predominant organisms followed by Gram negative rods; growth mainly anaerobic **Study limitations: assessed using GRADE risk of bias checklist** - Randomisation, concealment and blinding not described - Number bacteraemic at baseline not reported (unclear if subjects tested) - Unclear whether subjects bacteraemic at 30 minutes were same subjects bacteraemic at 10 minutes - Power calculation not reported

1 **Table 115**

Bibliographic reference	**Allan WR, Kumar A (1985) Prophylactic mezlocillin for transurethral prostatectomy. British Journal of Urology 57: 46–49. *[included in CG64]***
Study type	RCT
Aim	To test the efficiency of prophylactic mezlocillin in a prospective clinical trial
Patient characteristics	**Inclusion:** undergoing transurethral prostatectomy **Exclusion:** allergy to penicillin, known UTI, had received antibiotics in the week before surgery **Other characteristics**

Bibliographic reference	**Allan WR, Kumar A (1985) Prophylactic mezlocillin for transurethral prostatectomy. British Journal of Urology 57: 46–49. *[included in CG64]***
	Age in years, mean Mezlocillin group: 68.78 Control group: 70.72 There was NS difference between the groups in terms of age, presence of malignant prostate, time taken for operation.
Number of Patients	N = 100
Intervention	2g intravenous mezlocillin about the time of induction of anaesthesia (n=50)
Comparison	No prophylaxis (n=50)
Length of follow up	Not reported
Location	UK
Outcomes measures and effect size	**1) Bacteraemia levels/intensity: not reported** **2) Duration of bacteraemia: not reported** **3) Incidence of bacteraemia** After completion of operation n = 2 (4%) in mezlocillin group; n = 16 (32*%) in control group; p<0.001 First day post-op and after removal of catheter NS difference between the groups *Calculated by reviewer based on assumption that subjects were not lost
Source of funding	Bayer Company
Comments	**Statistical analyses** Not reported **Assessment of bacteraemia** Immediately after the operation blood was obtained for culture and further blood culture was carried out on the first post-operative day and again when the catheter was removed. Further details of microbiological analysis not reported. **Microbial identity** Mezlocillin group; blood (Escherichia coli, Bacteroides fragilis), urine (E. coli, proteus, enterococci, Staphylococcus aureus, Staphylococcus albus) Control group; blood (E. coli, proteus, enterococci, S. aureus, S. albus, Streptococcus faecalis), urine (E. coli, proteus, Pseudomonas spp, enterococci, S. aureus, S. albus, S. faecalis) **Study limitations: assessed using GRADE risk of bias checklist** - Unclear if subjects lost from control group as percentages reported in study do not match up with number randomised to

Bibliographic reference	**Allan WR, Kumar A (1985) Prophylactic mezlocillin for transurethral prostatectomy. British Journal of Urology 57: 46–49. *[included in CG64]***
	control arm - Blood culture methods not reported - Number bacteraemic at baseline not reported - Power calculation not reported

1 **Table 116**

Bibliographic reference	**Bhattacharya S, Parkin DE, Reid TM et al. (1995) A prospective randomised study of the effects of prophylactic antibiotics on the incidence of bacteraemia following hysteroscopic surgery. European Journal of Obstetrics, Gynecology & Reproductive Biology 63: 37–40 *[included in CG64]***
Study type	RCT
Aim	To examine the incidence of bacteraemia in women undergoing endometrial ablation with and without antibiotic prophylaxis
Patient characteristics	**Inclusion:** women with menorrhagia undergoing either transcervical resection (TCRE) or laser ablation of the endometrium (ELA) **Exclusion:** not reported **Other characteristics** Age, etc not reported
Number of Patients	N = 116 Power calculation: 80% power to detect a difference of 15% from 1% to 16% at the 5% significance level (based on review of data from first 100 cases)
Intervention	1.2 g augmentin IV at the induction of anaesthesia (n = 55)
Comparison	No antibiotic (n = 61)
Length of follow up	Discharged same or following day, given a diary to record events over the next 2 wks
Location	UK
Outcomes measures and effect size	**1) Bacteraemia levels/intensity: not reported** **2) Duration of bacteraemia: not reported** **3) Incidence of bacteraemia** n = 10 (16%) positive blood cultures in the no antibiotic group compared with n = 1 (2%) in the antibiotic group, p<0.02,

Bibliographic reference	**Bhattacharya S, Parkin DE, Reid TM et al. (1995) A prospective randomised study of the effects of prophylactic antibiotics on the incidence of bacteraemia following hysteroscopic surgery. European Journal of Obstetrics, Gynecology & Reproductive Biology 63: 37–40 *[included in CG64]***
	95%CI: 5 to 25. Infectious morbidity: post-operative outcome within 2 weeks of endometrial ablation No antibiotic; pain (n = 26, 43%); offensive discharge (n = 14, 23%); fever (n = 4, 7%); visit to GP (n = 11, 18%); antibiotics prescribed by GP (n = 7, 11.4%) Antibiotic; pain (n = 29, 53%); offensive discharge (n = 14, 26%); fever (n = 9, 16%); visit to GP (n = 11, 20%); antibiotics prescribed by GP (n = 5, 9%) None of the participants, regardless of their blood culture status, became seriously ill.
Source of funding	Chief Scientists Office of the Scottish Office
Comments	**Statistical analyses** Analysis by intention to treat. The chi square test was used for significance. **Assessment of bacteraemia** 20ml blood samples obtained immediately after the routine TCRE or ELA Sample divided equally between 2 culture bottles, one aerobic and one anaerobic. Blood culture bottles incubated in a non-radiometric Bactec 860 analyser at 37˚C for 5 days Any bottles giving a reading above the detection threshold were subcultured on to plates containing blood agar, MacConkey agar and incubated. Endocervical swabs were cultured on blood and MacConkey agar and chocolate agar. **Microbial identity** Organisms isolated from the endocervix were mixed anaerobes, Group B haemolytic Streptococcus and E.coli. **Study limitations: assessed using GRADE risk of bias checklist** - Incidence of bacteraemia at baseline not reported, unclear if subjects tested - Baseline characteristics not reported

1 **Table 117**

Bibliographic reference	**Selby WS, Norton ID, Pokorny CS et al. (1994) Bacteremia and bacterascites after endoscopic sclerotherapy for bleeding esophageal varices and prevention by intravenous cefotaxime: a randomized trial. Gastrointestinal Endoscopy 40: 680-4 *[included in CG64]***
Study type	RCT

Bibliographic reference	**Selby WS, Norton ID, Pokorny CS et al. (1994) Bacteremia and bacterascites after endoscopic sclerotherapy for bleeding esophageal varices and prevention by intravenous cefotaxime: a randomized trial. Gastrointestinal Endoscopy 40: 680-4 *[included in CG64]***
Aim	To examine the effect of prophylactic cefotaxime on the frequency of bacteraemia and bacterascites occurring after endoscopic injection of bleeding esophageal varices and its effect on clinical infection, in particular bacterial peritonitis.
Patient characteristics	**Inclusion:** all patients presenting with bleeding esophageal varices and who underwent emergency endoscopic sclerotherapy, defined as performed within 48hrs of bleeding **Exclusion:** antibiotics within 72hrs, antibiotics required for other indications, patients who met the criteria for spontaneous bacterial peritonitis*, allergy to penicillin or cephalosporins, refused entry to study or whose relative or attending physician declined. *Previous episodes of spontaneous bacterial peritonitis were not a reason for exclusion. **Other characteristics** Age in years, mean (SD) Antibiotic group: 58.9 (14.2) Control group: 49.5 (10.7) Gender, number male: number female Antibiotic group: 15:4 Control group: 13:7 There was no difference between the groups in cause of liver disease, use of ET tubes, need for vasopressin or balloon tamponade.
Number of Patients	n = 31 (39 episodes of bleeding)
Intervention	1g cefotaxime IV immediately before endoscopic sclerotherapy (n = 19)
Comparison	No antibiotic (n = 20)
Length of follow up	Study between August 1989 to December 1991
Location	Australia
Outcomes measures and effect size	**1) Bacteraemia levels/intensity: not reported** **2) Duration of bacteraemia: not reported** **3) Incidence of bacteraemia**

Bibliographic reference	**Selby WS, Norton ID, Pokorny CS et al. (1994) Bacteremia and bacterascites after endoscopic sclerotherapy for bleeding esophageal varices and prevention by intravenous cefotaxime: a randomized trial. Gastrointestinal Endoscopy 40: 680-4 *[included in CG64]***
	Antibiotic group: 1/19 (5.3%) positive at 5mins with cefotaxime, none positive at 4 hours or 24 hours. Control group*: 6/19 (31.6%) positive cultures at 5mins, 1 (out of the 6 positive at 5 mins) was positive at 4 hours, no patient was bacteraemic at 24 hours P at 5 minutes=0.04 *1 subjects was positive before procedure and therefore not considered in analysis <u>Mortality</u> 2/19 in antibiotics group vs 5/19 in control group.
Source of funding	Not stated
Comments	**Statistical analyses** Fisher's exact test **Assessment of bacteraemia** - Blood samples before endoscopy, 5mins, 4hrs and 24hrs after sclerotherapy - Cultures were performed using standard aerobic and anaerobic techniques at 37C, organisms were identified using conventional means **Microbial identity** Antibiotic group: organism identified was an alpha-haemolytic streptococcus Control group: organism identified included alpha-haemolytic streptococcus, Veillonella sp, Streptococcus milleri, Streptococcus salivarius, Neisseria sp. **Study limitations assessed using GRADE risk of bias checklist** - Blinding not described - Power calculation not reported

1 **Table 118**

Bibliographic reference	**Lockhart PB, Brennan MT, Kent ML, Norton HJ, Weinrib DA. Impact of amoxicillin prophylaxis on the incidence, nature, and duration of bacteraemia in children after intubation and dental procedures. Circulation 2004;109:2878-84. *[included in CG64]***
Study type	RCT

Bibliographic reference	**Lockhart PB, Brennan MT, Kent ML, Norton HJ, Weinrib DA. Impact of amoxicillin prophylaxis on the incidence, nature, and duration of bacteraemia in children after intubation and dental procedures. Circulation 2004;109:2878-84. *[included in CG64]***
Aim	To determine the impact of amoxicillin prophylaxis on the incidence, nature and duration of bacteremia from nasotracheal intubation and dental procedures in children.
Patient characteristics	**Inclusion:** children who required dental treatment (extraction) in the operating room setting because of behaviour, young age and/or the scope of treatment needs **Exclusion:** poorly controlled systemic illness, physical status level III or IV, medical conditions requiring antibiotic prophylaxis, allergy to penicillin-type drugs, weight <12kg, exposure to systemic antibiotics within the past 2wks **Other characteristics** Age in years, mean (SD) Amoxicillin group: 3.4 (1.3) Placebo group: 3.5 (1.5) Male, n (%) Amoxicillin group: 30 (61) Placebo group: 26 (51) There was NS difference in the baseline characteristics for all subjects, stratified by treatment group
Number of Patients	n = 100 Power calculation: based on proportion of subjects who had a development of bacteraemia. To detect a 30% difference in incidence with a power of 80%, 100 subjects would be required.
Intervention	Amoxicillin elixir 50mg/kg one hour before the anticipated time of intubation (n = 49)
Comparison	Placebo (n = 51)
Length of follow up	
Location	USA
Outcomes measures and effect size	**1) Bacteraemia levels/intensity: not reported** **2) Duration of bacteraemia:** Not reported as continuous outcome **3) Incidence bacteraemia**

Bibliographic reference	**Lockhart PB, Brennan MT, Kent ML, Norton HJ, Weinrib DA. Impact of amoxicillin prophylaxis on the incidence, nature, and duration of bacteraemia in children after intubation and dental procedures. Circulation 2004;109:2878-84.** ***[included in CG64]***
	The overall incidence from all 8 draws was greater in the placebo group than the amoxicillin group (n = 43, 84% vs. n = 16, 33%), p<0.0001 Highest incidence at a single time point occurred at 1.5mins (fifth draw) after extraction, placebo vs. amoxicillin (n = 34, 76% vs. n = 6, 15%), p<0.0001 Incidence at baseline after intubation (D1) 18% placebo vs. 4% amoxicillin , p=0.05 Incidence restorative and cleaning procedures (D2) 20% placebo vs. 6% amoxicillin, NS Bacteraemia incidence in the placebo group; 15mins (n = 7, 18%); 30mins (n = 6, 16%); 45mins (n = 5, 14%) Bacteraemia incidence in the amoxicillin group; n = 1 at 15mins, none positive at other time points Statistically significant decrease in the incidence of bacteraemia from amoxicillin at all but one draw (D2); D1 (p=0.05), D3 (p=0.03), D4 (p=0.0001), D5 (p=0.0001), D6 (p=0.04), D7 (p=0.01), D8 (p=0.03) No subject had a positive culture at D6,7 or 8 who did not have a positive extraction blood draw
Source of funding	Health Services Foundation Inc, Carolinas HealthCare System, Charlotte, NC
Comments	**Statistical analyses** Chi square and Fisher's exact test for nominal data. **Assessment of bacteraemia** Blood samples: 2mins after the initiation of intubation; dental restorations, pulp therapy and cleaning were then completed and a second sample drawn; 10mins later a third sample for a baseline culture before dental extraction, 90secs after the initiation of the first extraction a fourth draw was taken, the remaining teeth were extracted and a fifth blood draw 90secs after the final extraction. Further draws at 15, 30 and 45mins after the end of extraction Aerobic and anaerobic were processed according to standard methods, cultures with bacterial growth were gram stained and subcultured onto appropriate media; blood cultures were continued monitored for growth with the use of an automated Microscan (Baxter) system and standard biochemical tests were done manually to complete the identity; blood cultures were incubated for up to 14days before considered no growth to avoid missing more slow-growing oral pathogens **Microbial identity** There was a >5-fold difference in the number of positive blood cultures with placebo vs. amoxicillin, n = 128 vs. n = 24. Streptococci made up 45% (n = 57) of the total bacteria in the placebo group vs. 33% (n = 8) of the amoxicillin group **Study limitations assessed using GRADE risk of bias checklist** - Unclear if same subjects bacteraemic at different time points

Bibliographic reference	**Lockhart PB, Brennan MT, Kent ML, Norton HJ, Weinrib DA. Impact of amoxicillin prophylaxis on the incidence, nature, and duration of bacteraemia in children after intubation and dental procedures. Circulation 2004;109:2878-84. *[included in CG64]***
	- Some subjects lost at 15 minutes; unclear how many from each group

1 **Table 119**

Bibliographic reference	**Qiang W, Jianchen W, MacDonald R et al. (2005) Antibiotic prophylaxis for transurethral prostatic resection in men with preoperative urine containing less than 100,000 bacteria per ml: a systematic review. [Review] [40 refs]. Journal of Urology 173: 1175-81 *[included in CG64]***
Study type	Systematic review
Aim	To determine whether antibiotic prophylaxis can reduce the risk of postoperative infective complications in men undergoing transurethral resection of the prostate who have preoperative urine with less than 100,000 bacteria per ml.
Patient characteristics	**Inclusion:** electronic databases searched; MEDLINE 1966 to 2003, EMBASE from 1980 to 2002, Cochrane Library for RCTs and quasi-RCTs comparing antibiotic prophylaxis and placebo/or controls in men undergoing TURP. RCTs or quasi-RCT were included if they met the criteria of comparing antibiotic prophylaxis with placebo or no treatment control patients undergoing TURP, no local or systemic signs of urinary infection, sterile preoperative urine specimen, reports of at least 1 of postoperative bacteriuria, fever, bacteraemia, septicaemia, additional antibiotic treatment, urethral stricture, catheterisation or hospitalisation duration, and were published in English **Exclusion:** studies were excluded from analysis if patients had a preoperative temperature greater than 38C, a preoperative indwelling catheter, kidney dysfunction, bladder tumour, hypersensitivity to antibiotics, preoperative UTI and antibiotic treatment within a week before TURP Missing or additional information was sought from authors and sponsors **Other characteristics** n = 28 trials, n = 4694 patients, mean age 69yrs, n = 10 trials placebo controlled n = 18 no treatment control n = 23 compared a single type of antibiotic with placebo or no treatment, n = 5 compared 2 different antibiotic groups with placebo or no treatment
Number of Patients	10 trials of relevance to this review question (n=1394)
Intervention	Antibiotic prophylaxis
Comparison	Placebo or no prophylaxis
Length of follow up	Various
Location	Various

Bibliographic reference	**Qiang W, Jianchen W, MacDonald R et al. (2005) Antibiotic prophylaxis for transurethral prostatic resection in men with preoperative urine containing less than 100,000 bacteria per ml: a systematic review. [Review] [40 refs]. Journal of Urology 173: 1175-81 *[included in CG64]***
Outcomes measures and effect size	Incidence of bacteraemia after transurethral resection of the prostate Risk difference (95%CI): -0.02 (-0.04 to 0.00)
Source of funding	Not stated
Comments	

Study	Antibiotic agent/class	Dosing	Inclusion criteria
Charlton et al., 1987	Netilmicin 150mg/aminoglycoside	1 dose intramuscularly 1 hour before surgery	French men (100), mean age, 68 years, undergoing TURP for prostatic anomaly
Nielsen et al., 1981	Cefoxitin 1g/cephalosporin	1 dose IM 2 to 4 hours before surgery + 3 times/day after surgery as long as indwelling catheter remained	American men (10), 60 to 71 years old (mean 62), undergoing TURP
Qvist et al., 1984	Cefotaxime 2g/cephalosporin	1 dose iv 1 hour before surgery	Danish men (88), mean age 68 years
Botto et al., 1984	Cefotaxime 1g/cephalosporin	1 dose IV before surgery + 2 doses after surgery	French men (167), mean 69 years, undergoing TURP
Charlton et al., 1984	Mezlocillin 2g/penicillin	1 dose IV 1 hour before surgery	French men (100), 48-86 years, undergoing TURP
Morris et al., 1976	Kanamycin 1g/aminoglycoside, co-trimoxazole x2/co-trimoxazole	Kanamycin 1 dose IM before surgery, co-trimoxazole orally 2 times/day for 3 weeks after surgery	Australia men (101), mean age 71 years, undergoing TURP for prostatic obstruction
Stricker et al., 1988	Gentamicin 80mg/aminoglycoside + ampicillin 1g/penicillin	1 dose IV before surgery	Australian men (100) undergoing TURP
Taylor et al., 1988	Temocillin 1g/penicillin	1 dose IV before surgery + 2 doses after surgery	British men (308), 38-90 years undergoing TURP
Viitanen et al., 1993	Ceftriaxone 2g/cephalosporin (3rd generation),	Ceftriazone 1 dose IV before surgery, sulfamethoxazole-	Finnish men (599), 45-89 years, undergoing TURP

Bibliographic reference	**Qiang W, Jianchen W, MacDonald R et al. (2005) Antibiotic prophylaxis for transurethral prostatic resection in men with preoperative urine containing less than 100,000 bacteria per ml: a systematic review. [Review] [40 refs]. Journal of Urology 173: 1175-81 *[included in CG64]***

	sulfamethoxazole-trimethoprim 800/160mg/co-trimoxazole	trimethoprim 1 dose IV before surgery	
Weiss et al., 1983	Nitrofurantoin 50mg x 4/nitrofurantoin	Group 1 orally 4 times/day for 5 days after surgery, group 2 orally 4 times/day for 10 days after surgery	American men (223) undergoing TURP

Study limitations assessed using systematic review checklist in NICE guidelines manual 2012

Random effects model but unclear how heterogeneity was assessed; I squared or similar value not reported

1 **Table 120**

Bibliographic reference	**Morozumi T, Kubota T, Abe D, Shimizu T. (2010) Effects of irrigation with an antiseptic and oral administration of azithromycin on bacteraemia caused by scaling and root planning. Journal of Periodontology 81 (11): 1555-1563 *[included in CG64]***
Study type	Randomised controlled trial
Aim	To investigate the prevalence of bacteremia caused by scaling and root planning and to evaluate the efficacies of 2 prophylactic methods of bacteremia secondary to scaling and root planning
Patient characteristics	**Inclusion criteria** - systemically healthy subjects who possessed a minimum of 20 teeth and had generalised moderate to severe chronic periodontitis which was defined as having ≥3 teeth with probing depth ≥5mm in each quadrant **Exclusion criteria** - congenital valve defects or any other risk situation for infectious endocarditis - low levels of haematocrit or haemoglobin - high risk of cardiovascular disease and diabetes - allergy to macrolides - patients who had taken systemic antibiotics, anti-inflammatory drugs or immunosuppressive drugs within 3 months before the experiment - subjects receiving periodontal treatment within the previous 6 months - regularly used an oral irrigation device or mouthrinse

Bibliographic reference	**Morozumi T, Kubota T, Abe D, Shimizu T. (2010) Effects of irrigation with an antiseptic and oral administration of azithromycin on bacteraemia caused by scaling and root planning. Journal of Periodontology 81 (11): 1555-1563** ***[included in CG64]***
	- had an incompatible dentition (orthodontic bands, partial dentures, teeth unsuitable for extensive ultrasonic scaling **Other characteristics** Age in years, mean (SD) Control group: 55.4 (9.3) Azithromycin group: 56.9 (9.9) Gender, number male/female Control group: 8/2 Azithromycin group: 6/4
Number of Patients	N=30 Randomised to control, essential-oil containing antiseptic and oral azithromycin (10 subjects each)
Intervention	Azithromycin 500mg once a day 3 days before quadrant scaling and root planning was performed (n=10) The quadrant scaling and root planning was completed within 40 minutes. All clinical procedures were performed by one dentist. Subjects were requested not to brush their teeth and to consume only liquids for ≥2 hours before sampling to avoid the possibility of any toothbrushing or chewing-induced bacteraemia.
Comparison	No prophylaxis n=10
Length of follow up	1 week
Location	Japan
Outcomes measures and effect size	**1) Bacteremia levels/intensity: not reported** **2) Duration of bacteraemia: not reported** **3) Incidence of bacteraemia:** Baseline: control – 0/10, azithromycin – 0/10 After SRP: control – 9/10, azithromycin – 2/10
Source of funding	Grant in aid for young scientists from the Ministry of Education, Culture, Sports, Science and Technology
Comments	**Statistical analyses** Chi square/Fisher's exact tests **Assessment of bacteraemia** Blood was collected at baseline and 6 minutes after the initiation of scaling and root planning.

Bibliographic reference	**Morozumi T, Kubota T, Abe D, Shimizu T. (2010) Effects of irrigation with an antiseptic and oral administration of azithromycin on bacteraemia caused by scaling and root planning. Journal of Periodontology 81 (11): 1555-1563** ***[included in CG64]***
	Blood samples were inoculated into an anaerobic culture bottle that could both anaerobic and aerobic bacteria and immediately transported to the laboratory. Bottles were incubated and monitored over 6 days, any bottles signalled negative were discarded. Bottles that signalled positive were Gram stained and subcultured onto an appropriate plate. All plates were incubated up to 14 days and examined daily. Biochemical tests were performed. **Microbial identity** All isolates were facultative or obligate anaerobes. Organisms identified included alpha streptococcus, bete-streptococcus, streptococcus constellatus, streptococcus mutans, parvimonas micra, Peptostreptococcus anaerobius, Eubacterium spp, Eggerthella lenta, Fusobacterium nucleatum, Propionibacterium acnes and Actinomyces spp. **Study limitations assessed using GRADE risk of bias checklist** - Randomisation, blinding and concealment not described - Power calculation not reported

1 **Table 121**

Bibliographic reference	**Lockhart, PB., Brennan, MT., Sasser, HC., Fox, PC., Paster, BJ., Bahrani-Mougeot, FK. (2008). Bacteremia associated with toothbrushing and dental extraction. Circulation. 117: 3118-3125**
Study type	Double blind randomised controlled trial
Aim	To compare the incidence, duration, nature and magnitude of endocarditis-related bacteremia from single-tooth extraction and toothbrushing and to determine the impact of amoxicillin prophylaxis on single tooth extraction
Patient characteristics	**Inclusion criteria** - Patients presenting to urgent care service with the need for extraction of at least 1 erupted tooth **Exclusion criteria** - Fewer than 10 teeth - Use of systemic antibiotics within the previous 2 weeks - Need for antibiotic prophylaxis based on current practice guidelines - Active viral disease - Immunocompromised - Poorly controlled systemic disease - History of penicillin allergy - Temperature >100.5F - Facial cellulitis

Bibliographic reference	Lockhart, PB., Brennan, MT., Sasser, HC., Fox, PC., Paster, BJ., Bahrani-Mougeot, FK. (2008). Bacteremia associated with toothbrushing and dental extraction. Circulation. 117: 3118-3125
	- Manipulation of the gingival tissues (eg: chewing, toothbrushing) within one hour before the study **Other characteristics** 1. Age in years, mean (SD) Extraction-amoxicillin group: 39.7 (10.5) Extraction-placebo group: 40.5 (10.9) 2. Male, n (%) Extraction-amoxicillin group: 61 (64) Extraction-placebo group: 51 (53) 3. Ethnicity, n (%) Extraction-amoxicillin group: white – 18 (19), black – 73 (76), Hispanic – 3 (3), Other – 2(2) Extraction-placebo group: white – 23 (24), black- 73 (76), Hispanic – 1 (1), Other – 0 (0) 4. Diabetes, n (%) Extraction-amoxicillin group: 9 (9) Extraction-placebo group: 8 (8) 5. Surgery type, n (%) Extraction-amoxicillin group: simple – 83 (87), complex – 9 (9), missing – 4 (4) Extraction-placebo group: simple – 70 (73), complex – 18 (19), missing – 8 (8)
Number of Patients	N=290 Subjects randomised to the following groups: 1. Toothbrushing n=98 2. Single tooth extraction with amoxicillin prophylaxis n=96 3. Single tooth extraction with an identical placebo (placebo not defined) n=96 Power calculation: assuming a significance level of 0.05, 80 subjects per study arm would yield power of 90% to detect a difference in cumulative incidences of at least 20% (prior work suggested that the incidence of bacteraemia from single tooth extraction would range between 70% and 100%. No consenus available on incidence after toothbrushing).
Intervention	Amoxicillin prophylaxis according to AHA recommendations 1 hour before extraction

Bibliographic reference	**Lockhart, PB., Brennan, MT., Sasser, HC., Fox, PC., Paster, BJ., Bahrani-Mougeot, FK. (2008). Bacteremia associated with toothbrushing and dental extraction. Circulation. 117: 3118-3125**
Comparison	Identical placebo
Length of follow up	60 minutes after completion of brushing or extraction
Location	USA
Outcomes measures and effect size	**1) Bacteraemia levels/intensity: all analysed samples were below the detection threshold of 104 CFU per millilitre of blood** **2) Duration of bacteraemia: not reported as continuous outcome** **3) Incidence of bacteraemia** <u>Overall incidence</u> The overall incidence of bacteraemia at any of the 6 draws was 56% and 80% for the amoxicillin and placebo groups respectively* The highest incidence occurred at the time of the procedures; 79% (66/84) in placebo group and 56% (50/89) in amoxicillin group* *p value reported in study not for this specific comparison All baseline cultures negative apart from 3 – unclear which group <u>Incidence from endocarditis related species</u> All baseline samples in amoxicillin and placebo groups negative The cumulative incidence from all 6 draws was 33% and 60% in the amoxicillin and placebo groups The highest incidence of positive cultures occurred in the first 5 minutes; 33% (29/89) and 58% (49/84) for amoxicillin and placebo groups. The extraction placebo group had a greater incidence of positive cultures at 20 minutes; 10% (8/83) vs 1% (1/88) in the amoxicillin group. Pattern persisted to 40 minutes
Source of funding	Supported by National Institute of Dental and Craniofacial Research/National Institutes of Health grant
Comments	**Statistical analyses** - For analysis of incidence, each patient was assessed at each blood draw and coded as positive for any bacterium that was common to the list of 275 bacterial species reported to cause IE. Comparison by study arm at each blood draw and a summary comparison by study arm that combined all draws were made with Chi square tests. - Duration of bacteraemia was defined as the number of blood draws at which any target organism was cultured. - Intercurrent negative findings were rare (n=2), were judged to be spurious and were considered positive for analysis. - Duration of specific intervals by study arm was compared with x2 tests. - Statistical significance of 0.05 was used in all cases. **Assessment of bacteraemia**

Bibliographic reference	Lockhart, PB., Brennan, MT., Sasser, HC., Fox, PC., Paster, BJ., Bahrani-Mougeot, FK. (2008). Bacteremia associated with toothbrushing and dental extraction. Circulation. 117: 3118-3125
	- Baseline blood samples before prophjylaxis drawn (20ml) and 7 to 8ml inoculated directly into both aerobic and anaerobic BACTEC bottles for bacterial culturing - Extraction began one hour after ingestion of amoxicillin or placebo - Brushing arm subjects brushed all surfaces of the teeth adjacent to the gingiva with a new toothbrush without toothpaste for 2 minutes, timed as 30 seconds for each of the maxillary and mandibular quadrants of teeth. - Subsequent blood draws of 20ml were taken at 1.5 minutes and at 5 minutes after the initiation of surgery or brushing. - Additional blood samples (20ml) were drawn at 20, 40 and 60 minutes after the end of the procedure. 2mls of blood was drawn into a new syringe and discarded before each of the 6 blood draws and the catheter was flushed with 2ml of saline from a new syringe after each blood draw. - Blood samples were cultured in BACTEC Plus Aerobic/F and LYTIC/10 Anaerobic/F. All false-positive bottles were further incubated for a total of 2 weeks. - Bottles with positive cultures were kept for 2 weeks and subcultured periodically to ensure recover of additional species. - The 16S ribosomal RNA sequencing method was used for bacterial identification. - Bacterial lysates were used as templates in PCR with 16S rRNA universal primers according to standard protocols. - Identification of strains was based on comparisons of the first 500 bases with Database Project and GenBank by BLAST. - For those strains that were potentially new species, full 1500-base pair sequences were obtained. - Investigators involved in bacterial culturing and identification were blinded as to subject randomisation. - Sensitive, real time quantitative PCR was used to quantify bacteria - Bacterial DNA was isolated from patient blood draws and from blood seeded with known quantities of several common oral pathogens. - For real time quantitative PCR, TaqMan technology and probes and universal 16S rRNA primers conserved among oral pathogens were used with the Smart Cycler system. Standard curves were established for the seeded pathogens and calculated the levels of bacteria in subject blood cultures. - The sensitivity of the method was 25 CFU per PCR, which corresponds to 103 to 104 CFU per millilitre of blood. **Microbial identity of organisms identified in study** a) overall nature of bacteraemia 98 different bacterial species, the most common which belonged to Streptococcus (49%), Prevotella (9%), Actinomyces (5%) and Fusobacterium (5%) b) nature of bacteraemia from endocarditis related bacterial species 10 (31%) of the 32 IE associated oral bacterial species were viridans streptococci. 13 (48%) of 27 positive cultures in the brushing group were viridans streptococci compared with 23 (49%) of 47 in the extraction-amoxicillin group and 106 (70%) of 151 in the extraction-placebo group. With the exception of one subject in the placebo group, polymicrobial blood cultures occurred within the first 5 minutes of the procedure – 2%, 6% and 29% in the brushing, extraction-amoxicillin and extraction-

Bibliographic reference	Lockhart, PB., Brennan, MT., Sasser, HC., Fox, PC., Paster, BJ., Bahrani-Mougeot, FK. (2008). Bacteremia associated with toothbrushing and dental extraction. Circulation. 117: 3118-3125
	placebo group respectively. **Study limitations: assessed using GRADE risk of bias checklist** - Although the incidence and duration of bacteraemia at various other time points are reported, this is in graphical form without accompanying numbers and therefore could not be extracted - Numbers bacteraemic at each time point not explicitly reported - Unclear whether same subjects bacteraemic at different time points

1 **Table 122**

Bibliographic reference	Harris A, Chan AC, Torres-Viera C et al. (1999) Meta-analysis of antibiotic prophylaxis in endoscopic retrograde cholangiopancreatography (ERCP). Endoscopy 31: 718-24
Study type	Meta-analysis
Aim	To synthesise the data from all published clinical trials of antibiotic prophylaxis in ERCP in order to determine whether antibiotic prophylaxis reduces the rate of occurrence of bacteraemia and cholangitis among patients undergoing ERCP
Patient characteristics	Clinical trials were identified Medline using “ERCP”, “antibiotic”, “antibiotic prophylaxis” as subject words and text words; bibliography reviews of relevant articles, and contacts with experts in the fields of gastroenterology and infectious disease, the search was not limited to the English language. A similar search was completed in Pubmed. **Inclusion:** RCTs, placebo controlled studies of the efficacy of antibiotic prophylaxis in ERCP using oral or intravenous antibiotics. All studies included adult patients who underwent diagnostic or therapeutic ERCP and had a variety of underlying pathologies. **Exclusion:** studies in which patients had received other antibiotics in addition to prophylaxis, were diagnosed with sepsis or cholangitis prior to ERCP
Number of Patients	4 RCTs of relevance to this review question (n=478)
Intervention	Antibiotic prophylaxis for ERCP
Comparison	Placebo
Length of follow up	Various
Location	Various
Outcomes measures and effect size	Bacteraemia 4 studies reported bacteraemia, the RR in those receiving antibiotics compared with those receiving the placebo was NS; RR: 0.39 (0.12 to 1.29); p=0.12; Q test: 4.3 (p=0.23) Q test for heterogeneity was 4.3 with P 0.23; ‘little heterogeneity’

Bibliographic reference	**Harris A, Chan AC, Torres-Viera C et al. (1999) Meta-analysis of antibiotic prophylaxis in endoscopic retrograde cholangiopancreatography (ERCP). Endoscopy 31: 718-24**
Source of funding	Not reported
Comments	**Study characteristics**

Study	Study design	Treatment	Inclusion criteria	Exclusion criteria
Sauter et al., 1990	RCT (n=100)	Cefotaxime 2g i.v. 15 mins before ERCP	Unselected	History of endocarditis or valvular heart disease, history of allergy to antibiotics, antibiotic therapy less than a week before ERCP, outpatient ERCP
Niederau et al., 1994	RCT (n=100)	Cefotaxime 2g i.v. 15 mins before ERCP	Any patient having an ERCP	History of endocarditis or valvular heart disease, allergy to antibiotics, antibiotic less than 48 hours before ERCP, patient with signs of cholangitis, refusal to participate
Finkelstein et al., 1996	RCT (n=179)	Cefonicid 1g i.v. 1 hour before ERCP	Age > 18 years, written consent	Allergies to beta-lactams, sepsis, ascending cholangitis a week before ERCP or antibiotic therapy 72 hours before ERCP
Lorenz et al., 1996	RCT (n=99)	Cefuroxime 1.5g i.v. 30 mins before ERCP	Any patient having an ERCP or percutaneous transhepatic cholangiography	Not indicated

Statistical analyses

Bibliographic reference	Harris A, Chan AC, Torres-Viera C et al. (1999) Meta-analysis of antibiotic prophylaxis in endoscopic retrograde cholangiopancreatography (ERCP). Endoscopy 31: 718-24
	Relative risks and 95%Cis for bacteraemia were calculated based on raw data reported in studies. Using the DerSimonian and Laird random effects model, summary estimates of the risk ratios were calculated. A statistical test of homogeneity was done using the method of DerSimonian and Laird which produced a Q statistic. **Study limitations assessed using checklist from NICE guidelines manual 2012** Overall quality of individual studies assessed but not reported Unclear whether any subjects were bacteraemic before procedure in the individual studies

1 **Table 123**

Bibliographic reference	Rolando N, Gimson A, Philpott-Howard J et al. (1993) Infectious sequelae after endoscopic sclerotherapy of oesophageal varices: role of antibiotic prophylaxis. Journal of Hepatology 18: 290-4
Study type	RCT
Aim	To determine the incidence of infection following sclerotherapy and the role of antimicrobial prophylaxis
Patient characteristics	**Inclusion:** patients admitted for sclerotherapy for bleeding oesophageal varicies **Exclusion:** <18yrs, pregnant women, antimicrobials within the preceding 72hrs, history of allergy to imipenem/cilastatin **Other characteristics** Age in years, median (range) Antibiotic group: 54 (20 to 76) Control group: 46 (18 to 84) Gender, number male/female Antibiotic group: 30/17 Control group: 24/26 Groups were comparable for age, sex, encephalopathy grade, ascites and biochemical parameters
Number of Patients	n = 97 (n = 115 emergency endoscopy/sclerotherapy sessions and 80 routine endoscopy/sclerotherapy sessions)
Intervention	IV imipenem/cilastatin over 20min n = 47

Bibliographic reference	**Rolando N, Gimson A, Philpott-Howard J et al. (1993) Infectious sequelae after endoscopic sclerotherapy of oesophageal varices: role of antibiotic prophylaxis. Journal of Hepatology 18: 290-4**
Comparison	Control IV dextrose-saline n = 50
Length of follow up	Blood cultures taken up to 30 minutes post procedure
Location	London
Outcomes measures and effect size	**1) Bacteraemia levels/intensity: not reported** **2) Duration of bacteraemia: not reported** **3) Incidence of bacteraemia** n = 2/97 bacteraemia in the pre-endoscopy samples (excluded in the analysis for efficacy of prophylaxis) Early bacteraemia (isolation of any pathogen from cultures taken 30-min post-sclerotherapy without clinical signs of infection and with a negative blood culture taken before sclerotherapy); n = 1/57 (1.8%) sessions imipenem/cilastatin group; n = 5/58 (8.6%) sessions control group, NS difference (organisms; Staphylococcus aureus, Eschericha coli, Enterobacter cloacae, Xanthomonas maltophilia) Clinical bacteraemia (isolation of any pathogen from blood cultures with clinical signs of infection) was detected in n = 8 patients in the first 4days after sclerotherapy and occurred in equal numbers in both groups (organisms; Staphylococcus aureus, Staphylococcus epidermis, Escherichia coli, Kledsiella pneumoniae) – denominator unclear There were no adverse reactions to the antibiotic in the 50 patients that received any dose of this.
Source of funding	Merck, Sharpe & Dohme Ltd
Comments	**Statistical analyses** Chi square tests were performed with appropriate corrections for small numbers. **Assessment of bacteraemia** Blood samples were taken before and immediately after each endoscopic procedure and inoculated into aerobic and anaerobic blood culture bottles. Blood culture bottles examined twice a day for the first 2days and daily for a further 5days; analysed using conventional microbiological techniques. **Microbial identity** See results section **Study limitations assessed using GRADE risk of bias checklist** - Concealment and blinding not described

Bibliographic reference	Rolando N, Gimson A, Philpott-Howard J et al. (1993) Infectious sequelae after endoscopic sclerotherapy of oesophageal varices: role of antibiotic prophylaxis. Journal of Hepatology 18: 290-4
	- Denominator unclear for clinical bacteraemia cases - Power calculation not reported

1 **Table 124**

Bibliographic reference	Shanson DC, Cannon P, Wilks M. Amoxicillin compared with penicillin V for the prophylaxis of dental bacteremia Journal of Antimicrobial Chemotherapy 1978;4:431-436
Study type	Prospective cohort
Aim	To compare amoxicillin with penicillin V, given as a 2g oral dose 1 hour before extraction for the prophylaxis of dental bacteremia. Also, to compare the serum antibiotic levels of each drug after the 2g dose.
Patient characteristics	**Inclusion** - Healthy, non-fasting adults attending the outpatient department for dental extraction **Exclusion:** not reported **Other characteristics** Not reported
Number of Patients	n = 120 adults; 40 patients in each group
Intervention	Penicillin V, 2g given as eight 250mg tablets (n=40) or amoxicillin, 2g given as eight 250mg capsules administered under supervision 1 hour before extraction
Comparison	No antibiotic (n=40)
Length of follow up	Not reported
Location	London
Outcomes measures and effect size	**1) Bacteraemia levels/intensity: not reported** **2) Duration of bacteraemia: not reported** **3) Incidence of bacteraemia** <u>Streptococcal bacteraemia post extraction</u> 16/40 (40%) in control group; 5/40 (12%) in penicillin V group; 2/40 (5%) in amoxicillin group <u>Anaerobic bacteraemia</u> 10/20 (50%) in control group; 4/20 (20%) in penicillin V group; 3/20 (15%) in amoxicillin group

Bibliographic reference	**Shanson DC, Cannon P, Wilks M. Amoxicillin compared with penicillin V for the prophylaxis of dental bacteremia Journal of Antimicrobial Chemotherapy 1978;4:431-436**
	Bacteraemia due to aerobes or anaerobes 14/20 (70%) in control group; 4/20 (20%) in penicillin V group (20%); 5/20 (25%) amoxicillin group **4) Side-effects** None reported
Source of funding	Note reported
Comments	**Statistical analyses** Not reported **Assessment of bacteraemia** - Blood cultures were collected 2 mins after extraction and added to each aerobic and anaerobic bottle - Cultures were incubated and bacteria present determined **Microbial identity** - Penicillin V or amoxicillin assays were determined by plate diffusion methods with the Oxford staphylococcus or Bacillus subtlis, surface seeded onto Difco No.2 antibiotic assay medium **Study limitations: assessed using GRADE risk of bias checklist** - Number bacteraemic at baseline not reported (unclear if subjects were tested) - Power calculation not reported - Baseline characteristics not reported

G.8 Review question 7b

Table 125

Bibliographic reference	**Maharaj, B., Coovadia, Y., Vayej, AC. (2012). A comparative study of amoxicillin, clindamycin and chlorhexidine in the prevention of post-extraction bacteraemia. Cardiovascular journal of Africa. 23 (9): 491-494**
Study type	Randomised controlled trial
Aim	To assess and compare the effectiveness of amoxicillin, clindamycin, and the oral antiseptic chlorhexidine in eliminating post-extraction bacteraemia in black patients.
Patient characteristics	**Inclusion criteria**

Bibliographic reference	Maharaj, B., Coovadia, Y., Vayej, AC. (2012). A comparative study of amoxicillin, clindamycin and chlorhexidine in the prevention of post-extraction bacteraemia. Cardiovascular journal of Africa. 23 (9): 491-494
	- Adult black patients attending the dental clinic - Healthy - No history of cardiovascular disease - Had not received antibiotics in the previous 2 weeks - Not allergic to penicillin **Exclusion criteria** - Any patient found to have a dental abscess or who required the extraction of more than one tooth **Other characteristics** Males, n/N (%): chlorhexidine – 8/40 (20%), control – 12/40 (30%) Females, n/N (%): chlorhexidine – 32/40 (80%), control – 28/40 (70%) Age in years, mean (range): chlorhexidine – 28 (18 to 55), control – 32.1 (18 to 60)
Number of Patients	160 randomised to 4 groups (no therapy, chlorhexidine, amoxicillin or clindamycin) of 40 subjects each.
Intervention	Subjects rinsed their mouths vigorously with 10ml of 0.2% chlorhexidine for one minute and expectorated. Procedure repeated one minute later. Treatment was given one hour prior to dental extraction*. *dental extraction: only one tooth was extracted per patient. The same dental surgeon performed the procedure using dental forceps. No surgical procedures were used in any patient.
Comparison	No chlorhexidine prophylaxis: no therapy prior to dental extraction
Length of follow up	Not reported, post-extraction bacteraemia assessed based on blood sample drawn 3 minutes after extraction.
Location	South Africa
Outcomes measures and effect size	**1.Bacteraemia levels/intensity:** not reported **2. Duration of bacteraemia:** not reported **3. Incidence of positive blood culture after* dental extraction, n (%)** 0.2% chlorhexidine group: 16 (40) Control group: 14 (35) *blood drawn 3 minutes post extraction, before extraction data not reported
Source of funding	Not reported
Comments	**Statistical analysis** - Results in each group were arranged in a contingency table an analysed using Fisher's exact test - To analyse difference between control vs antibiotic groups and between antiseptic vs antibiotic group, the Chi Square test

Bibliographic reference	Maharaj, B., Coovadia, Y., Vayej, AC. (2012). A comparative study of amoxicillin, clindamycin and chlorhexidine in the prevention of post-extraction bacteraemia. Cardiovascular journal of Africa. 23 (9): 491-494
	was used, employing Yates correction for continuity - Power calculation not reported **Assessment of bacteraemia** - The skin at the site of the venepuncture was prepared using 0.5% chlorhexidine in 70% alcohol - 8-10ml of blood was drawn 3 minutes after the extraction in each patient - 3 to 5ml blood was injected into BACTEC blood culture vials - Blood culture bottles transported to Microbiology Department within 2 hours of collection - The blood culture vials were tested on days 1, 3, 5 and 7 and positive vials were sub-cultured and Gram stained smears were prepared - The aerobic vials were sub-cultured onto chocolate, blood and MacConkey agar plates which were inoculated for 48 hours in air plus 10% carbon dioxide. - The anaerobic vials were sub-cultured onto 10% blood agar plates with and without amikacin and incubated for 48 to 72 hours in anaerobic gas pak. - The organisms isolated were identified using conventional laboratory methods and the identity of streptococcal isolates was confirmed using the API Strep 20 system. **Microbial identity** A range of microbes were identified including Streptococcus mitis, Streptococcus sanguis, Streptococcus anginosus, Viridans Streptococci, Streptococcus pneumonia, Staphylococcus epidermis, Enterococcus faecalis, Neisseria species, Corynebacterium species, Gram negative bacilli, Moraxella species, Peptostreptococcus species, Prevotella melaninogenica, Eikenella corrodens, Gemella haemolysins and mixed growth. **Study limitations: assessed using GRADE risk of bias checklist** - Allocation concealment not described - Blinding not described - Number of positive blood cultures before extraction not reported – unclear if subjects were tested for bacteraemia - Power calculation not reported

1 **Table 126**

Bibliographic reference	Pineiro, A., Tomas, I., Blanco, J., Alvarez, M. (2010). Bacteraemia following dental implants' placement. Clinical oral implants research. 21: 913-918
Study type	Randomised controlled trial
Aim	To investigate the prevalence, duration and aetiology of bacteraemias following the placement of dental implants as well as

Bibliographic reference	Pineiro, A., Tomas, I., Blanco, J., Alvarez, M. (2010). Bacteraemia following dental implants' placement. Clinical oral implants research. 21: 913-918
	the prophylactic efficacy of a chlorhexidine digluconate mouth rinse
Patient characteristics	**Inclusion criteria** - Patients suitable for oral rehabilitation using osseointegrated implants **Exclusion criteria** - Patients <18 years - Use of antibiotics in the previous 3 months - Routine use of oral antiseptics - Immunodeficiency - Any other disease that could predispose them to infections or bleeding complications **Other characteristics** Gender, n (%) Chlorhexidine group: male – 11 (55), female – 9 (45) Control group: male – 8 (26.7), female – 22 (73.3) Age in years, mean (SD) Chlorhexidine group: 56.9 (12.5) Control group: 55 (13.5) Duration of surgical procedure, n (%) <60 minutes: chlorhexidine group – 3 (15), control group – 12 (40) 60 to 120 minutes: chlorhexidine group – 17 (85), control group – 18 (60) p=0.069
Number of Patients	N=50 0.2% chlorhexidine mouth rinse: n=20 Control group: n=30
Intervention	0.2% chlorhexidine (10ml for 1 min, Oraldine Perio, Johnson and Johnson) mouth rinse before surgery* and before the injection of local anaesthesia *all patients received intravenous sedation with midazolam and propofol , together with infiltrative local anaesthesia by injection of 2% lidocaine with epinephrine. A supracrestal mucosal incision was made and a full-thickness mucoperiosteal flap was lifted to expose the bone surface. All treatments performed by the same dental surgeon.

<table>
<tr><td>Bibliographic reference</td><td>Pineiro, A., Tomas, I., Blanco, J., Alvarez, M. (2010). Bacteraemia following dental implants' placement. Clinical oral implants research. 21: 913-918</td></tr>
<tr><td>Comparison</td><td>No prophylactic intervention before surgery</td></tr>
<tr><td>Length of follow up</td><td>Not reported, measurements up to 15 minutes following procedure</td></tr>
<tr><td>Location</td><td>Spain</td></tr>
<tr><td>Outcomes measures and effect size</td><td>1.Bacteraemia levels/intensity: not reported
2. Duration of bacteraemia: not reported
3. Incidence of positive blood culture before and after implant placement: see data at different time points in table below
<table>
<tr><td></td><td>Chlorhexidine group, n(%)</td><td>Controls, n(%)</td></tr>
<tr><td>Bacteraemia at baseline</td><td>0 (0)</td><td>1 (3.3) Streptococcus viridans (anginosus group)</td></tr>
<tr><td>Bacteraemia at 30 seconds following implant placement</td><td>0 (0)</td><td>2 (6.7) Streptococcus viridans (mitis group), Neisseria cinerea</td></tr>
<tr><td>Bacteraemia at 15 minutes following implant placement</td><td>0 (0)</td><td>1** (3.3) Streptococcus viridans (mitis group)</td></tr>
<tr><td colspan="3">*'the differences between the control and chlorhexidine group were not statistically significant'
**same subject who also had bacteraemia at 30 seconds</td></tr>
</table></td></tr>
<tr><td>Source of funding</td><td>Supported by the Xunta de Galicia and Research Intensification</td></tr>
<tr><td>Comments</td><td>Statistical analyses
Fisher's exact test or the Chi Square test was used to compare nominal qualitative variables eg: gender. Fisher's exact test was also used to compare prevalence of bacteraemia at 30 seconds and 15 minutes after the implant procedure between the control group and the chlorhexidine group. P<0.05 was considered significant.

Assessment of bacteraemia
- After disinfection with alcohol and poidone iodine, an intravenous catheter was inserted into the antecubital fossa or on the dorsum of the hand using an angiocath.
- A peripheral venous blood sample (10ml) was collected from each patient before the start of the procedure to determine the prevalence of bacteraemia before the intervention (baseline)
- Further peripheral blood samples (10ml) were taken 30 seconds and 15 minutes after the procedure to determine the prevalence and duration of bacteraemia secondary to the implant placement
The venous canula was flushed with 3ml of saline after each blood collection and the first 2ml of blood drawn was discarded</td></tr>
</table>

Bibliographic reference	Pineiro, A., Tomas, I., Blanco, J., Alvarez, M. (2010). Bacteraemia following dental implants' placement. Clinical oral implants research. 21: 913-918
	- Each sample was inoculated into containers with aerobic and anaerobic culture media and immediately transported to the laboratory - Blood samples processed using Bactec 9240 - Gram stain performed on each positive blood culture - Positive aerobic blood cultures were subcultured on blood agar, chocolate agar and MacConkey agar in an aerobic atmosphere - The same protocol was used for positive anaerobic blood cultures including subculture on Schaedler agar incubated in an anaerobic atmosphere - The bacteria isolated were identified using biochemical tests provided by the Vitek system **Microbial identity** See table under 'outcomes measure and effect size' section **Study limitations: assessed using GRADE risk of bias checklist** - Randomisation not described - Allocation concealment not described - Blinding not described - Power calculation not reported

1 **Table 127**

Bibliographic reference	Duvall, NB., Fisher, TD., Hensley, D. (2013). The comparative efficacy of 0.12% chlorhexidine and amoxicillin to reduce the incidence and magnitude of bacteraemia during third molar extractions. Oral surgery, oral medicine and oral pathology. 115 (6): 752-763
Study type	Randomised controlled trial
Aim	To compare the incidence and magnitude of bacteraemia of a 0.12% chlorhexidine pre-procedure rinse to the AHA and the ADA/AAOS recommended 2g amoxicillin antibiotic prophylaxis during third molar extractions.
Patient characteristics	**Inclusion criteria** - Subjects presenting to the surgical centre, oral surgery clinic for third molar extractions under conscious sedation from June 2011 to December 2011 -ASA I or II: healthy, no systemic disease - Diagnosed/planned extraction #1, 16, 17, 32 under conscious sedation - #17 and 32 required a mucogingival flap for extraction - 18 years of age or older - Previously received penicillin and/or amoxicillin without a hypersensitivity or allergic reaction

Bibliographic reference	**Duvall, NB., Fisher, TD., Hensley, D. (2013). The comparative efficacy of 0.12% chlorhexidine and amoxicillin to reduce the incidence and magnitude of bacteraemia during third molar extractions. Oral surgery, oral medicine and oral pathology. 115 (6): 752-763**
	Exclusion criteria - ASA III or IV: poorly controlled systemic disease - Known penicillin, amoxicillin or cephalosporin drug allergy - Pregnant women - Current immunosuppressed status - Active viral disease - Cardiac anomalies or another condition/situation requiring pre- or intra-operative use of antibiotics - Antibiotic use within the previous two months - Steroid therapy within the previous two months - Chlorhexidine use or other oral antimicrobial rinses within the previous 2 months - The routine use of an oral antiseptic at home - Gingival tissue manipulation within 2 hours of the procedure - 7 of the original 37 eligible subjects were excluded due to technical reasons (complications during blood draws and/or unavailable microbiological lab support) **Other characteristics** <u>Age in years, mean (range)</u> 21.8 (18 to 29) No significant difference among treatment arms, p=0.473 <u>Gender, n</u> Male – 23 Female – 7 No significant difference among treatment arms, p=0.475 <u>Surgical procedure length in minutes, mean (range)</u> 42 (11 to 78) No significant difference among treatment arms, p=0.632
Number of Patients	N=30 10 subjects per placebo chlorhexidine and amoxicillin groups
Intervention	0.12% chlorhexidine rinse and a placebo capsule.

<table>
<tr><td>Bibliographic reference</td><td>Duvall, NB., Fisher, TD., Hensley, D. (2013). The comparative efficacy of 0.12% chlorhexidine and amoxicillin to reduce the incidence and magnitude of bacteraemia during third molar extractions. Oral surgery, oral medicine and oral pathology. 115 (6): 752-763</td></tr>
<tr><td></td><td>The 0.12% chlorhexidine rinse (PerioGuard Oral Rinse, Colgate Oral Pharmaceuticals) was administered immediately prior to conscious sedation medication administration. The subjects rinsed with with 15ml of the chlorhexidine rinse for one minute and expectorated.
The placebo capsule for both the intervention and control groups were administered with a small amount of water 1 hour prior to the procedure.</td></tr>
<tr><td>Comparison</td><td>Placebo rinse and a placebo capsule.
The placebo rinse (1000ml sterile water for irrigation, [USP, Baxter Healthcare], where blue dye and mint extract was added until a similar appearance, taste and smell was obtained compared to the 0.12% chlorhexidine rinse). This was also administered immediately prior to conscious sedation medication administration. The subjects rinsed with 15ml of the placebo rinse for one minute and expectorated.</td></tr>
<tr><td>Length of follow up</td><td>Not reported</td></tr>
<tr><td>Location</td><td>USA</td></tr>
<tr><td>Outcomes measures and effect size</td><td>1) Bacteraemia levels/intensity

<table>
<tr><th colspan="3">Total mean magnitude of bacteraemia</th></tr>
<tr><td></td><td>Total bacteraemia in cfu/ml, mean (SD)</td><td>Total bacteraemia range</td></tr>
<tr><td>Placebo (n=10)</td><td>3.61 (7.09)</td><td>0.0 to 18.20</td></tr>
<tr><td>Chlorhexidine (n=10)</td><td>2.76 (4.28)</td><td>0.0 to 11.10</td></tr>
</table>

<table>
<tr><th colspan="6">Mean magnitude of bacteraemia per blood draw</th></tr>
<tr><td></td><td>Blood draw 1, mean (SD)</td><td>Blood draw 2, mean (SD)</td><td>Blood draw 3, mean (SD)</td><td>Blood draw 4, mean (SD)</td><td>P value</td></tr>
<tr><td>Placebo (n=10)</td><td>0 (0)</td><td>1.26 (3.67)</td><td>1.90 (5.36)</td><td>0.45 (0.83)</td><td>0.031</td></tr>
<tr><td>Chlorhexidine (n=10)</td><td>0.04 (0.13)</td><td>0.18 (0.29)</td><td>2.37 (4.11)</td><td>0.17 (0.24)</td><td>0.062</td></tr>
</table>

2) Duration of bacteraemia: not reported
3) Incidence of bacteraemia: defined as at least one positive culture of the four blood draws per subject and reported as n/N (%)
Placebo group: 5/10 (50)
Chlorhexidine group: 6/10 (60)
*P value not reported for the above comparison but for the comparison between all 3 groups in the study (amoxicillin, placebo</td></tr>
</table>

Bibliographic reference	**Duvall, NB., Fisher, TD., Hensley, D. (2013). The comparative efficacy of 0.12% chlorhexidine and amoxicillin to reduce the incidence and magnitude of bacteraemia during third molar extractions. Oral surgery, oral medicine and oral pathology. 115 (6): 752-763**
	and chlorhexidine) was 0.670
Source of funding	Funding provided by the 59th Clinical Research Training Division, Lackland, AFB, TX
Comments	**Statistical analyses** Incidence of bacteraemia analysed via Chi-square tests Magnitude of bacteraemia analysed using the non-parametric Kruskal-Wallis test and the Friedman test with Bonferroni correction applied as there were multiple comparisons between the groups **Assessment of bacteraemia** - Once the IV access line was established, the first blood draw was completed at baseline - A second IV access line for the conscious sedation medications was obtained in the opposite arm in a similar manner after the blood draw IV access line was obtained, blood draw 1 was collected and the placebo or amoxicillin capsules were administered. - The third molar extractions was completed in the order of #1, 32, 16 and 17. - Blood draw 2 was completed 1.5 minutes following initiation of the mucogingival flap #32, blood draw 3 was completed 1.5 minutes following initiation of the mucogingival flap #17 and blood draw 4 was completed 10 minutes following initiation of the mucogingival flap #17 - The 4 blood samples per subject were transported to an on-site microbiology laboratory for immediate processing. All blood samples were processed within 4 hours of blood draw 1. - The bacterial concentrate was removed with an Isostat concentrate pipet and distributed equally onto 3 different agar plates: Trypticase soy agar with 5% sheep blood (incubated aerobically), chocolate agar (incubated aerobically) and Brucella blood agar (incubated anaerobically) - Colonies were counted and grouped by colonial morphology. Haemolytic reaction was recorded for colony types growing on Trypticase soy agar. - Following primary isolation, each colony type was subcultured to Trypticase soy agar or Brucella blood agar to obtain a pure culture and verify the required environmental growth conditions - A gram stain was performed on each pure culture with bacterial isolate identification accomplished using the VITEK 2 Compact bacterial identification system or the Biolog Microsation System **Microbial identity** - 33 different bacterial species were isolated among the placebo, chlorhexidine and amoxicillin groups - There were 24 different bacterial species isolated in the placebo group, 15 isolated in the chlorhexidine group and 10 isolated in the amoxicillin group - Of the 33 different bacterial species, 7 (21%) were alpha-hemolytic and also belonged to the viridans group streptococci. In the placebo group, 5 bacterial species isolated were alpha-hemolytic/viridans group streptococci, two isolated in the

Bibliographic reference	**Duvall, NB., Fisher, TD., Hensley, D. (2013). The comparative efficacy of 0.12% chlorhexidine and amoxicillin to reduce the incidence and magnitude of bacteraemia during third molar extractions. Oral surgery, oral medicine and oral pathology. 115 (6): 752-763**
	chlorhexidine group and one isolated in the amoxicillin group. **Study limitations: assessed using GRADE risk of bias checklist** - Blinding not described, insufficient information to judge whether subjects and/or assessors were blind - Incidence of positive blood cultures at baseline not reported separately but together with incidence at any of the blood draws - Power calculation not reported

1 **Table 128**

Bibliographic reference	**Tuna, A., Delilbasi, C., Arslan, A., Gurol, Y., Tekkanat, ZT. (2012). Do antibacterial mouthrinses affect bacteraemia in third molar surgery? A pilot study. Australian dental journal. 57: 435-439**
Study type	Randomised controlled trial
Aim	To evaluate the effects of mouthrinses containing 0.2% chlorhexidine and 7.5% povidone iodine on bacteraemia following impacted third molar surgery
Patient characteristics	**Inclusion criteria** - Patients who underwent surgical removal of impacted mandibular third molar under local anaesthesia - Aged over 18 years - Requiring surgical removal of a third molar - Neither any systemic disorder nor any signs or symptoms of pericoronitis at the time of surgery nor during the previous month - No known risk factor for bacterial endocarditis - Received no antibiotic treatment during the previous 30 days - Was not using routine oral antiseptic mouthrinse nor suffering any type of congenital or acquired immunodeficiency - No other disease or condition which could predispose to infections or bleeding **Exclusion criteria** - Patients with an oral hygiene index and gingival bleeding index higher than 10% - Those with the presence of bacteraemia in preoperative blood culture **Other characteristics** Gender, n female; n male Chlorhexidine: 8;4 Controls: 5;5 p=0.451 (including povidone-iodine group data as well)

<table>
<tr><td>Bibliographic reference</td><td>Tuna, A., Delilbasi, C., Arslan, A., Gurol, Y., Tekkanat, ZT. (2012). Do antibacterial mouthrinses affect bacteraemia in third molar surgery? A pilot study. Australian dental journal. 57: 435-439</td></tr>
<tr><td></td><td><u>Age in years, mean (SD)</u>
Chlorhexidine: 27.7 (10.01)
Controls: 27.0 (8.30)
p=0.971 (including povidone-iodine group data as well)

<u>Operation time in minutes, mean (SD)</u>
Chlorhexidine: 23.1 (9.05)
Controls: 20.0 (13.30)
p=0.670 (including povidone-iodine group)</td></tr>
<tr><td>Number of Patients</td><td>N=38* randomised to the following groups:
1. Chlorhexidine group: n= 12
2. Povidone iodine group: n=12
3. Control group (NaCl sterile saline): 10
*4 (from 38 randomised) excluded (2 subjects from the control group due to injury of the venous pathway during the insertion of the angiocath and further 2 subjects from the chlorhexidine group due to presence of bacteraemia in the preoperative blood culture).</td></tr>
<tr><td>Intervention</td><td>Subjects were asked to rinse the mouth with 15ml 0.2% chlorhexidine mouthrinse for one minute following blood collection, before the surgical procedure*. Patients were supervised during mouthrinsing to ensure they were using the mouthrinse appropriately.

* surgical removal of impacted mandibular third molar under local anaesthesia (the indications for extractions were pericoronitis reported by the patient and/or the dentist (excluding patients who had experienced some episode in the month prior to enrolment) and extractions for non-infective reasons</td></tr>
<tr><td>Comparison</td><td>Subjects were asked to rinse the mouth with 0.9% NaCl (sterile saline) solution.</td></tr>
<tr><td>Length of follow up</td><td>Not reported, blood samples up to 15 minutes post-extraction</td></tr>
<tr><td>Location</td><td>Turkey</td></tr>
<tr><td>Outcomes measures and effect size</td><td>1) Bacteraemia levels/intensity: not reported
2) Duration of bacteraemia: not reported
3) Incidence of bacteraemia
<table>
<tr><td></td><td>Chlorhexidine group, n (%)</td><td>Control group, n(%)</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Tuna, A., Delilbasi, C., Arslan, A., Gurol, Y., Tekkanat, ZT. (2012). Do antibacterial mouthrinses affect bacteraemia in third molar surgery? A pilot study. Australian dental journal. 57: 435-439**

Bacteraemia present overall	4 (33)	5 (50)
Bacteraemia at 1st minute	3 (25)	4 (40)
Bacteraemia at 15th minute	2 (17)	3 (30)
McNemar's p value	0.250	0.810

* A further p value is reported in the study for the comparison of all treatment groups (povidone-iodine, chlorhexidine and control group) as opposed to the comparison we are interested in for this question and has therefore not been extracted.

**Those with bacteraemia in preoperative blood culture were excluded (n=2 from chlorhexidine group)

Source of funding	Not reported
Comments	**Statistical analyses** - Descriptive statistics (mean, SD) are presented and the Kruskal-Wallis test was used to compare multiple groups - For two sample comparisons, the Mann-Whitney U test was used and for comparisons of qualitative data, the chi-square test and McNemar's test were used. Significance was set at p ≤0.05. **Microbial identity** The positive blood cultures displayed 58% anaerobic bacteria and 42% aerobic bacteria. 92% were Streptococcus bacteria. Among them, Streptococcus viridans was most frequently observed; 38% of the 24 bacteria were S.anginosus, 13% were S.salivarius and 13% S.mitis. Statistical analyses Descriptive statistics are presented and the Kruskal-Wallis test was used to compare multiple groups. For two sample comparisons, the Chi Square test and McNemar's test were used. Statistical significance was set at p ≤0.05. Method of bacteraemia assessment - Peripheral venous blood samples were collected from each patient at baseline (before injection of local anaesthesia), 1 minute and 15 minutes after completion of the extraction - Every blood sample comprised 20ml of blood which was divided into 2 bottles with anaerobic culture medium (10ml) and aerobic culture medium (10ml) - Altogether, 60ml of blood was obtained from each patient by a researcher blind to the details of the study - After each sample was drawn, the angiocath needle and the line were flushed with 3ml of saline. The bottles were transported immediately to the microbiology laboratory. - All blood cultures were processed in the BACTEC 9120 system. At the 7th day of incubation, samples which showed no production were subcultured on 5% sheep blood agar and chocolate agar; those which did not show any production were designated negative. Positive samples were subcultured on 5% sheep blood agar and chocolate agar. At the end of 24 hours

Bibliographic reference	Tuna, A., Delilbasi, C., Arslan, A., Gurol, Y., Tekkanat, ZT. (2012). Do antibacterial mouthrinses affect bacteraemia in third molar surgery? A pilot study. Australian dental journal. 57: 435-439
	of incubation, these samples were further subjected to further biochemical tests using the mini API kit in line with the recommendations of the American Society for Microbiology and bacteria were isolated. - Samples identified as positive by BACTEC 9120 but no microorganism detected with the Gram stain were accepted as false positives. **Study limitations: assessed using GRADE risk of bias checklist** - Allocation concealment not described - Blinded not described in detail: 'blinded researcher', unclear if subjects were blinded too - Unclear whether it's the same subjects bacteraemic at different time points (possible double counting of subjects) - Power calculation not reported

1 **Table 129**

Bibliographic reference	Brown AR, Papasian CJ, Shultz P, et al (1998) Bacteremia and intraoral suture removal: can an antimicrobial rinse help? Journal of the American Dental Association 129: 1455–61. *[included in CG64]*
Study type	Randomised controlled trial
Aim	To determine whether a relationship exists between the incidence of bacteraemia and suture removal especially in patients who experience bleeding at the surgical site and to quantify the inoculum. Also, to determine whether a 0.12% chlorhexidine rinse, performed before the removal of sutures, could reduce or eliminate bacteraemia.
Patient characteristics	**Inclusion** - Healthy patients requiring the removal of a third molar which would require at least 8 sutures, **Exclusion** - Patients with systemic disease - Taking steroids - Had used systemic antibiotics or oral rinses within the previous 4wks - Moderate-to-severe periodontitis or residual pericoronitis - Required preoperative prophylactic antibiotics - Patients were dropped from the study if they required antibiotic therapy during the postoperative week - Extraction sites developing alveolar osteitis after surgery were selectively dropped from recovered data but the patient and his or her remaining uninvolved sites were retained **Other characteristics** Gender, n Female – 37

Bibliographic reference	**Brown AR, Papasian CJ, Shultz P, et al (1998) Bacteremia and intraoral suture removal: can an antimicrobial rinse help? Journal of the American Dental Association 129: 1455–61. *[included in CG64]***
	Male – 24 <u>Age in years, range</u> 15 to 35
Number of Patients	- 71 randomised - 10 lost to follow-up (2 from experimental and 8 from control) - 6 additional subjects eliminated because of contaminated cultures - Therefore, 55 subjects analysed; 31 in experimental arm and 24 in control arm
Intervention	30 cubic centimetres of 0.12% chlorhexidine preprocedural rinse (Peridex) for 1 min (n=31) Interventional procedure: The third molars were removed by one of the 3 board-certified oral surgeons. All used similar flap designs and 3–0 black silk suture placement, used no medication in the sockets, nor did they use preoperative irrigation or rinses. Subjects returned for suture removal seven days after the extraction and were randomly assigned to one of two groups.
Comparison	No-treatment control (n=24)
Length of follow up	All plates examined daily for 7 days
Location	USA
Outcomes measures and effect size	**1) Bacteraemia levels/intensity**: not reported **2) Duration of bacteraemia**: not reported **3) Incidence of bacteraemia** Pre-treatment blood samples were all negative Post-treatment*: 4/31 in chlorhexidine group and 2/24 in control group had positive cultures, total incidence 10.9% There was NS difference in the proportion of bacteraemia with experimental vs. control groups; P>0.05 (Fisher's exact test) *Blood drawn 90 seconds after suture removal
Source of funding	Not stated
Comments	**Statistical analyses** - Fisher's exact test for comparison of proportion of bacteraemia between experimental and control groups - 90% power at p=0.05, n=55 was determined from results obtained from an initial pilot study **Assessment of bacteraemia** - The first 10ml of blood withdrawn for the pre-and postprocedural specimens was discarded - 90 seconds after suture removal, a second 10ml blood sample was obtained for culturing

Bibliographic reference	**Brown AR, Papasian CJ, Shultz P, et al (1998) Bacteremia and intraoral suture removal: can an antimicrobial rinse help? Journal of the American Dental Association 129: 1455–61. *[included in CG64]***
	- All specimens were placed in an aerobic/anaerobic culture medium and immediately transported to the laboratory - Specimens were promptly transferred to a lysis centrifugation collection tube and centrifuged for 30 minutes - Supernatant fluid was discarded and the entire pellet was used to inoculate chocolate agar, blood agar and LKV agar - All plates were examined daily for 7 days before negative results were reported - Organisms were identified using morphologic criteria and routine bacteriologic methods **Microbial identity** Facultative organisms, predominantly Streptococcus were present in all specimens. Two samples yielded anaerobic growth of either Prevotella or Peptostreptococcus. **Study limitations: assessed using GRADE risk of bias checklist** - Randomisation and allocation concealment not described - Blinding not described: the doctor performing suture removal was unaware of whether or not a patient had used a rinse. Unclear whether subjects were blinded. - (Missing data but sufficient reasons given) - Power calculation not reported

1 **Table 130**

Bibliographic reference	**Jokinen MA. Prevention of postextraction bacteremia by local prophylaxis. International Journal of Oral Surgery 1978;7:450-2. *[included in CG64]***
Study type	RCT
Aim	To investigate the effect of various local preventative methods for postextraction bacteraemia
Patient characteristics	**Inclusion:** patients from various departments of the hospital for a cleaning of the mouth or because of acute symptoms in the teeth or periodontal tissues indicating dental extraction **Exclusion:** those who had systemic chemotherapeutic medication during the 10 previous days **Other characteristics:** Gender, male: 74% Age in years: 16 to 75 There were no significant differences among the 4 groups in regard to sex or age of the patients
Number of Patients	n = 152, 38 subjects in each treatment arm
Intervention	Operative field isolation and disinfection with 0.5% chlorhexidine gluconate solution (n=38)

Bibliographic reference	**Jokinen MA. Prevention of postextraction bacteremia by local prophylaxis. International Journal of Oral Surgery 1978;7:450-2. *[included in CG64]***
	(The other 2 treatment arms in this study [1% iodine solution and operative field isolation and disinfection with 10% iodine solution] are not of interest to this review question). Interventional procedure: dental extraction performed under local anaesthesia. Operating time was 1 to 2 hours postprandially.
Comparison	Operative field isolation with sterile cotton rolls and saliva ejector (n=38) – saliva from gingival crevices, the surfaces of the teeth and from the surrounding gum was dried with an air syringe. During and about 10 minutes after extraction, the saliva ejector and cotton rolls were kept in place.
Length of follow up	Not reported
Location	Finland
Outcomes measures and effect size	**1) Bacteraemia levels/intensity:** not reported **2) Duration of bacteraemia:** not reported **3) Incidence of bacteraemia post extraction** Positive cultures; operative field in isolation n = 13/38, operative field isolation and disinfection with chlorhexidine n = 5/38, 13%
Source of funding	Not stated
Comments	**Statistical analyses** The chi-square method **Assessment of bacteraemia** - Immediately after extraction, the vein was punctured and blood began to flow into the first anaerobic bottle 30 to 60 seconds after the termination of the extraction - The bacteriologic determinations were made in the laboratory without the investigator having any knowledge of the nature of the individual samples (Jokinen 1970 referred to for further details of methods) **Microbial identity** 78% of the bacterial strains isolated from the positive cultures in the prophylactic groups were streptococci of the viridans type The strains isolated were most sensitive to chloramphenicol, ampicillin, erythromycin and penicillin

Bibliographic reference	**Jokinen MA. Prevention of postextraction bacteremia by local prophylaxis. International Journal of Oral Surgery 1978;7:450-2. *[included in CG64]***
	Study limitations: assessed using GRADE risk of bias checklist - Study design difficult to judge based on description given - Randomisation not described - Allocation concealment not described - Blinding of subjects not described - Blinding of subjects not described - Insufficient information to permit judgment of selective reporting (outcomes not pre-specified) - Incidence of bacteraemia before extraction not reported - Power calculation not reported

1 **Table 131**

Bibliographic reference	**Lockhart PB. An analysis of bacteremias during dental extractions. A double-blind, placebo-controlled study of chlorhexidine. Archives of Internal Medicine 1996;156:513-20 *[included in CG64]***
Study type	RCT, double blind
Aim	To determine the incidence and nature of bacteraemia during single tooth extraction in adults
Patient characteristics	**Inclusion:** study patients were selected consecutively from a large pool of outpatients who underwent dental extractions; >18yrs, no valvular heart disease, not pregnant, no infectious disease, no poorly controlled systemic disease or facial cellulitis or if the patient's risk classification was more than II based on the American Society of Anesthesiologists' criteria **Exclusion:** use of steroids or chlorhexidine during the previous 2mths, use of antibiotics during the previous 2wks, any manipulation of the gingiva (eg: brushing, eating) within 1hr of the extraction **Other characteristics** Gender, n 37 male, 37 women Age in years, mean (range) 37 (21 to 72) There was an equal distribution between maxillary and mandibular teeth
Number of Patients	82 eligible, 12 dropped out (technical reasons), therefore a total of 70 subjects

Bibliographic reference	**Lockhart PB. An analysis of bacteremias during dental extractions. A double-blind, placebo-controlled study of chlorhexidine. Archives of Internal Medicine 1996;156:513-20 *[included in CG64]***
	Power calculation: based on previous studies; a need of 70 patients to ensure statistical significance. Sample size of 35 per group would be sufficient for detecting a decrease in positive culture rate from 60% in the placebo group to 25% in chlorhexidine group, with 80% power at significance of 0.05.
Intervention	10ml 0.2% chlorhexidine hydrochloride (peridex) rinse for 30sec and expectorated, rinsing was repeated 1min later (n=37) Interventional procedure: dental extraction, all extractions were performed by one of three general practice dental residents with essentially equal skills.
Comparison	10ml placebo rinse(identical to chlorhexidine without active ingredient) for 30sec, rinsing was repeated 1min later (n=33)
Length of follow up	Not reported, measurements up to 3 minutes following extraction
Location	USA
Outcomes measures and effect size	**1) Bacteraemia levels/intensity:** not reported **2) Duration of bacteraemia** Not reported **3) Incidence of bacteraemia** There was NS difference between the 1 and 3min samples in either the incidence of blood cultures or between the chlorhexidine and the placebo groups; placebo group positive cultures in n = 31/33 (94%); chlorhexidine group n = 31/37 (84%); p=0.27
Source of funding	Not stated
Comments	**Statistical analyses** A chi-square or Fisher's exact test was performed on the data **Assessment of bacteraemia** - The first blood draw of 20ml began at 1 minute following initiation of surgery - A second drawing of 20ml was begun at the 3 minute mark - A blood specimen was drawn into a separate syringe continuously between the two 20ml drawings and discarded - Any additional extractions were performed after the completion of the 2nd blood drawing - Blood specimens were processed and tested on a blood culture system – BACTEC 660 for 5 days until yields were positive - Blood culture bottles that were flagged as positive were gram stained - If microorganisms were found in the aerobic bottle, the mixture was subcultured onto separate plates - Identification of gram positive organisms was performed using conventional and chromogenic tests - Gram negative organisms were identified using biochemical tests

Bibliographic reference	**Lockhart PB. An analysis of bacteremias during dental extractions. A double-blind, placebo-controlled study of chlorhexidine. Archives of Internal Medicine 1996;156:513-20 *[included in CG64]***
	Microbial identity The majority of organisms at the 1 and 3min samples were gram-positive cocci, with a predominance of Streptococci viridans and α-haemolytic pyogenic streptococci **Study limitations: assessed using GRADE risk of bias checklist** - Numbers in each group not explicitly stated, calculated by reviewer based on %'s reported in study - Incidence of bacteraemia at baseline not reported, subjects not tested

1 **Table 132**

Bibliographic reference	**MacFarlane TW, Ferguson MM, Mulgrew CJ. Post-extraction bacteremia : role of antiseptics and antibiotics. Br Dent J 1984;156:179-81. *[included in CG64]***
Study type	RCT
Aim	To test the effect of two different topical antiseptics, chlorhexidine and povidone-iodine on reducing bacteraemia consequent to tooth extraction. In addition, the antibiotic sensitivity of the microorganisms isolated from the bacteremia was tested against 8 antibiotics.
Patient characteristics	**Inclusion:** patients attending the department of oral surgery for tooth extraction, 16 to 70 years of age, had normal medical history and required an uncomplicated extraction of a single premolar or first or second molar tooth under local anaesthetic, extractions were confined to lower teeth in order to reduce variability **Exclusion:** cases of gross decay, advanced periodontal disease, or dental abscess with facial swelling, a history of antibiotic therapy during the previous 3mths **Other characteristics** The groups were matched for age and sex, and the ratios of premolar to molar teeth in each group were similar
Number of Patients	n = 60
Intervention	n = 20, 10mls 1% chlorhexidine solution n = 20, 10mls 1% povidine-iodine (not of interest to this review question) Solutions irrigated the gingival crevice through a blunted needle, the patient was asked to retain the solution in the mouth for 2mins before rinsing out

<table>
<tr><td>Bibliographic reference</td><td>MacFarlane TW, Ferguson MM, Mulgrew CJ. Post-extraction bacteremia : role of antiseptics and antibiotics. Br Dent J 1984;156:179-81. [included in CG64]</td></tr>
<tr><td>Comparison</td><td>n = 20, 10mls normal saline</td></tr>
<tr><td>Length of follow up</td><td>Not reported, cultures subcultured up to 8 days after initial collection</td></tr>
<tr><td>Location</td><td>Glasgow</td></tr>
<tr><td>Outcomes measures and effect size</td><td>1) Bacteraemia levels/intensity: not reported
2) Duration of bacteraemia: not reported
3) Incidence of bacteremia (positive cultures) pre- and post-extraction
<table>
<tr><th>Irrigant</th><th>Pre extraction, number positive</th><th>30 seconds post extraction, number positive</th></tr>
<tr><td>Saline</td><td>0/20</td><td>16/20</td></tr>
<tr><td>Chlorhexidine</td><td>0/20</td><td>5/20</td></tr>
<tr><td></td><td></td><td>chlorhexidine vs controls p<0.001</td></tr>
</table></td></tr>
<tr><td>Source of funding</td><td>Not stated</td></tr>
<tr><td>Comments</td><td>Statistical analyses
Chi square test
Assessment of bacteraemia
- Venous blood (10ml) was removed via an indwelling intravenous cannula immediately before and 30 seconds after tooth extraction
- Part of the culture was incubated into a diphasic culture medium for aerobic growth and the other half inoculated into thioglycollate broth
- The samples were immediately sent to the laboratory for incubation and subcultured on days 1, 4 and 8 after initial collection
- Pure cultures of all bacteria were prepared and identified using standard techniques after which the antibiotic sensitivity of each isolate was assessed according to the Stokes method

Microbial identity
46 isolates; anaerobic streptococci (n = 11), Streptococcus sanguis (n = 8), Streptococcus mitior (n = 5), Streptococcus mutans (n = 6), Diptheroids (n = 3), other n = 2 or less

Study limitations: assessed using GRADE risk of bias checklist
- Study design not described in detail, assumption is that it is an RCT
- Randomisation, allocation concealment and blinding not described
- Power calculation not reported</td></tr>
</table>

1 **Table 133**

Bibliographic reference	**Rahn R, Schneider S, Diehl O, Schafer V, Shah PM. Preventing post-treatment bacteremia: comparing topical povidone-iodine and chlorhexidine.[see comment]. Journal of the American Dental Association 1995;126:1145-9** ***[included in CG64]***
Study type	RCT Single-blind
Aim	To determine whether irrigation of the gingival sulcus with one of two antiseptic solutions would affect the incidence and type of bacteraemia after dental treatment
Patient characteristics	**Inclusion:** those who were scheduled for dental treatment involving either intraligamental injection (n = 60), or elective extraction of a molar (n = 60) **Exclusion:** those receiving antibiotics or immunosuppressive therapy or who had a history of bacterial endocarditis, rheumatic fever or congenital heart disease **Other characteristics** Gender n = 28 female, 92 male Age in years, mean (range) 33.6 (22 to 77) The mean oral hygiene scores and periodontal scores (plaque index, gingival index, sulcus bleeding index, clinical pocket depth) were similar among the patients of all three groups
Number of Patients	n = 120, 40 in each of the three arms (chlorhexidine, povidone-iodine and control)
Intervention	0.2% chlorhexidine solution [Corsodyl Losung] (n=40) The above solution was delivered Into the sulcus of the affected tooth with an endodontic syringe, the solution was left in place for 2 minutes
Comparison	n = 40 control sterile water
Length of follow up	Not reported, blood samples drawn up to 6 minutes after procedure
Location	Germany
Outcomes measures and effect size	**1) Bacteraemia level/intensity:** not reported **2) Duration of bacteraemia:** not reported **3) Incidence of bacteraemia** - The blood samples obtained before the dental procedure were completely negative for bacteraemia in all groups - Post-procedure bacteraemia; control (n = 21/40, 52.5%), chlorhexidine (n = 18/40, 45.0%); NS difference chlorhexidine vs

Bibliographic reference	**Rahn R, Schneider S, Diehl O, Schafer V, Shah PM. Preventing post-treatment bacteremia: comparing topical povidone-iodine and chlorhexidine.[see comment]. Journal of the American Dental Association 1995;126:1145-9 *[included in CG64]***
	control
Source of funding	Mundipharma/Limburg
Comments	**Statistical analyses** The chi-square test **Assessment of bacteraemia** - Four 10ml blood samples were drawn from each patient by the physician before the dentist administered the antiseptic, and at 2, 4 and 6 minutes after the dental procedure was finished - The blood samples were inoculated into blood culture bottles (BACTEC 6A and 7A, Becton-Dickinson) and the bottles were processed as recommended by the American Society for Microbiology. - All microorganisms were identified by standard identification procedures **Microbial identity** - A total of 206 organisms; 87 in the control group, 42 in the iodine group and 77 in the chlorhexidine group - Viridans streptococci was detected in 13 cultures of the control group and 14 of the chlorhexidine group **Study limitations: assessed using GRADE risk of bias checklist** - Randomisation not described - Allocation concealment not described - Single blind only, details not described - Unclear whether the same subjects were bacteraemia at the 2, 4 and 6 minute cultures as data presented together - Power calculation not reported

1 **Table 134**

Bibliographic reference	**Tomas I, Alvarez M, Limeres J, Tomas M, Medina J, Otero JL et al. Effect of a chlorhexidine mouthwash on the risk of postextraction bacteremia. Infection Control & Hospital Epidemiology 2007;28:577-82 *[included in CG64]***
Study type	RCT
Aim	To investigate the prevalence, duration and etiology of bacteraemia following dental extractions performed after a single administration of chlorhexidine mouthwash
Patient characteristics	**Inclusion:** patients with mental and behavioural disabilities who underwent dental extractions under general anaesthesia. **Exclusion:** use of antibiotics in the previous 3mths, use of oral antiseptics, any type of congenital or acquired

Bibliographic reference	**Tomas I, Alvarez M, Limeres J, Tomas M, Medina J, Otero JL et al. Effect of a chlorhexidine mouthwash on the risk of postextraction bacteremia. Infection Control & Hospital Epidemiology 2007;28:577-82 *[included in CG64]***
	immunodeficiency , disease that predisposes the patient to infections or bleeding **Other characteristics** Age in years, mean (SD) Chlorhexidine: 25.5 (10.3) Control: 26.1 (12.3) Gender, n (%) Chlorhexidine: Male – 23 (43), Female – 30 (57) Control: Male – 29 (55), Female – 24 (45) Number of dental extractions, mean (SD) Chlorhexidine: 5.4 (4.3) Control: 5.7 (4.7) There were NS differences between the groups with regard to age, sex, oral health status, or number of teeth extracted
Number of Patients	106 randomised to: - Chlorhexidine: n=53 - Control: n=53
Intervention	Endotracheal intubation and oesophageal packing and then had their mouths filled with 0.2% chlorhexidine digluconate solution (Oraldine Perio;Pfizer) for 30 seconds before dental manipulation was performed
Comparison	No chlorhexidine prophylaxis before dental manipulation
Length of follow up	Blood samples obtained up to 1 hour after procedure
Location	Spain
Outcomes measures and effect size	**1) Bacteraemia levels/intensity:** not reported **2) Duration of bacteraemia:** not reported **3) Incidence of bacteraemia** Positive blood cultures at baseline; 9% chlorhexidine, 8% control, p=ns (n=53 in each group) Bacteraemia 30sec; chlorhexidine 79% vs. control 96%, p=0.008 (n=53 in each group) Bacteraemia 15min; chlorhexidine 30% vs. control 64%, p<0.001 (n=53 in each group) Bacteraemia 1hr; chlorhexidine 2% vs. control 20%, p=0.005 (n=50 in each group, numbers lost to due technical reasons)

Bibliographic reference	**Tomas I, Alvarez M, Limeres J, Tomas M, Medina J, Otero JL et al. Effect of a chlorhexidine mouthwash on the risk of postextraction bacteremia. Infection Control & Hospital Epidemiology 2007;28:577-82 *[included in CG64]***
	The risk of bacteraemia after dental extraction at 30sec was x1.21 (1.04 to 1.40, 95%CI) higher in the control group; x2.12 (1.34 to 3.35, 95%CI) higher at 15mins; x10 (1.32 to 75.22, 95%CI) higher at 1hr Percentage blood cultures with positive results 48% chlorhexidine vs. 30% control, p<0.001 Incidence of polymicrobial culture results 29% vs. 11%, p=0.005
Source of funding	Xunta de Galicia, Spain
Comments	**Statistical analyses** - The Fisher's exact test was used to compare the prevalence of bacteraemia at baseline, 30 seconds, 15 minutes and 1 hour after dental extractions; the percentage of blood cultures with positive results and the frequency of polymicrobial culture finding. P<0.05 was used. - The relative risk was calculated to estimate the risk of bacteraemia after dental extraction and significance was evaluated using 95%CIs **Assessment of bacteraemia** - A peripheral venous blood sample (10ml) was collected at baseline, 30 seconds after the final dental extraction, and at 15 minutes and 1 hour after finishing the surgical procedure - Each blood sample was divided into 2 bottles, one aerobic culture media and one anaerobic culture media; they were immediately transported to the laboratory and processed using Bactec 9240 - Gram staining was performed on each blood culture that showed microbial growth - The bacteria isolated were identified using the battery of biochemical tests provided by the Vitek system - Facklam's criteria was used to identify unusual Streptococcus species and other gram positive cocci in chains **Microbial identity** The most frequently identified were Streptococcus species (64% control, 68% chlorhexidine), then Staphylococcus species (11% control, 8% chlorhexidine), Neisseria species (8% control, 5% chlorhexidine) **Study limitations: assessed using GRADE risk of bias checklist** - Allocation concealment and blinding not described - Unclear whether it's the same subjects bacteraemic at different time points (possible double counting of subjects) - Power calculation not reported

1

Appendix H: GRADE profiles/Result summary tables

H.1 Review question 1a and 1b

Table 135: Congenital Heart Disease (where available, abnormality specified)

				Effect Estimate		Quality comment
Study ID	N	N IE cases (%)	Controls Number (%)	Unadjusted Rate Ratio (RR) (95% CI)	Multivariate analysis Adjusted Rate Ratio (aRR) (95% CI) P-value	
Outcome: IE (Cyanotic CHD)						
Rushani et al.	3885	62/185	348/3700	6.38 (4.02-10.13) P=NR	6.44 (3.95-10.5) P=NR	Low risk bias
Outcome: IE (Endocardial cushion)						
Rushani et al.	3885	18/185	154/3700	4.37 (2.35-8.15) P=NR	5.47 (2.89-10.36) P=NR	Low risk bias
Outcome: IE (Left-sided lesions)						
Rushani et al.	3885	18/185	414/3700	1.57 (0.86-2.88) P=NR	1.88 (1.01-3.49) P=NR	Low risk bias
Outcome: IE (R sided lesions)						
Rushani et al.	3885	7/185 (4)	216/3700 (6)	1.12 (0.49-2.59) P=NR	1.22 (0.52-2.86) P=NR	Low risk bias
Outcome: IE (Patent ductus arteriosus)						
Rushani et al.	3885	6/185 (3)	161/3700 (4)	1.33 (0.54-3.27) P=NR	1.25 (0.50-3.13) P=NR	Low risk bias
Outcome: IE (Ventricular septal defect)						
Rushani et al.	3885	27/185 (15)	988/3700 (27)	0.95 (0.56-1.62) P=NR	0.97 (0.56-1.66) P=NR	Low risk bias
Outcome: IE (Atrial septal defect)						
Rushani et al.	3885	29/185 (16) (156)	1004/3700 (27)	0.449 (0.33-0.75)* P= NR	NR	Low risk bias

* Calculated by reviewer, NR = not reported

				Effect Estimate		Quality comment
Study ID	N	N IE cases (%)	Controls Number (%)	Univariate analysis OR (95% CI) P-Value	Multivariate analysis Adjusted OR (aOR) (95% CI) P-Value	
Outcome: IE						
Strom et al (CG64)	546	26/273 (9.5)	7/273 (2.6)	NR	6.7 (2.3-19.4) P=NR	Low risk bias
Outcome: IE						
Ammar et al	350	15/350 (8.6)	12/350 (6.9)	1.26 (0.58-2.73)* P=NR	NR. P=NR - NS only	High risk bias
Outcome: Single episode IE vs >1 episode						
Alagna et al	1874	165/1783 (9.2) (Single cases)	8/91 (8.7) (repeat cases)	1.06 (0.50-2.22)* P=NR	NR. P=1.00	High risk bias

1 * Calculated by reviewer, NR = not reported, NS = non significant

2 **Table 136: Rheumatic Heart Disease**

				Effect Estimate		Quality comment
Study ID	N	N IE cases (%)	Controls Number (%)	Univariate analysis OR (95% CI) P-Value	Multivariate analysis Adjusted OR (aOR) (95% CI) P-Value	
Outcome: IE						
Strom (CG64)[1]	546	32/273 (11.7)	10/273 (3.7)	NR	13.4 (4.5-39.5) P=NR	Low risk bias

3 [1] Rheumatic heart fever with heart involvement, NR = not reporte

4 **Table 137: Known Structural Heart Disease**

				Effect Estimate		Quality comment

Study ID	N	N IE cases (%)	Controls Number (%)	Univariate Analysis OddsRatio(OR) 95% CI P-Value	Multivariate analysis Adjusted OR (aOR) (95% CI) P-Value	
Outcome: IE						
Ammar et al	350	117/175 (66.9)	111/175 (63.4)	1.16 (0.74-1.80)* P=NR	NR. NS	High risk bias

1 *Calculated by reviewer, NR = not reported, NS = non significant

2 **Table 138: Valvular Heart Disease**

				Effect Estimate		Quality comment
Study ID	**N**	**N IE cases (%)**	**Controls Number (%)**	**Univariate Analysis OddsRatio(OR) 95% CI P-Value**	**Multivariate analysis Adjusted OR (aOR) (95% CI) P-Value**	
Outcome: IE						
Ammar et al	350	53/175 (30.3)	54/175 (30.9)	0.97 (0.62-1.53)* P=NR	NR. NS.	High risk bias
Outcome: IE						
Strom (CG64)	546	104/273 (38.1)	17/273 (6.2)	NR. NR.	16.7 (7.4-37.4) P=NR	Low risk bias

3 *Calculated by reviewer, NR = not reported, NS = non significant

4 **Table 139: Mitral Valve Prolapse**

				Effect Estimate		Quality comment
Study ID	**N**	**N IE cases (%)**	**Controls Number (%)**	**Matched OR (95% CI) P-Value**	**Multivariate analysis OR (95% CI) P-Value**	
Outcome: IE						
Clemens et al	204	13/51 (25)	10/153 (7)	4.7 (1.1-19.5)	NR. NR.	Low risk bias

				Effect Estimate		Quality comment
Study ID	N	N IE cases (%)	Controls Number (%)	Matched OR (95% CI) P-Value	Multivariate analysis OR (95% CI) P-Value	
(CG64)				P=NR		
Hickey et al (CG64)	224	11/56 (20)	7/168 (4)	6.8 (2.1-22.0) P=NR	NR. NR.	High risk bias
Strom et al (CG64)	546	52/273 (19)	6/273 (2.2)	19.4 (6.4-58.4) P=NR	NR. NR.	Low risk bias

1 NR = not reported, NS = non significant

2 **Table 140: Prosthetic Heart Valve**

				Effect Estimate		Quality comment
Study ID	N	N IE cases (%)	Controls Number (%)	Univariate Analysis OddsRatio(OR) 95% CI P-Value	Multivariate analysis Adjusted Rate Ratio (aRR) (95% CI) P-value	
Outcome: IE - Single episode IE vs >1 episode						
Alagna et al	1874	431/1783 (24) (Single episode)	16/91 (18) (repeat episode)	1.49 (0.86-2.59)* P=0.17	NR.	High risk bias
Outcome: IE						
Ammar et al	350	49/175 (28.0)	45/175 (25.7)	1.12 (0.70-1.80)* P=NR	NR. NS	High risk bias

3 *calculated by reviewer, NR = not reported, NS = non significant

4 **Table 141: Cardiac Surgery A**

				Effect Estimate		Quality comment
Study ID	N	N IE cases (%)	Controls Number (%)	Unadjusted Rate Ratio (RR) (95% CI) P Value	Multivariate analysis Adjusted Rate Ratio (aRR) (95% CI) P-value	

				Effect Estimate		Quality comment
Study ID	N	N IE cases (%)	Controls Number (%)	Unadjusted Rate Ratio (RR) (95% CI) P Value	Multivariate analysis Adjusted Rate Ratio (aRR) (95% CI) P-value	
Outcome: IE						
Rushani et al[1]	3885	17/185 (9)	25/3700 (1)	15.52 (8.08-29.80) P=NR	5.34 (2.49-11.43) P=NR	Low risk bias

[1]Cardiac valvular surgery, NR = not reported, NS = non significant

Table 142: Cardiac Surgery B

				Effect Estimate		Quality comment
Study ID	N	N IE cases (%)	Controls Number (%)	Univariate Analysis OddsRatio(OR) 95% CI P-Value	Multivariate analysis OR (95% CI) P Value	
Outcome: IE						
Strom (CG64)[2]	546	37/273 (13.6)	2/273 (0.7)	NR. NR.	74.6 (12.5-447) P=NR	Low risk bias

[2] In previous 6 months, NR = not reported, NS = non significant

Table 143: Previous IE

				Effect Estimate		Quality comment
Study ID	N	N (%) IE cases	N (%) controls	Univariate Analysis OddsRatio(OR) 95% CI P-Value	Multivariate analysis OR (95% CI) P Value	
Outcome: IE (Single episode IE vs >1 episode)						
Alagna et al	1874	135/1783 (7.4) (Single cases)	17 (19) (Repeat cases)	NR. NR.	2.81 (1.5-5.1) P=0.001	High risk bias
Outcome: IE						
Ammar et al	350	9/175 (5.1)	2/175 (1.1)	4.69 (0.998-22.03)	5.841 (1.2-28.4) P=0.029	High risk bias

				Effect Estimate		Quality comment
Study ID	N	N (%) IE cases	N (%) controls	Univariate Analysis OddsRatio(OR) 95% CI P-Value	Multivariate analysis OR (95% CI) P Value	
Strom (CG64)	546	17/273 (6.2)	1/273 (0.4)	NR. NR.	37.2 (4.4-317) NR	Low risk bias

1 NR = not reported, NS = non significant

2 **Table 144: Composite risk factors - Prior valve damage (Prosthetic heart valves, pacemaker or congenital heart disease)**

				Effect Estimate		Quality comment
Study ID	N	N (%) with valvular heart damage	N (%) without	Univariate Analysis OddsRatio(OR) 95% CI P-Value	Multivariate analysis OR (95% CI) P Value	
Outcome: IE						
Richet et al		1152/1939 (59.4)	787/1939 (41.6)	NR. NR.	8.2 (5-13.3) P<0.00001	Low risk bias

3 NR = not reported, NS = non significant

H.24 Review question 2

5 **Table 145: Congenital Heart Disease and IE**

						Effect Estimate		Quality comment
Study ID	N with risk factor/ total	N with RF with outcome	N without RF with outcome	N With RF without outcome	N without RF Without outcome	Univariate Analysis OddsRatio(OR) 95% CI P-Value	Multivariate analysis OR (95% CI) P Value	
Outcome: Mortality (in hospital)								
Erbay et al	7/107	2	29	5	78	1.08 (0.20-5.86)* p=0.613	NR. NS.	Low risk bias
Lin et al	31/48	6	7	25	41	1.41 (0.42-4.66)* P=NR	NA. NA.	High risk bias

						Effect Estimate		Quality comment
Study ID	**N with risk factor/ total**	**N with RF with outcome**	**N without RF with outcome**	**N With RF without outcome**	**N without RF Without outcome**	**Univariate Analysis OddsRatio(OR) 95% CI P-Value**	**Multivariate analysis OR (95% CI) P Value**	
Murdoch et al	311/2656	NR	NR	NR	NR	NR. NR.	1.22 (0.74-2.02) p=0.44	Low risk bias
Yoshinaga et al[1]	40/137	9	40	31	123	5.34 (1.66-17.2) p=0.005	NR. NS.	High risk bias
Outcome: Mortality (5 year)								
Aksoy et al	36/333	10	162	26	171	0.41 (0.19-0.87)* p = 0.008	NA. NA.	Low risk bias
Outcome: Cardiac Surgery								
Lin et al	31/48	9	17	22	31	0.75 (0.28-1.98)* P=NR	NR. NR.	High risk bias
Lin et al[2]	31/48	3	11	28	37	0.36 (0.09-1.42)* P=NR	NR. NR.	High risk bias
Murakami et al	61/239	49	216	12	23	0.27 (0.11-0.65) P=0.0044	NR. NS.	Low risk bias
Outcome: Recurrence								
Alagna et al	173/1874	8	91	165	1783	0.95 (0.45-1.99)* P=NR	NR. P=1.00	High risk bias

1 *calculated by reviewer [1] Cyanotic congenital heart disease only. [2] Lin – Valve replacement surgery specifically. NR = not reported, NS = non significant, NA= not available

2 **Table 146: Composite risk factors – predisposing cardiac diseases and IE**

						Effect Estimate		Quality comment
Study ID	**N with risk factor/ total**	**N with RF with outcome**	**N without RF with outcome**	**N With RF without outcome**	**N without RF Without outcome**	**Univariate Analysis OddsRatio(OR) 95% CI P-Value**	**Multivariate analysis OR (95% CI) P Value**	
Outcome: Mortality (in-hospital)								
Erbay et al1	87/107	25	29	62	78	1.09 (0.58-2.04)* p=0.312	NIIM NA	Low risk bias

						Effect Estimate		Quality comment
Study ID	**N with risk factor/ total**	**N with RF with outcome**	**N without RF with outcome**	**N With RF without outcome**	**N without RF Without outcome**	**Univariate Analysis OddsRatio(OR) 95% CI P-Value**	**Multivariate analysis OR (95% CI) P Value**	
Outcome: Mortality (after recovery from acute phase of IE, median follow-up 2.2 years)								
Thuny et al (2012)[2]	206/328	30	55	176	273	0.85 (0.52-1.37)* p = 0.16	EHR – NR. NR.	Low risk bias
Outcome: Stroke (Cerebrovascular complications, silent embolism, ischaemic stroke, TIA, primary ICH)								
Thuny (2007) et al [3]	275/496	59	109	216	387	0.97 (0.68-1.39)* p = 0.75	NA. NA.	Low risk bias

calculated by reviewer. EHR = extended hazard ratio, NR = not reported, NS = non significant, NA= not available, NIIM = not entered in model
1 Pre-existing heart disease not specified
2 Underlying heart disease (not defined)
3Underlying heart disease included RHD, non-rheumatic valve disease, congenital heart disease and degenerative cardiac disease.

Table 147: Rheumatic Heart Disease and IE

						Effect Estimate		Quality comment
Study ID	**N with risk factor/ total**	**N with RF with outcome**	**N without RF with outcome**	**N With RF without outcome**	**N without RF Without outcome**	**Univariate Analysis OddsRatio(OR) 95% CI P-Value**	**Multivariate analysis OR (95% CI) P Value**	
Outcome: Mortality								
Da Costa et al	45/186	9	49	36	137	0.70 (0.31-1.56)* p = 0.365	NR. NS(no value)	Low risk bias
Delahaye et al	13/559	NR	NR	NR	NR	NR. P=0.01	NR. NS(no value)	High risk bias
Erbay et al	11/107	5	29	6	78	2.24 (0.64-7.91)* p = 0.148	NIIM. NA.	Low risk bias
Outcome: Recurrence								
Wong et al	9/47	1	8	8	39	0.61 (0.07-5.58)* p=1.00	NA. NA.	Low risk bias
Outcome: Events (Death OR Surgery)								

						Effect Estimate		Quality comment
Study ID	**N with risk factor/ total**	**N with RF with outcome**	**N without RF with outcome**	**N With RF without outcome**	**N without RF Without outcome**	**Univariate Analysis OddsRatio(OR) 95% CI P-Value**	**Multivariate analysis OR (95% CI) P Value**	
San Roman et al	32/317	17	187	15	130	0.79 (0.38-1.63)* p = 0.47	NIIM. NA.	Low risk bias

1 *calculated by reviewer, NR = not reported, NS = non significant, NA= not available, NIIM = not entered in model

2 **Table 148: Degenerative Heart Disease and IE**

						Effect Estimate		Quality comment
Study ID	**N with risk factor/ total**	**N with RF with outcome**	**N without RF with outcome**	**N With RF without outcome**	**N without RF Without outcome**	**Univariate Analysis OddsRatio(OR) 95% CI P-Value**	**Multivariate analysis OR (95% CI) P Value**	
Outcome: Mortality								
Erbay et al	15/107	4	29	11	78	0.98 (0.29-3.32)* p = 0.608	NIIM NA	Low risk bias
Outcome: Events (Death OR Surgery)								
San Roman et al	29/317	16	187	13	130	0.86 (0.40-1.84)* p = 0.65	NIIM. NA.	Low risk bias

3 *calculated by reviewer, NR = not reported, NS = non significant, NA= not available, NIIM = not entered in model

4 **Table 149: Aortic Valve Disease/Disorder and IE**

						Effect Estimate		
Study ID	**N with risk factor/ total**	**N with RF with outcome**	**N without RF with outcome**	**N With RF without outcome**	**N without RF Without outcome**	**Univariate Analysis OddsRatio(OR) 95% CI P-Value**	**Multivariate analysis OR (95% CI) P Value**	**Quality comment**
Outcome: Mortality (in hospital)								
Erbay et al [1]	3/107	2	29	1	78	5.38 (0.47-61.60)* p = 0.178	NIIM. NA.	Low risk bias

						Effect Estimate		
Study ID	**N with risk factor/ total**	**N with RF with outcome**	**N without RF with outcome**	**N With RF without outcome**	**N without RF Without outcome**	**Univariate Analysis OddsRatio(OR) 95% CI P-Value**	**Multivariate analysis OR (95% CI) P Value**	**Quality comment**
Outcome: Mortality (5 Year)								
Aksoy et al	5/333	5	162	0	171	11.61 (0.64-211.63)* p = 0.003	NA. NA.	Low risk bias
Outcome: Recurrence								
Wong et al[2]	4/47	2	8	2	39	4.88 (0.60-39.91)* p = 1.00	NA. NA.	Low risk bias

1 *calculated by reviewer 1 Bicuspid aortic valve. 2 Aortic stenosis specifically. NR = not reported, NS = non significant, NA= not available, NIIM = not entered in model

2 **Table 150: Mitral Valve Prolapse and IE**

						Effect Estimate		Quality comment
Study ID	**N with risk factor/ total**	**N with RF with outcome**	**N without RF with outcome**	**N With RF without outcome**	**N without RF Without outcome**	**Univariate Analysis OddsRatio(OR) 95% CI P-Value**	**Multivariate analysis OR (95% CI) P Value**	
Outcome: Recurrence								
Wong et al	8/47	1	8	7	39	0.70 (0.08-6.47)* p = 1.00	NA. NA.	Low risk bias

3 *calculated by reviewer, NA= not available.

4 **Table 151: Previous valve replacement/Prosthetic valve and IE A**

						Effect Estimate		Quality comment
Study ID	**N with risk factor/ total**	**N with RF with outcome**	**N without RF with outcome**	**N With RF without outcome**	**N without RF Without outcome**	**Univariate Analysis OddsRatio(OR) 95% CI P-Value**	**Multivariate analysis OR (95% CI) P Value**	
Outcome: Mortality (in-hospital)								
Galvez-Acebal et al	171/705	67	208	104	497	1.48 (1.17-1.87). P=0.001	1.99 (1.26-3.14) P=0.003	Low risk bias

						Effect Estimate		Quality comment
Study ID	**N with risk factor/ total**	**N with RF with outcome**	**N without RF with outcome**	**N With RF without outcome**	**N without RF Without outcome**	**Univariate Analysis OddsRatio(OR) 95% CI P-Value**	**Multivariate analysis OR (95% CI) P Value**	
Yoshinaga et al	4/137	0	14	4	123	NR. P=0.99	NR. NS	High risk bias
Murdoch et al	563/2636	NR	NR	NR	NR	NR. NR.	1.47 (1.13-1.90) P=0.004	Low risk bias
Da Costa et al	55/186	20	49	137	186	NR	4.77 (1.44-15.76) P<0.01	Low risk bias
Alonso-Valle et al	133	NR	NR	NR	NR	0.9 (RR) (0.4-2.1). NR	NR. NS.	High risk bias
Delahaye et al	95/559(17)	NR	NR	NR	NR	NR. P=0.04	NR. NS.	High risk bias
Erbay et al	47/107	10	29	37	78	0.73 (0.32-1.65)* p=0.230	NIIM. NA.	Low risk bias
Wang et al	556/2670	127	310	429	1585	1.51 (1.2-1.9)*	NR	Low risk bias
Outcome: Mortality (in hospital and within 30 days of discharge)								
Fernandez-Guerrero et al 2007[1]	17/44	2	17	15	27	0.21 (0.04-1.04)* P=NR	NIIM. NA.	High risk bias
Fernandez-Guerrero et al 2010[2]	28/84	12	28	16	56	0.53 (0.21-1.37) NR (NS)	NA	High risk bias
Outcome: Mortality (after recovery from acute phase of IE, median follow-up 2.2 years)								
Thuny et al (2012)	206/328	30	55	176	273	0.85 (0.52-1.37)* P=0.16	EHR 0.72 (0.35-1.50) P=0.39	Low risk bias
Outcome: Mortality (In hospital + 5 year)								
Bannay et al	160/449	NR	NR	NR	NR	HR 1.09 (0.72-1.67) 0.677	Low risk bias	

						Effect Estimate		Quality comment
Study ID	**N with risk factor/ total**	**N with RF with outcome**	**N without RF with outcome**	**N With RF without outcome**	**N without RF Without outcome**	**Univariate Analysis OddsRatio(OR) 95% CI P-Value**	**Multivariate analysis OR (95% CI) P Value**	
Outcome: Cardiac Surgery								
Bannay et al[1]	71/449	37	240	34	209	0.95 (0.57-1.56)* P=NR	NR P=0.897	Low risk bias
Bannay et al [2]	257/449	142	240	115	209	1.08 (0.79-1.46)* P=NR	NR P=0.446	Low risk bias
Fernandez-Guerrero et al 2007[3]	17/44	6	17	11	27	0.87 (0.27-2.78)* P=NR	NIIM. NA	High risk bias
Fernandez-Guerrero et al 2010[4]	28/84	20	41	8	43	0.24 (0.09-0.64) P=NR	NA.	High risk bias
Outcome: Events (Death OR Surgery)								
San Roman et al	124/317	72	187	52	130	0.96 (0.63-1.47)* p = 0.76	NIIM. NA	Low risk bias
Outcome: Recurrence								
Wong et al	13/47	1	8	12	39	0.41 (0.05-3.58)* p = 0.41	NA.	Low risk bias
Alagna et al	447/1874	16	91	431	1783	0.73 (0.42-1.25)* p=1.00	NR.	High risk bias
Outcome: Stroke								
Fernandez-Guerrero et al 2007[3]	9/44	4	17	5	27	1.27 (0.30-5.41)* P=NR	NIIM. NA	High risk bias
Fernandez-Guerrero et al 2010[4]	28/84	10	26	18	58	0.72 (0.27-1.89) P=NR	NA	High risk bias
Thuny et al	110/496	24	109	86	387	0.99 (0.60-1.63)* p = 0.96	NA	Low risk bias

						Effect Estimate		Quality comment
Study ID	**N with risk factor/ total**	**N with RF with outcome**	**N without RF with outcome**	**N With RF without outcome**	**N without RF Without outcome**	**Univariate Analysis OddsRatio(OR) 95% CI P-Value**	**Multivariate analysis OR (95% CI) P Value**	
(2007)[5]								

1 *calculated by reviewer, NR = not reported, NS = non significant, NA= not available, NIIM = not entered in model
2 1 Valvular prosthesis only. 2 Both native and prosthetic vavles. 3 Specifically IE caused by enterococci. OUTCOME = Brain emboli. 4 L-sided IE only caused by staphylococcus
3 aureus. OUTCOME = CNS complications including "brain bleeding". 5 Complications defined as silent cerebral embolism, ischaemic stroke, TIA, Primary ICH)

4 **Table 152: Prosthetic Valve Replacement/Prosthetic Valve and IE B**

				Effect Estimate	Quality comment
Study ID	**N with Risk Factor/ total**	**Number (%) observed deaths**	**Expected number of deaths**	**SMR 95% CI**	
Outcome: Mortality (In hospital)					
Ternhag et al	890	154 (17.3)	68	2.3 (1.9-2.7) P=NR	Low risk bias

5 NR = not reported, NS = non significant, NA= not available, NIIM = not entered in model

6 **Table 153: Previous Valve Replacement (Mechanical prosthesis) and IE**

						Effect Estimate		Quality comment
Study ID	**N with risk factor/ total**	**N with RF with outcome**	**N without RF with outcome**	**N With RF without outcome**	**N without RF Without outcome**	**Univariate Analysis OddsRatio(OR) 95% CI P-Value**	**Multivariate analysis OR (95% CI) P Value**	
Outcome: Mortality (in-hospital)								
Alonso-Valle et al[1]	64/133	NR	NR	NR	NR	1.1 (RR) 0.5-2.4. P= NR (NS)	NIIM NA	High risk bias
Smith et al	22/87	2	10	20	77	0.77 (0.16-3.80)* p = 0.665	NIIM NA	Low risk bias

7 *calculated by reviewer using OR but p-value reported by authors related to their analysis which was RR. NR = not reported, NS = non significant, NA= not available, NIIM = not
8 entered in model

1 1 Population was people with prosthetic valves (compared mechanical valve with bio-prostheses for this outcome)

2 **Table 154: Previous cardiac surgery and IE**

						Effect Estimate		Quality comment
Study ID	**N with risk factor/ total**	**N with RF with outcome**	**N without RF with outcome**	**N With RF without outcome**	**N without RF Without outcome**	**Univariate Analysis OddsRatio(OR) 95% CI P-Value**	**Multivariate analysis OR (95% CI) P Value**	
Outcome: Mortality								
Yoshinaga et al	14/137	11	65	3	72	4.69 (1.25-17.6) p=0.02	NR. NS	High risk bias
Outcome: Surgery								
Murakami et al[1]	119/239	26	61	93	178	0.68 (0.38-1.22) p=0.24	NIIM. NA	Low risk bias
Smith et al	24/87	3	10	21	77	1.10 (0.28-4.36)* p = 1.00	NIIM. NA	Low risk bias

3 *calculated by reviewer, NR = not reported, NS = non significant, NA= not available, NIIM = not entered in model
4 1 Previous surgery for CHD specifically

5 **Table 155: Previous IE and IE**

						Effect Estimate		Quality comment
Study ID	**N with risk factor/ total**	**N with RF with outcome**	**N without RF with outcome**	**N With RF without outcome**	**N without RF Without outcome**	**Univariate Analysis OddsRatio(OR) 95% CI P-Value**	**Multivariate analysis OR (95% CI) P Value**	
Outcome: Mortality (in hospital)								
Alonso-Valle et al [1]	NR	NR	NR	NR	NR	1.7 (RR) 0.7-4.4 p=NR	NR. NS	High risk bias
Erbay et al	10/107	6	29	4	78	NR. 0.023	HR 3.5 (1.2-11.0) p=0.026	Low risk bias
San Roman et al	28/317	16	187	12	130	0.93 (0.42-2.03)* p = 0.80	NIIM. NA.	Low risk bias
Yoshinaga et al	12/137	3	14	9	123	3.46 (0.81-14.7) p=0.09	NR. NS	High risk bias

						Effect Estimate		Quality comment
Study ID	**N with risk factor/ total**	**N with RF with outcome**	**N without RF with outcome**	**N With RF without outcome**	**N without RF Without outcome**	**Univariate Analysis OddsRatio(OR) 95% CI P-Value**	**Multivariate analysis OR (95% CI) P Value**	
Outcome: Cardiac Surgery								
Bannay et al	38/449	24	240	14	209	1.49 (0.75-2.96)* p=0.237	NR	Low risk bias
Murakami	21/239	4	61	17	178	0.67 (0.22-2.06) p=0.61	NIIM. NS	Low risk bias
Tleyjeh	59/546	16	129	43	417	1.20 (0.66-2.21)* p = 0.50	NA	High risk bias

*calculated by reviewer, NR = not reported, NS = non significant, NA= not available, NIIM = not entered in model
1 Population was previous IE in patients with prosthetic valve endocarditis

H.3 Review question 6a

Table 156: Antibiotic vs placebo/no prophylaxis for infective endocarditis in those undergoing interventional procedures (dichotomous outcomes)

Quality assessment							No of patients		Effect estimate		Quality
No of studies	**Design**	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Other considerations**	**Antibiotic**	**No antibiotic**	**Relative (96% CI)**	**Absolute**	
Outcome: incidence of IE											
Reported in study as incidence of prosthetic valve endocarditis in those undergoing various interventional procedures (dental, urological, oropharyngeal and gynaecological)											
1 (Horstkotte, 1987)	Retrospective cohort	Serious[1]	None	N/A[2]	Very serious[3]	None	0/287 (0%).	6/390 (1.5%)	RR: 0.1 (0.01 to 1.85)	14 fewer per 1000 (from 15 fewer to 13 more)	Very low
Reported in study as incidence of IE in those undergoing dental procedures											
1 (Lacassin, 1995)	Case-control	Serious[4]	None	N/A[2]	Very serious[3]	None	6/12 (50%)	20/36 (56%)	RR: 0.9 (0.48 to 1.7)	56 fewer per 1000 (from 289 fewer to	Very low

Quality assessment							No of patients		Effect estimate		Quality
										389 more)	
Reported in study as incidence of IE in those undergoing largely dental procedures											
1 (Van der Meer, 1992)	Case-control	Serious[5]	None	N/A[2]	Very serious[3]	None	8/34 (24%)	40/214 (19%)	RR: 1.26 (0.65 to 2.45)	49 more per 1000 (from 65 fewer to 271 more)	Very low

[1] Serious risk of bias because 1) study design unclear 2) retrospective study reliant on patient's memory for data regarding interventional procedures undergone and prophylaxis use, no indication that data provided by subject was verified in any way 3) unclear how similar the interventional procedures the 2 groups underwent were; numbers not reported 4) unclear whether confounding factors were taken into account 5) age, gender not reported 6) Some subjects underwent more than one procedure 7) Power calculation not reported

[2] Single study analysis

[3] Very serious risk of imprecision as 95%Cis crosses both the default appreciable benefit and harm (0.75 and 1.25)

[4] Serious risk of bias because 1) retrospective nature of study reliant on subjects memory for interventional procedures undergone and antibiotic use 2) of the 171 cases, only 34% had definite infective endocarditis; 48% probable IE and 18% possible IE 3) in the case of medical consultation or procedure, information cited was checked by the cited practitioner; unclear whether what proportion of subjects this was possible for 4) Power calculation not reported

[5] Serious risk of bias because 1) retrospective study; data collected via structured questionnaire which although checked with medical and dental specialists, was highly reliant on patient's memory and reliability of medical records 2) cases who were very ill or who died were included in the analysis via the use of proxy responders, however this did not occur for the 53/889 controls who died 3) cases and controls did not undergo entirely the 'same' procedure however % undergoing dental procedures in both groups was comparable (92% and 91% cases and controls)

H.42 Review question 7a

Table 157: Antibiotic vs placebo/no prophylaxis for bacteraemia in those undergoing dental procedures (dichotomous outcomes)

Quality assessment							No of patients		Effect estimate		Quality
No of studies	**Design**	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Other considerations**	**Antibiotic**	**No prophylaxis/ placebo**	**Relative (95% CI)**	**Absolute**	
Outcome: Incidence of positive blood culture following prophylaxis versus before											
1 (Maharaj et al., 2012)	RCT	Serious[1]	No serious	N/A[2]	No serious for amoxicillin and serious[3] for clindamycin	No serious	**At baseline**		**At baseline**		**At baseline**
							NR	NR	NR	NR	-
							At 3 minutes post extraction; amoxicillin		**At 3 minutes post extraction; amoxicillin**		**At 3 minutes post extraction;**

Quality assessment							No of patients		Effect estimate		Quality
											amoxicillin
							3/40 (7.5%)	14/40 (35%)	RR: 0.21 (0.07 to 0.69)	276 fewer per 1000 (from 108 fewer to 325 fewer)	Moderate
							At 3 minutes post extraction; clindamycin		**At 3 minutes post extraction; clindamycin**		**At 3 minutes post extraction; clindamycin**
							8/40 (20%)	14/40 (35%)	RR: 0.57 (0.27 to 1.21)	150 fewer per 1000 (from 255 fewer to 74 more)	Low
1 (Duvall et al., 2013)	RCT	Serious[4]	No serious	N/A[2]	Very serious[5]	No serious	**Reported in study as incidence of at least one positive culture of the 4 blood draws per subject including baseline; amoxicillin**		**Reported in study as incidence of at least one positive culture of the 4 blood draws per subject including baseline; amoxicillin**		
							4/10 (40%)	5/10 (50%)	RR: 0.8 (0.3 to 2.13)	100 fewer per 1000 (from 350 fewer to 565 more)	Very low
1 (Diz et al., 2006)	RCT	Serious[6]	No serious	N/A[2]	Not assessable[7]	No serious	**Amoxicillin: at baseline**		**Amoxicillin: at baseline**		Low
							5%	9.4%	-	-	
							Amoxicillin: at 30		**Amoxicillin: at 30**		

Quality assessment							No of patients		Effect estimate		Quality
							seconds		**seconds**		
							46.4%	96.2%	P<0.001[8]		
							Amoxicillin: at 1 hour		**Amoxicillin: at 1 hour**		
							3.7%	20%	P≤0.01[8]		
							Clindamycin: at baseline		**Clindamycin: at baseline**		
							12.5%	9.4%	-	-	
							Clindamycin: at 30 seconds		**Clindamycin: at 30 seconds**		
							85.1%	96.2%	P=NS[8]		
							Clindamycin: at 1 hour		**Clindamycin: at 1 hour**		
							22.2%	20%	P=NS[8]		
							Moxifloxacin: at baseline		**Moxifloxacin: at baseline**		
							7.5%	9.4%	-	-	
							Moxifloxacin: at 30 seconds		**Moxifloxacin: at 30 seconds**		
							56.9%	96.2%	P<0.001[8]		
							Moxifloxacin: at 1 hour		**Moxifloxacin: at 1 hour**		
							7.1%	20%	P<0.05[8]		
1 (Hall et al., 1993)	RCT	Serious[9]	No serious	N/A[2]	No serious during extraction; penicillin V; very serious[5] 10 minutes after extraction; penicillin V; serious[3] during extraction;	No serious	**At baseline**		**At baseline**		
							0/20 (0%)	0/20 (0%)	-	-	-
							During extraction; penicillin V		**During extraction; penicillin V**		
							18/20 (90%)	18/20 (90%)	RR: 1.00 (0.81 to 1.23)	0 fewer per 1000 (from 171 fewer to 207 more)	Moderate

Quality assessment							No of patients		Effect estimate		Quality
					amoxicillin, serious[3] 10 minutes after extraction; amoxicillin		**10 minutes after extraction; penicillin V**		**10 minutes after extraction; penicillin V**		
							14/20 (70%)	16/20 (80%)	RR: 0.88 (0.61 to 1.26)	96 fewer per 1000 (from 312 fewer to 208 more)	Very low
							During extraction; amoxicillin		**During extraction; amoxicillin**		
							17/20 (85%)	18/20 (90%)	RR: 0.94 (0.75 to 1.19)	54 fewer per 1000 (from 225 fewer to 171 more)	Low
							10 minutes after extraction: amoxicillin		**10 minutes after extraction: amoxicillin**		
							12/20 (60%)	16/20 (80%)	RR: 0.75 (0.49 to 1.14)	200 fewer per 1000 (from 408 fewer to 112 more)	Low
1 (Roberts et al., 1987)	RCT	Serious[10]	No serious	N/A[2]	Very serious[5] 2 minutes post intubation, no serious 2 minutes post extraction	No serious	**At baseline pre-intubation; amoxicillin**		**At baseline pre-intubation; amoxicillin**		
							0/47 (0%)	0/47 (0%)	-	-	
							2 minutes after intubation		**2 minutes after intubation**		
							0/47 (0%)	3/47 (6.4%)	RR: 0.14 (0.01 to 2.69)	55 fewer per 1000 (from 63 fewer to	Very low

Quality assessment							No of patients		Effect estimate		Quality
										108 more)	
							2 minutes post extraction		**2 minutes post extraction**		
							1/47 (2.1%)	18/47 (38.3%)	RR: 0.06 (0.01 to 0.40)	360 fewer per 1000 (from 230 fewer to 379 fewer)	Moderate
1 (Hall et al., 1996)	RCT	Serious[11]	No serious	N/A[2]	Very serious[5]	No serious	**At baseline; cefaclor**		**At baseline; cefaclor**		Very low
							0/19 (0%)	0/20 (0%)	-	-	
							During extraction[12]		**During extraction**		
							15/19 (79%)	17/20 (85%)	RR: 0.93 (0.69 to 1.25)	59 fewer per 1000 (from 264 fewer to 213 more)	
							10 minutes after extraction[13]		**10 minutes after extraction**		
							10/19 (53%)	9/19 (47%)	RR: 1.11 (0.59 to 2.10)	52 more per 1000 (from 194 fewer to 521 more)	
1 (Shanson et al., 1985)	RCT	Serious[14]	No serious	N/A[2]	Serious[3]	No serious	**At baseline; erythromycin**		**At baseline; erythromycin**		Low
							NR	NR	-	-	
							1 to 2 minutes post extraction; erythromycin		**1 to 2 minutes post extraction; erythromycin**		
							6/40 (15%)	18/42 (43%)	RR: 0.35 (0.15 to	279 fewer per 1000	

Quality assessment							No of patients		Effect estimate		Quality
									0.79)	(from 90 fewer to 364 fewer)	
1 (Wahlmann et al., 1999)	RCT	Serious[15]	No serious	N/A[2]	No serious	No serious	**At baseline; cefuroxime**		**At baseline; cefuroxime**		
							NR	NR	-	-	
							10 minutes after surgery; cefuroxime		**10 minutes after surgery; cefuroxime**		
							7/30 (23%)	23/29 (79%)	RR: 0.29 (0.15 to 0.58)	563 fewer per 1000 (from 333 fewer to 674 fewer)	Moderate
							30 minutes after surgery ; cefuroxime		**30 minutes after surgery ; cefuroxime**		
							6/30 (20%)	20/29 (69%)	RR: 0.29 (0.14 to 0.62)	490 fewer per 1000 (from 262 fewer to 593 fewer)	Moderate
1 (Lockhart et al., 2004)	RCT	Serious[16]	No serious	N/A[b]	Not assessable [7]	No serious	**At baseline after intubation; amoxicillin**		**At baseline after intubation; amoxicillin**		Low
							4%	18%	P=0.05[8]		
							15 minutes after extraction; amoxicillin		**15 minutes after extraction; amoxicillin**		
							~2%	18%	P=0.04[8]		
							45 minutes after extraction; amoxicillin		**45 minutes after extraction; amoxicillin**		
							0%	14%	P=0.03[8]		

Quality assessment							No of patients		Effect estimate		Quality
1 (Morozumi et al., 2010)	RCT	Serious[17]	No serious	N/A[2]	Serious[3]	No serious	**Baseline; azithromycin**		**Baseline; azithromycin**		
							0/10 (0%)	0/10 (0%)	-	-	
							6 minutes after scaling and root planning; azithromycin		**6 minutes after scaling and root planning; azithromycin**		
							2/10 (20%)	9/10 (90%)	RR: 0.22 (0.06 to 0.78)	702 fewer per 1000 (from 198 fewer to 846 fewer)	Low
1 (Lockhart et al., 2008)	RCT	Serious[18]	No serious	N/A[2]	Serious[3]	No serious	**At baseline**		**At baseline**		
							0/96 (0%)	0/96 (0%)	-	-	
							First 5 minutes of procedure; amoxicillin		**First 5 minutes of procedure; amoxicillin**		
							29/89 (32.6%)	49/84 (58.3%)	RR: 0.56 (0.39 to 0.79)	257 fewer per 1000 (from 122 fewer to 356 fewer)	Low
							20 minutes after; amoxicillin		**20 minutes after; amoxicillin**		
							1/88 (1.1%)	8/83 (9.6%)	RR: 0.12 (0.02 to 0.92)	85 fewer per 1000 (from 8 fewer to 94 fewer)	Low
1 (Shanson et al.,	Prospective cohort	Serious[19]	No serious	N/A[2]		No serious	**At baseline**		**At baseline**		Very low
							NR	NR	-	-	
							2 mins post extraction		**2 mins post**		

Quality assessment							No of patients		Effect estimate		Quality
1978)							**(streptococcal bacteraemia); penicillin V**		**extraction (streptococcal bacteraemia); penicillin V**		
					Serious[3]		5/40 (12%)	16/40 (40%)	RR: 0.31 (0.13 to 0.77)	276 fewer per 1000 (from 92 fewer to 348 fewer)	
							2 mins post extraction (anaerobic bacteraemia); penicillin V		**2 mins post extraction (anaerobic bacteraemia); penicillin V**		
					Serious[3]		4/20 (20%)	10/20 (50%)	RR: 0.40 (0.15 to 1.07)	300 fewer per 1000 (from 425 fewer to 35 more)	
							2 mins post extraction (aerobic or anaerobic bacteraemia); penicillin V		**2 mins post extraction (aerobic or anaerobic bacteraemia); penicillin V**		
					No serious		4/20 (20%)	14/20 (70%)	RR: 0.29 (0.11 to 0.72)	497 fewer per 1000 (from 196 fewer to 623 fewer)	
							2 mins post extraction (streptococcal bacteraemia); amoxicillin		**2 mins post extraction (streptococcal bacteraemia); amoxicillin**		
					No serious		2/40 (5%)	16/40 (40%)	RR: 0.13 (0.03 to	352 fewer per 1000	

Quality assessment							No of patients		Effect estimate		Quality
									0.51)	(from 196 fewer to 388 fewer)	
							2 mins post extraction (anaerobic bacteraemia); amoxicillin		**2 mins post extraction (anaerobic bacteraemia); amoxicillin**		
					Serious[3]		3/20 (15%)	10/20 (50%)	RR: 0.30 (0.10 to 0.93)	350 fewer (from 35 fewer to 450 fewer)	
							2 mins post extraction (aerobic or anaerobic bacteraemia); amoxicillin		**2 mins post extraction (aerobic or anaerobic bacteraemia); amoxicillin**		
					Serious[3]		5/20 (25%)	14/20 (70%)	RR: 0.36 (0.16 to 0.80)	448 fewer (from 140 fewer to 588 fewer)	
Adverse events											
Reported in study as side effects including mild or transient nausea, abdominal discomfort or flatulence usually occurring within a few hours of extraction (no vomiting)											
1 (Shanson et al., 1985)	RCT	Serious[20]	No serious	N/A[2]	No serious	No serious	29/56 (52%)	10/53 (19%)	RR: 2.74 (1.49 to 5.07)	328 more per 1000 (from 92 more to 768 more)	Moderate

[1] Serious risk of bias because 1) allocation concealment not described 2) blinding not described 3) number of positive blood cultures before extraction not reported – unclear if subjects were tested for bacteraemia 4) Power calculation not reported
[2] Single study analysis
[3] Serious imprecision as the 95%CIs are wide and crosses over the default appreciable benefit (0.75)
[4] Blinding not described, insufficient information to judge whether subjects and/or assessors blind. Incidence of positive blood cultures at baseline not reported separately but together with incidence at any of the blood draws, power calculation not reported

[5] Very serious imprecision as the 95%CIs are wide and crosses over both the default appreciable benefit and harm (0.75 and 1.25)
[6] Allocation concealment not described, baseline blood samples obtained in 40 subjects in each group (reasons for missing cultures not given), unclear if same subjects bacteraemic at different timepoints, incidence of bacteraemia at baseline not comparable between groups. Number of subjects at different timepoints unclear
[7] Imprecision could not be assessed due to the way data was presented in the article
[8] P value as reported in study. Relative risk and absolute risk could not be calculated as denominator unclear
[9] Randomisation, concealment and blinding not described. Unclear if subjects bacteraemic at 10 minutes were same subjects bacteraemic during surgery and power calculation not reported.
[10] Randomisation, concealment and blinding not described, subjects 'satisfactorily' consumed antibiotic, unclear whether those positive post extraction were those positive post intubation and power calculation not reported.
[11] Randomisation, concealment not described, unclear if those positive after extraction are those positive during extraction, unclear if one subject lost from control group at 10 minutes measurement and power calculation not reported.
[12] Based on percentages reported in study, assumption is that data was available for all subjects
[13] Study reports 47% for placebo group so assumption is that a subject was lost from control group although this is not clearly stated
[14] Number bacteraemic at baseline not reported and power calculation not reported.
[15] Randomisation, concealment and blinding not described, number bacteraemic at baseline not reported, unclear how many of the same subjects were bacteraemic at different time points and power calculation not reported.
[16] Unclear if same subjects bacteraemic at different time points, some subjects lost for measurements taken 15 minutes or later – unclear how many subjects lost from each group
[17] Randomisation, concealment and blinding not described, power calculation not reported.
[18] Unclear whether same subjects bacteraemic at different time points
[19] Number bacteraemic at baseline not reported (unclear if subjects were tested), power calculation not reported, baseline characteristics not reported
[20] Number bacteraemic at baseline not reported

Table 158: Antibiotic vs placebo/no prophylaxis for bacteraemia in those undergoing dental procedures (continuous outcomes)

Quality assessment							No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Antibiotic	Placebo	Mean difference (95% CI)	
Outcome: Bacteraemia levels/intensity following prophylaxis versus before										
Reported in study as total mean magnitude of bacteraemia (cfu/ml)										
1 (Duvall et al., 2013)	RCT	Serious[1]	None	N/A[2]	Very serious[3]	No serious	N=10 Mean (SD): 0.63 (1.33)	N=10 Mean (SD): 3.61 (7.09)	MD: -2.98 (-7.45 to 1.49)	Very low
Reported in study as mean magnitude of bacteraemia per blood draw (cfu/ml):										
Blood draw 1 (at baseline once the IV access line was established)										
1 (Duvall et al., 2013)	RCT	Serious[1]	None	N/A[2]	Not assessable[4]	No serious	N=10 Mean (SD): 0.05 (0.16)	N=10 Mean (SD): 0 (0)	-	Moderate
Blood draw 2 (1.5 minutes following initiation of the mucogingival flap#32)										
1 (Duvall et al.,	RCT	Serious[1]	None	N/A[2]	Very serious[3]	No serious	N=10 Mean (SD): 0.02	N=10 Mean (SD): 1.26 (3.67)	MD: -1.24 (-3.51 to 1.03)	Very low

Quality assessment							No of patients		Effect estimate	Quality
2013)							(0.06)			
Blood draw 3 (1.5 minutes following initiation of mucogingival flap #17)										
1 (Duvall et al., 2013)	RCT	Serious[1]	None	N/A[2]	Very serious[3]	No serious	N=10 Mean (SD): 0.30 (0.73)	N=10 Mean (SD): 1.90 (5.36)	MD: -1.60 (-4.95 to 1.75)	Very low
Blood draw 4 (10 minutes following initiation of mucogingival flap #17)										
1 (Duvall et al., 2013)	RCT	Serious[1]	None	N/A[2]	Serious[5]	No serious	N=10 Mean (SD): 0.26 (0.60)	N=10 Mean (SD): 0.45 (0.83)	MD: -0.19 (-0.82 to 0.44)	Low

[1] Serious risk of bias because blinding not described and incidence of positive blood cultures at baseline not reported separately but together with incidence at any of the blood Draws, power calculation not reported.
[2] Single study analysis
[3] Very serious imprecision as 95%CIs crosses over both the default appreciable benefit and harm (-0.5 and 0.5)
[4] Not assessable as mean and SD in comparator arm is zero
[5] Serious imprecision as 95%CI crosses over the default appreciable benefit (-0.5)

Table 159: Antibiotic vs placebo/no prophylaxis for bacteraemia in those undergoing respiratory procedures

Quality assessment							No of patients		Effect estimate		Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Antibiotic	No prophylaxis/ placebo	Relative (95% CI)	Absolute	
Outcome: Incidence of positive blood culture following prophylaxis versus before											
1 (Sanchez-Carrion et al., 2006)	RCT	Serious[1]	No serious	N/A[2]	No serious at 30 seconds, very serious[3] at 20 minutes	No serious	**At baseline**		**At baseline**		
							NR	NR	-	-	
							30 seconds after adenoidectomy; cefazolin		**30 seconds after adenoidectomy**		
							2/51 (3.9%)	16/50 (32.7%)	RR: 0.12 (0.03 to 0.51)	282 fewer per 1000 (from 157 fewer to 310 fewer)	Moderate

Quality assessment							No of patients		Effect estimate		Quality
							20 minutes after adenoidectomy; cefazolin		**20 minutes after adenoidectomy; cefazolin**		
							2/51 (3.9%)	7/50 (14.3%)	RR: 0.28 (0.06 to 1.28)	101 fewer per 1000 (from 132 fewer to 39 more)	Very low

[1] Randomisation, concealment not described. Incidence of bacteraemia at baseline not reported and power calculation not reported.
[2] Single study analysis
[3] Very serious imprecision as 95%Cis crosses over both the default appreciable benefit and harm (0.75 and 1.25)

Table 160: Antibiotic vs placebo/no prophylaxis for bacteraemia in those undergoing gastrointestinal procedures

Quality assessment							No of patients		Effect estimate		Quality
No of studies	**Design**	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Other considerations**	**Antibiotic**	**No prophylaxis/ placebo**	**Relative (95% CI)**	**Absolute**	
Outcome: Incidence of positive blood culture following prophylaxis versus before											
1 (Selby et al., 1994)	RCT	Serious[1]	No serious	N/A[2]	Very serious[3]	No serious	**At baseline**		**At baseline**		Very low
							0/19	1/20[4]	RR: 0.35 (0.02 to 8.1)	33 fewer per 1000 (from 49 fewer to 355 more)	
							5 minutes after endoscopic sclerotherapy; cefotaxime		**5 minutes after endoscopic sclerotherapy; cefotaxime**		
							1/19 (5.3%)	6/19 (31.6%)	RR: 0.17 (0.02 to 1.26)	262 fewer per 1000 (from 309 fewer to 82 more)	
							20 minutes after endoscopic		**20 minutes after endoscopic**		

Quality assessment							No of patients		Effect estimate		Quality
							sclerotherapy; cefotaxime		**sclerotherapy; cefotaxime**		
							0/19 (0%)	0/19 (0%)	-	-	
1 (Rolando et al., 1993)	RCT	Serious[5]	No serious	N/A[2]	Very serious[3]	No serious	**At baseline[4]**		**At baseline**		Very low
							NR	NR	-	-	
							30 minutes post-sclerotherapy; imipenem/cilastatin		**30 minutes post-sclerotherapy; imipenem/cilastatin**		
							1/57[7] (2%)	5/58[6] (8%)	RR: 0.2 (0.02 to 1.69)	69 fewer per 1000 (from 84 fewer to 59 more)	
1 (Harris et al., 1999)	Meta-analysis of 4 RCTs	Serious[8]	No serious	No serious	Very serious[3]	No serious	**At baseline**		**At baseline**		Very low
							NR	NR	-	-	
							Post ERCP		**Post ERCP**		
							NR	NR	RR: 0.39 (0.12 to 1.29)[9]	NR	
Adverse events											
Mortality											
1 (Selby et al., 1994)	RCT	Serious[1]	No serious	N/A[2]	Very serious[3]	No serious	2/19 (10.5%)	5/19 (26.3%)	RR: 0.4 (0.09 to 1.81)	158 fewer per 1000 (from 239 fewer to 213 more)	Very low

[1] Blinding not described and power calculation not reported.
[2] Single study analysis
[3] Very serious imprecision as the 95%Cis crosses over both the default appreciable benefit and harm (0.75 and 1.25)
[4] Excluded from further analysis as subject positive before procedure
[5] Serious risk of bias as concealment and blinding not described, power calculation not reported.
[6] 2/97 subjects were positive for bacteraemia before the endoscopy and therefore excluded; unclear which group subjects were from
[7] Some subjects had more than one sclerotherapy session
[8] Serious risk of bias because overall quality of individual studies assessed but not reported, also unclear whether any subjects were bacteraemic before the procedure in the individual studies
[9] As reported in study

Table 161: Antibiotic vs placebo/no prophylaxis for bacteraemia in those undergoing genitourinary procedures

Quality assessment							No of patients		Effect estimate		Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Antibiotic	No prophylaxis/ placebo	Relative (95% CI)	Absolute	
Outcome: Incidence of positive blood culture following prophylaxis versus before											
1 (Allan et al., 1985)	RCT	Serious[1]	No serious	N/A[2]	No serious	No serious	**At baseline**		**At baseline**		
							NR	NR	-	-	
							After completion of transurethral prostatectomy; mezlocillin		**After completion of transurethral prostatectomy; mezlocillin**		
							2/50 (4%)	16/50 (32 %)[3]	RR: 0.12 (0.03 to 0.52)	282 fewer per 1000 (from 154 fewer to 310 fewer)	Moderate
							First day post-op and after removal of catheter		**First day post-op and after removal of catheter**		
							NR	NR	NS[4]		
1 (Bhattacharya et al., 1995)	RCT	Serious[5]	No serious	N/A[2]	Serious[6]	No serious	**At baseline**		**At baseline**		
							NR	NR	-	-	
							Immediately after transcervical resection or laser ablation of endometrium; augmentin		**Immediately after transcervical resection or laser ablation of endometrium; augmentin**		
							1/55 (2%)	10/61 (16%)	RR: 0.11 (0.01 to 0.84)	146 fewer per 1000 (from 26 fewer to 162 fewer)	Low

Quality assessment							No of patients		Effect estimate		Quality
1 (Qiang et al., 2005)	Systematic review of 10 RCTs	Serious[7]	No serious	N/A[8]	Not assessable	No serious	**After transurethral resection of prostate** 8/792 (1%)	24/602 (4%)	**After transurethral resection of prostate** Risk difference: -0.02 (-0.04 to 0.00)[9]	31 fewer per 1000 (from 12 fewer to 37 fewer)	Moderate
Adverse events											
Reported in study as post-operative outcome within 2 weeks of endometrial ablation:											
Pain											
1 (Bhattacharya et al., 1995)	RCT	Serious[10]	No serious	N/A[2]	Serious[11]	No serious	29/55 (52.7%)	26/61 (42.6%)	RR: 1.24 (0.84 to 1.82)	102 more per 1000 (from 68 fewer to 350 more)	Low
Offensive discharge											
1 (Bhattacharya et al., 1995)	RCT	Serious[12]	No serious	N/A[2]	Very serious[13]	No serious	14/55 (25.5%)	14/61 (23%)	RR: 1.11 (0.58 to 2.11)	25 more per 1000 (from 96 fewer to 255 more)	Very low
Fever											
1 (Bhattacharya et al., 1995)	RCT	Serious[14]	No serious	N/A[2]	Serious[9]	No serious	9/55 (16.4%)	4/61 (6.6%)	RR: 2.5 (0.81 to 7.65)	98 more than per 1000 (from 12 fewer to 436 more)	Low

[1] Unclear if subjects lost from control arm as percentages do not match up to number randomised, blood culture methods not reported, number bacteraemic before procedure not reported. power calculation not reported.
[2] Single study analysis
[3] Percentage calculated by reviewer based on assumption that denominator is 50 (i.e. no subjects lost)
[4] As reported in study. Relative risk and absolute measures could not be calculated as raw data not reported in study
[5] Characteristics of subjects not reported, incidence of bacteraemia before procedure not reported
[6] Serious imprecision as 95%Cis wide and crosses over the default appreciable benefit (0.75)
[7] Serious risk of bias as unclear how heterogeneity was assessed

[8] Not reported in study therefore could not be assessed
[9] As reported in study
[10] Characteristics of subjects not reported, incidence of bacteraemia before procedure not reported
[11] Serious imprecision as 95%CI crosses over the default appreciable harm (1.25)
[12] Characteristics of subjects not reported, incidence of bacteraemia before procedure not reported
[13] Very serious imprecision as 95% CIs crosses over both the default appreciable benefit and harm (0.75 and 1.25)
[14] Characteristics of subjects not reported, incidence of bacteraemia before procedure not reported

H.58 Review question 7b

Table 162: 0.12% chlorhexidine studies vs no prophylaxis/placebo for bacteraemia (dichotomous outcomes)

Quality assessment							No of patients		Effect estimate		Quality
No of studies	**Design**	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Other considerations**	**0.12% chlorhexidine rinse**	**No prophylaxis/ placebo**	**Relative (96% CI)**	**Absolute**	
Outcome: Incidence of positive blood culture following prophylaxis versus before											
1 (Duvall et al., 2013)	RCT	Serious[1]	None	N/A[2]	Very serious[3]	No serious	**Reported in study as incidence of at least one positive culture of the 4 blood draws per subject (including baseline)**		RR: 1.2 (0.54 to 2.67)	100 more per 1000 (from 230 fewer to 835 more)	Very low
							6/10 (60%)	5/10 (50%)			
1 (Brown et al., 1998)	RCT	Serious[4]	None	N/A[2]	Very serious[3]	No serious	**At baseline**		**At baseline**		Very low
							0/31 (0%)	0/24 (0%)	-	-	
							At 90 seconds after intraoral suture removal		**At 90 seconds after intraoral suture removal**		
							4/31 (12.9%)	2/24 (8.3%)	RR: 1.55 (0.31 to 7.76)	46 more per 1000 (from 57 fewer to 563 more)	

[1] Serious risk of bias because blinding not described and incidence of positive blood cultures at baseline not reported separately but together with incidence at any of the blood Draws, power calculation not reported and study only gave one dose of rinse before procedure.
[2] Single study analysis

[3] Very serious imprecision as 95%CIs are wide and cross over both the default appreciable benefit and harm (0.75 and 1.25)
[4] Serious risk of bias because randomisation, allocation concealment and blinding not described. Power calculation not reported and study only gave one dose of rinse before procedure.

Table 163: 0.12% chlorhexidine studies vs no prophylaxis/placebo for bacteraemia (continuous outcomes)

Quality assessment							No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	0.12% chlorhexidine	Placebo	Mean difference (95% CI)	
Outcome: Bacteraemia levels/intensity following prophylaxis versus before										
Reported in study as total mean magnitude of bacteraemia (cfu/ml)										
1 (Duvall et al., 2013)	RCT	Serious[1]	None	N/A[2]	Very serious[3]	No serious	N=10 Mean (SD): 2.76 (4.28)	N=10 Mean (SD): 3.61 (7.09)	MD = 0.85 lower (5.98 lower 4.28 higher)	Very low
Reported in study as mean magnitude of bacteraemia per blood draw (cfu/ml)										
Blood draw 1 (at baseline once the IV access line was established)										
1 (Duvall et al., 2013)	RCT	Serious[1]	None	N/A[2]	Not assessable[4]	No serious	N=10 Mean (SD): 0.04 (0.13)	N=10 Mean (SD): 0 (0)	MD = 0 higher (0 to 0 higher)	Moderate
Blood draw 2 (1.5 minutes following initiation of the mucogingival flap#32)										
1 (Duvall et al., 2013)	RCT	Serious[1]	None	N/A[2]	Very serious[3]	No serious	N=10 Mean (SD): 0.18 (0.29)	N=10 Mean (SD): 1.26 (3.67)	MD = 1.08 lower (3.36 lower to 1.2 higher)	Very low
Blood draw 3 (1.5 minutes following initiation of mucogingival flap #17)										
1 (Duvall et al., 2013)	RCT	Serious[1]	None	N/A[2]	Very serious[3]	No serious	N=10 Mean (SD): 2.37 (4.11)	N=10 Mean (SD): 1.90 (5.36)	MD = 0.47 higher (3.72 lower to 4.66 higher)	Very low
Blood draw 4 (10 minutes following initiation of mucogingival flap #17)										
1 (Duvall et al., 2013)	RCT	Serious[1]	None	N/A[2]	Serious[5]	No serious	N=10 Mean (SD): 0.17 (0.24)	N=10 Mean (SD): 0.45 (0.83)	MD = 0.28 lower (0.82 lower to 0.26 higher)	Low

[1] Serious risk of bias because blinding not described and incidence of positive blood cultures at baseline not reported separately but together with incidence at any of the blood draws, power calculation not reported and study only gave one dose of rinse before procedure.

[2] Single study analysis
[3] Very serious imprecision as 95%CIs are wide and cross over the default appreciable benefit and harm (-0.5 and +0.5)
[4] Not assessable as mean and SD in comparator arm is zero
[5] Serious imprecision as 95%CIs are wide and cross over the default appreciable benefit (-0.5)

Table 164: 0.2% chlorhexidine vs no prophylaxis/placebo for bacteraemia

Quality assessment							No of patients		Effect estimate		Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	0.2% chlorhexidine rinse	No prophylaxis/ placebo	Relative (95% CI)	Absolute	
Outcome: Incidence of positive blood culture following prophylaxis versus before											
1 (Maharaj et al., 2012)	RCT	Serious[1]	No serious	N/A[2]	Very serious[3]	No serious	**At baseline**		**At baseline**		Very low
							NR	NR	NR	NR	
							At 3 minutes post extraction		**At 3 minutes post extraction**		
							16/40 (40%)	14/40 (35%)	RR: 1.14 (0.65 to 2.02)	49 more per 1000 (from 123 fewer to 357 more)	
1 (Pineiro et al., 2010)	RCT	Serious[4]	No serious	N/A[2]	Very serious[3]	No serious	**At baseline**		**At baseline**		Very low
							0/20 (0%)	1/30 (3.3%)	RR: 0.49 (0.02 to 11.51)	17 fewer per 1000 (from 33 fewer to 350 more)	
							At 30 seconds following dental implant placement		**At 30 seconds following dental implant placement**		
							0/20 (0%)	2/30 (6.7%)	RR: 0.30 (0.01 to 5.84)	47 fewer per 1000 (from 66 fewer to 323 more)	
							At 15 minutes following		**At 15 minutes**		

Quality assessment							No of patients		Effect estimate		Quality
							dental implant placement		**following dental implant placement**		
							0/20 (0%)	1/30 (3.3%)	RR: 0.49 (0.02 to 11.51)	17 fewer per 1000 (from 33 fewer to 350 more)	
1 (Tuna et al., 2012)	RCT	Serious[5]	No serious	N/A[2]	Very serious[3]	No serious	**At baseline[6]**		**At baseline**		Very low
							0/12 (0%)	0/10 (0%)	-	-	
							At 1st minute following extraction		**At 1st minute following extraction**		
							3/12 (25%)	4/10 (40%)	RR: 0.62 (0.18 to 2.16)	152 fewer per 1000 (from 328 fewer to 464 more)	
							At 15th minute following extraction		**At 15th minute following extraction**		
							2/12 (17%)	3/10 (30%)	RR: 0.56 (0.11 to 2.7)	132 fewer per 1000 (from 267 fewer to 510 more)	
1 (Lockhart et al., 1996)	RCT	Serious[7]	None	N/A[2]	No serious	No serious	**At baseline**		**At baseline**		Moderate
							NR	NR	-	-	
							At 1 or 3 minute postextraction		**At 1 or 3 minute postextraction**		
							31/37 (84%)	31/33 (94%)	RR: 0.89 (0.76 to 1.05)	103 fewer per 1000 (from 225 fewer to	

Quality assessment							No of patients		Effect estimate		Quality
										47 more)	
1 (Tomas et al., 2007)	RCT	Serious[8]	None	N/A[2]	**At baseline**	No serious	**At baseline**		**At baseline**		**At baseline**
					Very serious[3]		5/53 (9%)	4/53 (8%)	RR: 1.25 (0.36 to 4.4)	19 more per 1000 (from 48 fewer to 257 more)	Very low
					At 30 seconds		**At 30 seconds**		**At 30 seconds**		**At 30 seconds**
					Serious[9]		42/53 (79%)	51/53 (96%)	RR: 0.82 (0.71 to 0.95)	173 fewer per 1000 (from 48 fewer to 279 fewer)	Low
					At 1 hour		**At 1 hour postextraction**		**At 1 hour postextraction**		**At 1 hour**
					Serious[9]		1/50 (2%)	10/50 (20%)	RR: 0.1 (0.01 to 0.75)	180 fewer per 1000 (from 50 fewer to 198 fewer)	Low
1 (Rahn et al., 1995)	RCT	Serious[10]	None	N/A[2]	Very serious[3]	No serious	**At baseline**		**At baseline**		Very low
							0/40 (0%)	0/40 (0%)	-	-	
							At post dental treatment (2, 4 and 6 minutes cultures)		**At post dental treatment (2, 4 and 6 minutes cultures)**		
							18/40 (45%)	21/40 (52.5%)	RR: 0.86 (0.55 to 1.35)	73 fewer per 1000 (from 236 fewer to	

Quality assessment							No of patients		Effect estimate		Quality
										184 more)	

[1] Serious risk of bias because 1) allocation concealment not described 2) blinding not described 3) number of positive blood cultures before extraction not reported – unclear if subjects were tested for bacteraemia 4) Power calculation not reported 5) Study only gave one dose of rinse before procedure.
[2] Single study analysis
[3] Very serious imprecision as the 95%CIs are wide and crosses over both the default appreciable benefit and harm (0.75 and 1.25)
[4] Serious risk of bias because randomisation, allocation concealment and blinding not described, power calculation not reported, study only gave one dose of rinse before procedure.
[5] Serious risk of bias because allocation concealment and blinding not described, unclear whether it's the same subjects bacteraemic at different time points (possible double counting of subjects), power calculation not reported and study only gave one dose of rinse before procedure.
[6] Those with bacteraemia in the preoperative blood culture were excluded (n=2 from chlorhexidine group)
[7] Numbers in each group not explicitly stated – calculated by reviewer based on percentages reported in study. Incidence of bacteraemia at baseline not reported, power calculation not reported and study only gave one dose of rinse before procedure.
[8] Serious risk of bias because allocation concealment and blinding not described. Unclear if same subjects bacteraemic at different time points, power calculation not reported, study only gave one dose of rinse before procedure.
[9] Serious imprecision as 95%CIs are wide and cross over the default appreciable benefit (0.75)
[10] Serious risk of bias because randomisation and concealment not described. Also, single blind only, details not described. Unclear whether same subjects were bacteraemic at the 2, 4 and 6 minutes cultures as data presented together, power calculation not reported and study only gave one dose of rinse before procedure.

Table 165: 0.5% chlorhexidine studies vs control for bacteraemia

Quality assessment							No of patients		Effect estimate		Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	0.5% chlorhexidine rinse	Sterile cotton rolls and saliva ejector	Relative (96% CI)	Absolute	
Outcome: Incidence of positive blood culture following prophylaxis versus before											
1 (Jokinen et al., 1978)	RCT	Very serious[1]	None	N/A[2]	Serious[3]	None	**At baseline**		**At baseline**		Very low
							NR	NR	-	-	
							At 30 to 60 seconds post extraction		**At 30 to 60 seconds post extraction**		
							5/38 (13%)	13/38 (34%)	RR: 0.38 (0.15 to 0.97)	212 fewer per 1000 (from 10 fewer to 291 fewer)	

[1] Study design not clearly described, randomisation, concealment and blinding not described, outcome not pre-specified (therefore selective reporting difficult to judge), incidence of bacteraemia before extraction not reported, power calculation not reported and study only gave one dose of rinse before procedure.
[2] Single analysis study
[3] Serious imprecision as 95%CIs are wide and cross over the default appreciable benefit (0.75)

Table 166: 1% chlorhexidine vs placebo for bacteraemia

Quality assessment							No of patients		Effect estimate		Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	1% chlorhexidine rinse	Placebo	Relative (95% CI)	Absolute	
Outcome: Incidence of positive blood culture following prophylaxis versus before											
1 (MacFarlane et al., 1984)	RCT	Serious[1]	No serious	N/A[2]	No serious	No serious	**At baseline**		**At baseline**		Moderate
							0/20 (0%)	0/20 (0%)	-	-	
							At 30 seconds post extraction		**At 30 seconds post extraction**		
							5/20 (25%)	16/20 (80%)	RR: 0.31 (0.14 to 0.69)	528 fewer per 1000 (from 248 fewer to 668 fewer)	

[1] Serious risk of bias because study design not described in detail, randomisation, allocation concealment and blinding not described, power calculation not reported and study only gave one dose of rinse before procedure.
[2] Single study analysis

Appendix I: Economic search strategy

Databases that were searched, together with the number of articles retrieved from each database are shown in Table 167. The economic search strategy is shown in Table 168. The same strategy was translated for the other databases listed.

Table 167: Economic search summary

Databases	Date searched	No. retrieved
MEDLINE (Ovid)	20/11/2014	144
MEDLINE In-Process (Ovid)	20/11/2014	8
EMBASE (Ovid)	20/11/2014	629
NHS Economic Evaluation Database - NHS EED (CRD, Ovid, Wiley)*	20/11/2014	3
Health Economic Evaluations Database – HEED (Wiley)	20/11/2014	13
PubMed	20/11/2014	323
HTA database (Wiley)	20/11/2014	1

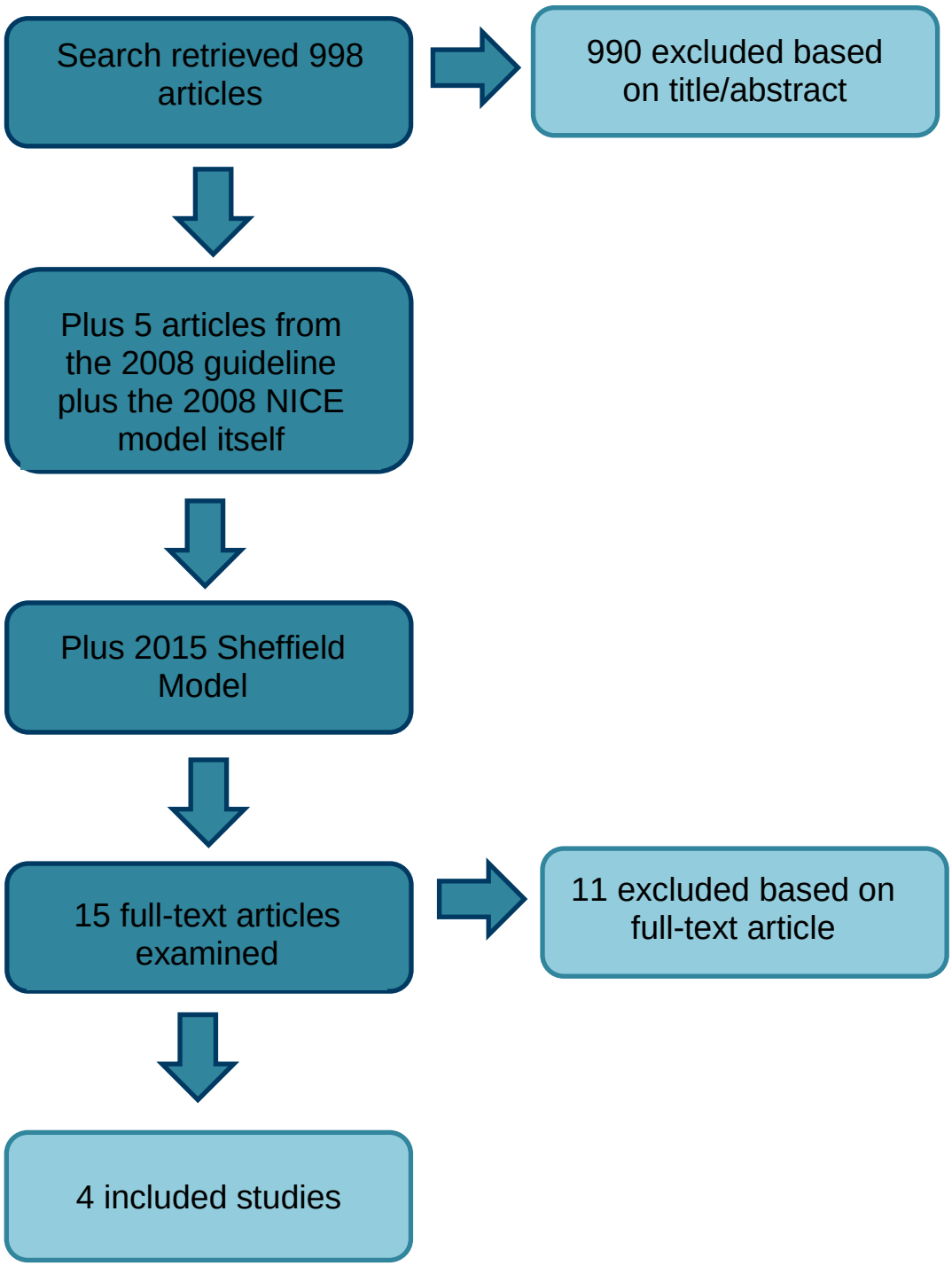
Table 168: Economic search strategy

Database: Medline
Database: Ovid MEDLINE(R) <1946 to November Week 1 2014> Search Strategy: --- 1 exp Endocarditis/ (24453) 2 endocardit$.tw. (25708) 3 1 or 2 (31159) 4 Economics/ (27421) 5 exp "Costs and Cost Analysis"/ (189530) 6 Economics, Dental/ (1867) 7 exp Economics, Hospital/ (20161) 8 exp Economics, Medical/ (13982) 9 Economics, Nursing/ (4025) 10 Economics, Pharmaceutical/ (2601) 11 Budgets/ (9957) 12 exp Models, Economic/ (10669) 13 Markov Chains/ (10687) 14 Monte Carlo Method/ (21237) 15 Decision Trees/ (9157) 16 econom$.tw. (162263) 17 cba.tw. (8891) 18 cea.tw. (16656) 19 cua.tw. (819) 20 markov$.tw. (12445) 21 (monte adj carlo).tw. (21903) 22 (decision adj3 (tree$ or analys$)).tw. (8758) 23 (cost or costs or costing$ or costly or costed).tw. (319228) 24 (price$ or pricing$).tw. (23936) 25 budget$.tw. (17705) 26 expenditure$.tw. (36910) 27 (value adj3 (money or monetary)).tw. (1418)

Database: Medline

28 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (3521)
29 or/4-28 (680212)
30 "Quality of Life"/ (125912)
31 quality of life.tw. (145261)
32 "Value of Life"/ (6025)
33 Quality-Adjusted Life Years/ (7609)
34 quality adjusted life.tw. (6428)
35 (qaly$ or qald$ or qale$ or qtime$).tw. (5256)
36 disability adjusted life.tw. (1266)
37 daly$.tw. (1235)
38 Health Status Indicators/ (20938)
39 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (16200)
40 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1012)
41 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (2822)
42 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (22)
43 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (344)
44 (euroqol or euro qol or eq5d or eq 5d).tw. (4098)
45 (qol or hql or hqol or hrqol).tw. (25908)
46 (hye or hyes).tw. (54)
47 health$ year$ equivalent$.tw. (39)
48 utilit$.tw. (118446)
49 (hui or hui1 or hui2 or hui3).tw. (895)
50 disutili$.tw. (228)
51 rosser.tw. (72)
52 quality of wellbeing.tw. (7)
53 quality of well-being.tw. (350)
54 qwb.tw. (176)
55 willingness to pay.tw. (2290)
56 standard gamble$.tw. (678)
57 time trade off.tw. (778)
58 time tradeoff.tw. (205)
59 tto.tw. (616)
60 or/30-59 (336218)
61 29 or 60 (970661)
62 3 and 61 (566)
63 animals/ not humans/ (3998169)
64 62 not 63 (540)
65 limit 64 to english language (455)
66 limit 65 to ed=20070921-20141120 (144)

Appendix J: Economic review flowchart



Appendix K: Ecomonic excluded studies

Reference	Reason for exclusion
CADTH (2013) Antibiotic prophylaxis for patients with cardiac or orthopedic implants undergoing dental procedures: a review of the clinical effectiveness and guidelines (Structured abstract). Health Technology Assessment Database	Not an economic evaluation, narrative review only
Clemens JD, Ransohoff DF (1984) A quantitative assessment of pre-dental antibiotic prophylaxis for patients with mitral-valve prolapse. Journal of Chronic Diseases, 37 (7): 531-544.	Insufficiently applicable and the analysis has been superseded by more recent studies (NICE 2008; Agha et al. 2005) that are more applicable
Devereux RB, Cynthia JF, Kramer-Fox R, Roberts RB, Ruchlin HS (1994) Cost-effectiveness of infective endocarditis prophylaxis for mitral valve prolapse with or without a mitral regurgitant murmur. Valvular Heart Disease, 74: 1024-1029.	Insufficiently applicable and the analysis has been superseded by more recent studies (NICE 2008; Agha et al. 2005) that are more applicable
Glenny AM, Oliver R, Roberts GJ et al. (2013) Antibiotics for the prophylaxis of bacterial endocarditis in dentistry. [Review][Update of Cochrane Database Syst Rev. 2008;(4):CD003813; PMID: 18843649]. Cochrane Database of Systematic Reviews 10: CD003813.	No economic evaluations included
Guay DR (2012) Antimicrobial prophylaxis in noncardiac prosthetic device recipients. [Review]. Hospital practice (1995) Hospital practice 40: 44-74.	Narrative review only
Gould IM, Buckingham JK (1993) Cost effectiveness of prophylaxis in dental practice to prevent infective endocarditis. British Heart Journal. 70:79-83.	Insufficiently applicable and the analysis has been superseded by more recent studies (NICE 2008; Agha et al. 2005) that are more applicable
Kaye D, Zuckerman JM (2003) Antibiotic Prophylaxis of Endocarditis: What Is Accomplished and at What Cost? Curr Infect Dis Rep 5: 1-3.	Not an economic evaluation
Lockhart PB, Blizzard J, Maslow AL et al. (2013) Drug cost implications for antibiotic prophylaxis for dental procedures. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology 115: 345-53.	Analysis of national spending on antibiotic prophylaxis in the United States
Marks DJ, Hyams C, Koo CY et al. (2014) Clinical features, microbiology and surgical outcomes of infective endocarditis: a 13-year study from a UK tertiary cardiothoracic referral centre. QJM.	Not an economic evaluation
Oliver R, Roberts GJ, Hooper L et al. (2008) Antibiotics for the prophylaxis of bacterial endocarditis in dentistry. Cochrane Database of Systematic Reviews	No economic evaluations included
Tempelhof MW, Reeves G (2012) Infective endocarditis and antibiotic prophylaxis: A systematic review of efficacy and safety of the AHA guidelines. Research Journal of Medical Sciences.6 (4) (pp 193-202), 2012. 193-202.	Narrative review only

Appendix L:Economic evidence tables

L.1 Full economic evidence for dental procedures

The full economic evidence for The Univeristy of Sheffield's 2015 update of the 2008 NICE model is not provided here because it has not been published and is considered academic in confidence. Please refer to Appendix P for further information and an abstract of the analysis.

Bibliographic reference	**Agha Z, Lofgren RP, VanRuiswyk JV (2005) Is antibiotic prophylaxis for bacterial endocarditis cost-effective? Medical Decision Making 25:308-320.**
Evaluation design	

Interventions	Predental antibiotic prophylaxis regimens as per the American Heart Association guidelines at the time: 1. Oral amoxicillin 2 gm, administered 1 hour before the procedure 2. Oral clarithromycin 500 mg, administered 1 hour before the procedure 3. Oral clindamycin 600 mg, administered 1 hour before the procedure 4. Oral cephalexin 2 mg, administered 1 hour before the procedure 5. Intravenous or intramuscular ampicillin 2 mg, administered 30 minutes before the procedure 6. Intravenous or intramuscular cefazolin 1 gm, administered 30 minutes before the procedure 7. Intravenous clindamycin 600 mg, administered 30 minutes before the procedure
Comparator	No prophylaxis
Base-line cohort characteristics	Patients with underlying heart disease with moderate or high risk for developing endocarditis 40 years old
Type of Analysis	Cost-utility analysis and cost-effectiveness sub-analyses (cases of endocarditis prevented and lives saved)
Structure	Decision tree for short term consequences and Markov model for long term survival
Cycle length	1 year
Time horizon	55 years
Perspective	Societal perspective for costs and benefits
Country	United States
Currency unit	US dollars
Cost year	2003
Discounting	3%
Other comments	The authors note that there is no evidence for the effectiveness of antibiotics in preventing

Bibliographic reference	Agha Z, Lofgren RP, VanRuiswyk JV (2005) Is antibiotic prophylaxis for bacterial endocarditis cost-effective? Medical Decision Making 25:308-320.	
		endocarditis, citing 4 small case-control studies, 2 of these failing to show any protective effect, 1 of these showing a protective effective that did not meet statistical significance, and 1 showing a benefit but limited by the potential for recall and misclassification bias. Key assumptions: • Antibiotic effectiveness and compliance is similar for all regimens due to a lack of evidence of effectiveness. • There is no disutility applied to the base case study cohort despite having underlying cardiac conditions associated with moderate or high risk of endocarditis. In other words, it is assumed this health state is equivalent to good health.
Results		

Comparison	7 antibiotic prophylaxis regimes vs. no prophylaxis for **moderate or high risk** cardiac conditions
Incremental cost	Not reported
Incremental effects	Incremental QALYs gained per 10 million patients 1. Oral amoxicillin: -3303 2. Oral clarithromycin: +1125 3. Oral clindamycin: +1118 4. Oral cephalexin: +827 5. Intravenous or intramuscular ampicillin: -3030 6. Intravenous or intramuscular cefazolin: +827 7. Intravenous clindamycin: +1118 Deaths per 10 million patients 1. Oral amoxicillin: +181 (net loss of life) 2. Oral clarithromycin: -19 3. Oral clindamycin: -19 4. Oral cephalexin: -9 5. Intravenous or intramuscular ampicillin: +181 (net loss of life) 6. Intravenous or intramuscular cefazolin: -9 7. Intravenous clindamycin: -19 Cases of endocarditis prevented 1. Oral amoxicillin: 119 2. Oral clarithromycin: 119 3. Oral clindamycin: 119 4. Oral cephalexin: 119

Bibliographic reference	Agha Z, Lofgren RP, VanRuiswyk JV (2005) Is antibiotic prophylaxis for bacterial endocarditis cost-effective? Medical Decision Making 25:308-320.	
		5. Intravenous or intramuscular ampicillin: 119 6. Intravenous or intramuscular cefazolin: 119 7. Intravenous clindamycin: 119
	Incremental cost effectiveness ratio	Per quality adjusted life year [a] 1. Oral amoxicillin: dominated 2. Oral clarithromycin: US$88,007 (2003) or £76,155 (2015) 3. Oral clindamycin: US$101,142 (2003) or £87,522 (2015) 4. Oral cephalexin: US$99,373 (2003) or £85,991 (2015) 5. Intravenous or intramuscular ampicillin: dominated 6. Intravenous or intramuscular cefazolin: US$199,430 (2003) or £172,574 (2015) 7. Intravenous clindamycin: US$411,093 (2003) or £355,733 (2015)
	Conclusion	"Our results suggest that the routine use of amoxicillin and ampicillin for endocarditis prophylaxis is not safe. If the decision to provide prophylaxis for moderate-risk lesions is made, then clarithromycin should be recommended as the 1st-choice regimen, followed by oral cephalexin and oral clindamycin as 2nd-line drugs."
	Comparison	7 antibiotic prophylaxis regimes vs. no prophylaxis for **high risk** cardiac conditions due to **prior endocarditis**
	Incremental cost	Not reported
	Incremental effects	Incremental QALYs gained per 10 million patients 1. Oral amoxicillin: -1885 2. Oral clarithromycin: +2271 3. Oral clindamycin: +2271 4. Oral cephalexin: +1973 5. Intravenous or intramuscular ampicillin: -1885 6. Intravenous or intramuscular cefazolin: +1973 7. Intravenous clindamycin: +2271 Deaths per 10 million patients 1. Oral amoxicillin: +162 (net loss of life) 2. Oral clarithromycin: -38 3. Oral clindamycin: -38 4. Oral cephalexin: -28 5. Intravenous or intramuscular ampicillin: +162 (net loss of life)

Bibliographic reference	Agha Z, Lofgren RP, VanRuiswyk JV (2005) Is antibiotic prophylaxis for bacterial endocarditis cost-effective? Medical Decision Making 25:308-320.	
		6. Intravenous or intramuscular cefazolin: -28 7. Intravenous clindamycin: -38 Cases of endocarditis prevented 1. Oral amoxicillin: 237 2. Oral clarithromycin: 237 3. Oral clindamycin: 237 4. Oral cephalexin: 237 5. Intravenous or intramuscular ampicillin: 237 6. Intravenous or intramuscular cefazolin: 237 7. Intravenous clindamycin: 237
	Incremental cost effectiveness ratio	Per quality adjusted life year [a] 1. Oral amoxicillin: dominated 2. Oral clarithromycin: US$40,334 (2003) or £34,902 (2015) 3. Oral clindamycin: US$199,029 (2003) or £172,227 (2015) 4. Oral cephalexin: US$37,916 (2003) or £32,810 (2015) 5. Intravenous or intramuscular ampicillin: dominated 6. Intravenous or intramuscular cefazolin: US$79,886 (2003) or £69,128 (2015) 7. Intravenous clindamycin: US$199,029 (2003) or £172,226 (2015)
	Conclusion	"For patients with high-risk cardiac lesions (prosthetic valve or history of prior endocarditis) cephalexin should be the 1st choice and clarithromycin or clindamycin 2nd-choice agents. Intravenous regimens are less cost-effective, except in the case of cefazolin for patients with prosthetic valves."

Comparison	7 antibiotic prophylaxis regimes vs. no prophylaxis for **high risk** cardiac conditions due to **a prosthetic valve**
Incremental cost	Not reported
Incremental effects	Incremental QALYs gained per 10 million patients 1. Oral amoxicillin: +407 2. Oral clarithromycin: +4562 3. Oral clindamycin: +4562 4. Oral cephalexin: +4264 5. Intravenous or intramuscular ampicillin: +407 6. Intravenous or intramuscular cefazolin: +4264

Bibliographic reference	Agha Z, Lofgren RP, VanRuiswyk JV (2005) Is antibiotic prophylaxis for bacterial endocarditis cost-effective? Medical Decision Making 25:308-320.	
		7. Intravenous clindamycin: +4562 Deaths per 10 million patients 1. Oral amoxicillin: +124 (net loss of lives) 2. Oral clarithromycin: -76 3. Oral clindamycin: -76 4. Oral cephalexin: -66 5. Intravenous or intramuscular ampicillin: +124 (net loss of lives) 6. Intravenous or intramuscular cefazolin: -66 7. Intravenous clindamycin: -76 Cases of endocarditis prevented 1. Oral amoxicillin: 475 2. Oral clarithromycin: 475 3. Oral clindamycin: 475 4. Oral cephalexin: 475 5. Intravenous or intramuscular ampicillin: 475 6. Intravenous or intramuscular cefazolin: 475 7. Intravenous clindamycin: 475
	Incremental cost effectiveness ratio	Per quality adjusted life year [a] 1. Oral amoxicillin: US$160,871 (2003) or £139,207 (2015) 2. Oral clarithromycin: US$16,818 (2003) or £14,553 (2015) 3. Oral clindamycin: US$19,936 (2003) or £17,251 (2015) 4. Oral cephalexin: US$14,060 (2003) or £12,167 (2015) 5. Intravenous or intramuscular ampicillin: US$498,488 (2003) or £431,359 (2015) 6. Intravenous or intramuscular cefazolin: US$33,480 (2003) or £28,971 (2015) 7. Intravenous clindamycin: US$19,936 (2003) or £17,251 (2015)
	Conclusion	“For patients with high-risk cardiac lesions (prosthetic valve or history of prior endocarditis) cephalexin should be the 1st choice and clarithromycin or clindamycin 2nd-choice agents. Intravenous regimens are less cost-effective, except in the case of cefazolin for patients with prosthetic valves.”

Bibliographic reference	Agha Z, Lofgren RP, VanRuiswyk JV (2005) Is antibiotic prophylaxis for bacterial endocarditis cost-effective? Medical Decision Making 25:308-320.	
Data sources		
	Base-line data	• Moderate or high risk cardiac conditions and dental procedures requiring endocarditis prophylaxis defined by American Heart Association criteria at the time • Population incidence of bacterial endocarditis from 1 study from the literature, 3.8/100,000 person years • Endocarditis cases that occur in patients after a high-risk dental procedure estimated from 1 study, base case 16.8%, range 4% to 23% • Endocarditis cases with a pre-existing cardiac lesion estimated from 1 study as 53%, range 21% to 91% • Number of dental visits in patients with underlying cardiac lesions from a survey from the literature, 2.7 visits per year • Dental procedures requiring antibiotic prophylaxis from 1 study from the literature, 75% • Prevalence of moderate or high risk cardiac lesions was estimated as 10% for the base case, range 5% to 35%
	Effectiveness data	• Antibiotic effectiveness in preventing bacterial endocarditis from 4 studies from the literature, base case RR 0.46, range 0.01 to 1 • Mortality from an acute episode of endocarditis from 1 study from the literature, base case 16%, range 5% to 55% • Valve replacement surgery during or immediately following an acute endocarditis infection, base case 28%, range 20% to 80% • Fatal anaphylactic reactions due to oral amoxicillin or IV ampicillin estimated from two studies from the literature, base case 20 per million, range 0.5 to 40 per million • Fatal anaphylactic reactions due to cephalexin or cefazolin, base case 1 per million, range 0.5 to 5 per million • Fatal anaphylactic reactions due to clarithromycin and clindamycin was estimated, base case 0 per million, varied up to 5 per million in sensitivity analysis • Nonfatal hypersensitivity to amoxicillin or ampicillin estimated from 1 study from the literature, base case 2%, range 0.5% to 10% • Nonfatal hypersensitivity to clarithromycin estimated from 1 study from the literature, base case 0.3%, range 0.1% to 5% • Nonfatal hypersensitivity to clindamycin estimated from 1 study from the literature, base case 0.4%, range 0.1% to 10% • Nonfatal hypersensitivity to cephalexin or cefaxolin estimated from 1 study from the literature, base case 1.7% to 0.5% to 3% • Patients that survived endocarditis go on to require valve surgery at a rate of 4.2% per year for years 1 through 15 and then decreases to 1% per year, from 1 study from the literature • The risk of death was obtained from 1 study from the literature, 12.5%

Bibliographic reference	Agha Z, Lofgren RP, VanRuiswyk JV (2005) Is antibiotic prophylaxis for bacterial endocarditis cost-effective? Medical Decision Making 25:308-320.	
		• Patients who require valve replacement after endocarditis have a 50% annual probability of developing congestive heart failure, from 2 studies from the literature • Patients who do not require valve replacement have a 5% annual probability of developing congestive heart failure, from 2 studies from the literature • Patients who transition to valve replacement or valve replacement with congestive heart failure health states were assigned 3.3 times greater annual mortality compared to the general population based on 3 studies from the literature
	Cost data	• Antibiotics from the Drug Topics Red Book 2000 • Hospital costs based on Medicare diagnosis related groups • Outpatient visits based on published estimates • Treating an antibiotic side effect based on a published estimate • Indirect cost of patient or caregiver time lost were estimated
	Utility data	• Utility score for congestive heart failure was based on a study from the literature that used to the Quality of Well-Being measure, base case 0.63, range 0.25 to 1 • Utility score for valve replacement was an estimate obtained from the literature, base case 0.9, range 0.25 to 1 • Utility score for valve replacement and congestive heart failure was derived by multiplying these two utility scores, base case 0.57, range 0.25 to 1
Uncertainty		

	One-way sensitivity analysis	One way sensitivity analyses for many input parameters were conducted with the target thresholds of US$50,000 and US$100,000 per QALY in mind. All interventions below were compared against no prophylaxis. All ICERs are reported in 2003 US dollars.
		
		Risk of antibiotic fatal side effects
		• Raising the risk of fatal anaphylaxis for clarithromycin from zero to 0.65 per million reached the $100,000 per QALY threshold.
		• Amoxicillin became the favoured strategy with an ICER of $85,421 per QALY when the rate of fatal anaphylaxis was reduced from a base case of 20 per million to 2 per million and the nonfatal side effects rate was reduced to 0.5% from a base case rate of 2% (two way sensitivity analysis).
		
		Incidence of bacterial endocarditis
		• When the incidence of bacterial endocarditis was increased to 62 per million:
		  ○ the ICER was $49,997 per QALY for cephalexin and
		  ○ the ICER was $56,372 per QALY for clarithromycin.
		
		Potentially preventable cases

Bibliographic reference	Agha Z, Lofgren RP, VanRuiswyk JV (2005) Is antibiotic prophylaxis for bacterial endocarditis cost-effective? Medical Decision Making 25:308-320.	

		• When the proportion of BE cases in the population with underlying valve disease was raised from the base case value of 53% to 87%:
		  ○ cephalexin had an ICER of $49,586 per QALY and
		  ○ clarithromycin had an ICER of $56,372 per QALY.
		
		Cost of antibiotics
		• When the cost of clarithromycin was reduced by 42% from $10.43 to $6.10 the ICER was $49,592 per QALY.
		• When the cost of oral clindamycin was reduced by 49% from $11.77 to $6.00 the ICER was $49,715 per QALY.
		• When the price of oral cephalexin was reduced by 54% from $7.65 to $3.50 the ICER was $49,552 per QALY.
		
		Incidence of dental visits that require prophylaxis
		• When the average number of dental visits was decreased from 2 to 1 per year:
		  ○ cephalexin had an ICER of $37,916 per QALY and
		  ○ clarithromycin had an ICER of $56,371 per QALY.
		
		Age of population
		• When the population age was reduced from 40 years of age to 20:
		  ○ cephalexin had an ICER of $41,651 per QALY and
		  ○ clarithromycin had an ICER of $50,788 per QALY.
		• All prophylaxis interventions had ICERs greater than $100,000 per QALY for ages greater than 43 years.
		• All prophylaxis interventions had ICERs greater than $200,000 per QALY for ages above 55 years.
		
		Discount rate
		• At a discount rate of 0% clarithromycin had an ICER of $48,719 per QALY.
		• At a discount rate of 5% clarithromycin had an ICER of $120,329 per QALY.
		
		One way sensitivity analyses of all other variables did not result in any of the antibiotic prophylaxis strategies achieving the thresholds of $50,000 or $100,000 per QALY.

	Probabilistic sensitivity analysis	Not conducted

Bibliographic reference	**Agha Z, Lofgren RP, VanRuiswyk JV (2005) Is antibiotic prophylaxis for bacterial endocarditis cost-effective? Medical Decision Making 25:308-320.**
Applicability	**Partially Applicable** • The analysis was based on the United States healthcare system. • A societal perspective was adopted for both cost and health consequences. • The discount rate used in the base case was 3% rather than 3.5%. • Utilities used to derive quality adjusted life years were based on the Quality of Well-being index of a United States population rather than the EQ-5D with United Kingdom general population preferences. Some utility values were also estimated or a combination of the QWB and the estimations.
Limitations	**Potentially Serious Limitations** • Many of the key parameters driving the model are based on poor and conflicting evidence from literature sources. • Estimates of resource use include productivity losses due to the societal perspective. • Probabilistic sensitivity analysis was not conducted. **Conflicts** No declarations were provided.

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Bibliographic reference	**National Institute for Health and Clinical Excellence (2008) NICE clinical guideline 64 Prophylaxis against infective endocarditis: antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures.**
Evaluation design	

Interventions	Pre-dental antibiotic prophylaxis regimens as specified in the British National Formulary at the time: 1. Oral amoxicillin, 3 g, 1 hour before procedure for people who have not received more than a single dose of a penicillin in the previous, including those with a prosthetic valve (but not those who have had infective endocarditis) 2. Oral clindamycin, 600 mg, 1 hour before procedure for people who are penicillin-allergic or have received more than a single dose of a penicillin in the previous month 3. Intravenous amoxicillin, 1 g, at induction, then oral amoxicillin 500 mg, 6 hours later for people with no special risk including people who have not received more than a single dose of a penicillin in the previous month 4. Oral amoxicillin, 3 g, 4 hours before induction, then oral amoxicillin, 3 g, as soon as possible after the procedure for people with no special risk including people who have not received more than a single dose of a penicillin in the previous month

Bibliographic reference	National Institute for Health and Clinical Excellence (2008) NICE clinical guideline 64 Prophylaxis against infective endocarditis: antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures.	
		5. Amoxicillin plus gentamicin as under general anaesthesia for people with previous endocarditis 6. Intravenous vancomycin, 1 g, over at least 100 minutes, then intravenous gentamicin, 120 mg, at induction or 15 minutes before the procedure for patients who are penicillin-allergic or who have received more than a single dose of a penicillin in the previous month 7. Intravenous teicoplanin 400 mg, plus gentamicin, 120 mg, at induction or 15 minutes before procedure for patients who are penicillin-allergic or who have received more than a single dose of a penicillin in the previous month 8. Intravenous clindamycin, 300 mg, over at least 10 minutes at induction or 15 minutes before procedure, then oral or intravenous clindamycin, 150 mg, 6 hours later for patients who are penicillin-allergic or who have received more than a single dose of a penicillin in the previous month
	Comparators	No prophylaxis
	Base-line cohort characteristics	50 years of age Male
	Type of Analysis	Cost-utility analysis
	Structure	Decision tree for short term impacts, Markov model for long term outcomes
	Cycle length	1 year
	Time horizon	Lifetime
	Perspective	NHS
	Country	United Kingdom
	Currency unit	£
	Cost year	Not stated, 2005-06 reference costs were used
	Discounting	Costs and health outcomes at 3.5%
	Other comments	"Given the paucity of data in key parameters (e.g. risk of developing infective endocarditis following a dental procedure, antibiotic efficacy), the analysis aimed to estimate cost effectiveness based on certain 'what if' scenarios." Key assumptions: • Individual dental procedures can lead directly to the development of infective endocarditis • Antibiotic prophylaxis can reduce that risk • All antibiotic strategies were of equal effectiveness

Bibliographic reference	**National Institute for Health and Clinical Excellence (2008) NICE clinical guideline 64 Prophylaxis against infective endocarditis: antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures.**

Results

Comparison	Antibiotic regimens vs. no prophylaxis **excluding** costs and benefits of future antibiotic prophylaxis 1. Oral amoxicillin 2. Oral clindamycin 3. Intravenous amoxicillin then oral amoxicillin 4. Oral amoxicillin before and oral amoxicillin after 5. Amoxicillin plus gentamicin 6. Intravenous vancomycin then intravenous gentamicin 7. Intravenous teicoplanin plus gentamicin 8. Intravenous clindamycin then oral or intravenous clindamycin
Incremental cost	1. Oral amoxicillin: £1 2. Oral clindamycin: £6 3. Intravenous amoxicillin then oral amoxicillin: £2 4. Oral amoxicillin before and oral amoxicillin after: £2 5. Amoxicillin plus gentamicin then oral amoxicillin: £186 6. Intravenous vancomycin then intravenous gentamicin: £29 7. Intravenous teicoplanin plus gentamicin: £58 8. Intravenous clindamycin then oral or intravenous clindamycin: £14
Incremental effects	1. Oral amoxicillin: 0.00001 2. Oral clindamycin: 0.00001 3. Intravenous amoxicillin then oral amoxicillin: 0.00001 4. Oral amoxicillin before and oral amoxicillin after: 0.00001 5. Amoxicillin plus gentamicin: 0.00001 6. Intravenous vancomycin then intravenous gentamicin: 0.00001 7. Intravenous teicoplanin plus gentamicin: 0.00001 8. Intravenous clindamycin then oral or intravenous clindamycin: 0.00001
Incremental cost effectiveness ratio	1. Oral amoxicillin: £88,069 2. Oral clindamycin: £551,284 3. Intravenous amoxicillin then oral amoxicillin: £179,356 4. Oral amoxicillin before and oral amoxicillin after: £179,769 5. Amoxicillin plus gentamicin: £17,953,043 6. Intravenous vancomycin then intravenous gentamicin: £2,750,466 7. Intravenous teicoplanin plus gentamicin: £5,571,067 8. Intravenous clindamycin then oral or intravenous clindamycin: £1,340,889

Bibliographic reference	National Institute for Health and Clinical Excellence (2008) NICE clinical guideline 64 Prophylaxis against infective endocarditis: antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures.	
	Conclusion	The model suggested that prophylactic antibiotic strategies are not cost effective under all scenarios explored in the present analysis unless optimistic assumptions are made with regard to a number of parameters, chiefly the risk of developing IE following a dental procedure.
	Comparison	Antibiotic regimens vs. no prophylaxis **including** costs and benefits of future antibiotic prophylaxis 1. Oral amoxicillin 2. Oral clindamycin 3. Intravenous amoxicillin then oral amoxicillin 4. Oral amoxicillin before and oral amoxicillin after 5. Amoxicillin plus gentamicin 6. Intravenous vancomycin then intravenous gentamicin 7. Intravenous teicoplanin plus gentamicin 8. Intravenous clindamycin then oral or intravenous clindamycin
	Incremental cost	3. Oral amoxicillin: £26 4. Oral clindamycin: £160 5. Intravenous amoxicillin then oral amoxicillin: £53 6. Oral amoxicillin before and oral amoxicillin after: £53 7. Amoxicillin plus gentamicin then oral amoxicillin: £5193 8. Intravenous vancomycin then intravenous gentamicin: £796 9. Intravenous teicoplanin plus gentamicin: £1612 10. Intravenous clindamycin then oral or intravenous clindamycin: £389
	Incremental effects	9. Oral amoxicillin: 0.00001 10. Oral clindamycin: 0.00001 11. Intravenous amoxicillin then oral amoxicillin: 0.00001 12. Oral amoxicillin before and oral amoxicillin after: 0.00001 13. Amoxicillin plus gentamicin: 0.00001 14. Intravenous vancomycin then intravenous gentamicin: 0.00001 15. Intravenous teicoplanin plus gentamicin: 0.00001 16. Intravenous clindamycin then oral or intravenous clindamycin: 0.00001
	Incremental cost effectiveness ratio	9. Oral amoxicillin: £248,912 10. Oral clindamycin: £1,513,095 11. Intravenous amoxicillin then oral amoxicillin: £498,047 12. Oral amoxicillin before and oral amoxicillin after: £499,175 13. Amoxicillin plus gentamicin: £49,005,022 14. Intravenous vancomycin then intravenous gentamicin: £7,514,982

Bibliographic reference	**National Institute for Health and Clinical Excellence (2008) NICE clinical guideline 64 Prophylaxis against infective endocarditis: antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures.**	
		15. Intravenous teicoplanin plus gentamicin: £15,212,810 16. Intravenous clindamycin then oral or intravenous clindamycin: £3,668,040
	Conclusion	The model suggested that prophylactic antibiotic strategies are not cost effective under all scenarios explored in the present analysis unless optimistic assumptions are made with regard to a number of parameters, chiefly the risk of developing IE following a dental procedure.
Data sources		
	Base-line data	• Risk of IE following a dental procedure from one study from the literature, base case 4.1 per million procedures, range 22 to 93 per million • Dental procedures per year estimated, base case 1.5 procedures per year • Probability of mortality from infective endocarditis, native valves from two studies from the literature, base case 16.4%, range +/- 50% • Probability of mortality from acute endocarditis, prosthetic valves, base case 22.8% from one study from the literature, not varied • Annual probability of developing congestive heart failure following endocarditis estimated from one study from the literature, 8.3%, range +/- 50% • Annual probability of developing congestive heart failure in non-endocarditis cases estimated from one study from the literature, 0.6%, range +/- 50% • Annual probability of valve replacement during or immediately following IE from one study from the literature, base case 34%, range +/- 50% • Probability of valve replacement in years 1 to 10 for endocarditis cases from one study from the literature based on UK valve registry data, base case 1.3%, range +/- 0% • Probability of redo valve replacement, years 1 to 10 from one study from the literature based on UK valve registry data, base case 1.3%, range +/- 50% • Probability of valve replacement after ten years all people from one study from the literature, base case 0.4%, range +/- 50% • Probability of death from valve surgery from one study from the literature, base case 8.2%, range +/- 50% • Overall mortality risk by age and sex from national data set
	Effectiveness data	• Efficacy of prophylaxis assumed, base case RR 0.5, range 0.25 to 0.75 • Probability of non-fatal hypersensitivity to amoxicillin from one study in the literature, base case 0, range 0 to 0.1 per million • Probability of non-fatal hypersensitivity to clindamycin assumed, base case 0, range 0 to 0.1 per million • Probability of non-fatal hypersensitivity to vancomycin assumed, base case 0, range 0 to 0.1 per

Bibliographic reference	National Institute for Health and Clinical Excellence (2008) NICE clinical guideline 64 Prophylaxis against infective endocarditis: antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures.	
		million • Probability of non-fatal hypersensitivity to gentamicin assumed, base case 0, range 0 to 0.1 per million • Probability of non-fatal hypersensitivity to teicoplanin assumed, base case 0, range 1 to 0.1 per million • Probability of fatal anaphylaxis from amoxicillin from two studies from the literature, base case 0 per million, range 0 to 40 per million • Probability of fatal anaphylaxis from other antibiotics assumed and one study from the literature for clindamycin, base case 0 per million, range from 0 to 5 per million
	Cost data	• Hospitalisation costs – NHS reference costs 2005-06 • Medication costs – BNF September 2007 • Labour costs – Personal Social Services Research Unit's Unit Costs of Health and Social Care 2005-06
	Utility data	Most utilities were based on the New York Heart Association functional classification scheme with values estimated from literature sources. • Well – NYHA class I – base case 0.930, range 0.923 to 0.945 • Valve replacement / repair needed – NYHA classes III and IV – base case 0.525, range 0.506 to 0.546 • Successful valve replacement – NYHA classes I and II – base case 0.855, range 0.838 to 0.879 • Congestive heart failure – NYHA class III – base case 0.610, range 0.591 to 0.631 • Hospitalisation with heart failure – one study from the literature – base case 0.570, range 0.480 to 0.800
Uncertainty		
	One-way sensitivity analysis	• The risk of developing IE had to be at least 16 per million procedures for the ICER to reduce to £20,000 per QALY. • When the estimated costs and potential benefits of future prophylaxis are included in the analysis, this threshold rises to 48 per million. • When a 10 year timeframe was adopted, the scenario excluding estimated costs and potential benefits of future antibiotic prophylaxis resulted in a minimum ICER of £204,167 per QALY for amoxicillin (strategy 1) and a maximum ICER of £41,562,056 per QALY for IV amoxicillin and IV gentamycin then oral amoxicillin (strategy 5). • When a 10 year timeframe was adopted, the scenario including the estimated costs and potential benefits of future prophylaxis, the minimum ICER was £427,682 per QALY for strategy 1 (oral amoxicillin) and the maximum ICER was £85,231,144 per QALY for strategy 5 (IV amoxicillin and IV gentamycin followed by oral amoxicillin). • When costs were varied between their upper and lower limits, ICERs ranged from £248,723 per QALY for strategy 1 (oral amoxicillin) to £49,004,833 per QALY for strategy 5 (IV amoxicillin and

Bibliographic reference	National Institute for Health and Clinical Excellence (2008) NICE clinical guideline 64 Prophylaxis against infective endocarditis: antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures.	
		IV gentamycin followed by oral amoxicillin). • When utilities were varied between their upper and lower estimates, ICERs ranged from £244,636.69 per QALY for strategy 1 (oral amoxicillin) to £48,163,308 for strategy 5 (IV amoxicillin plus IV gentamycin followed by oral amoxicillin). • When the starting age of the cohort was reduced to 20 years of age (from 50), the ICER of strategy 1 (oral amoxicillin) was £234,000 per QALY. • When overall mortality risk was changed from an estimate of all-cause mortality to one that excluded deaths from cardiac causes, the ICER was £244,000 per QALY. • When the efficacy of prophylaxis was varied between 25% to 75%, the ICER for strategy 1 was £503,448 and £164,069 per QALY respectively, and the ICER for strategy 2 was £3,031,864 and £1,006,853 respectively. • When the risk of developing IE for all patients with a pre-existing cardiac condition was increased to 22 per million cases per dental procedure (from 4.1 per million), the ICERs ranged from £44,880 per QALY for strategy 1 to £9,057,252 per QALY for strategy 5. • When the risk of developing IE for all patients with a pre-existing cardiac condition was increased to 93 per million cases per dental procedure, strategies 1, 3 and 4 had ICERs that were below the £20,000 per QALY cost-effectiveness threshold with ICERs of £5,124, £12,187 and £12,219 per QALY respectively. The ICERs for all other strategies ranged from £40,962 to £1,387,296 per QALY. • All other one way sensitivity analyses resulted in ICERs that ranged from £169,728 to £867,343 per QALY for strategy 1.
	Three-way sensitivity analysis	The risk of fatal anaphylaxis with amoxicillin, antibiotic efficacy and the risk of developing IE for all patients with a pre-existing cardiac condition per dental procedure were varied concurrently and there were 4 scenarios under which strategy 1 was considered cost-effective: • Risk of developing IE per dental procedure 93 per million, fatal anaphylaxis 0.9 per million, antibiotic efficacy 75%: ICER was £1,667 per QALY • Risk of developing IE per dental procedure 93 per million, fatal anaphylaxis 0.9 per million, antibiotic efficacy 50%: ICER was £5,531 per QALY • Risk of developing IE per dental procedure 93 per million, fatal anaphylaxis 0.9 per million, antibiotic efficacy 25%: ICER was £18,497 per QALY • Risk of developing IE per dental procedure 93 per million, fatal anaphylaxis 10 per million, antibiotic efficacy 75%: ICER was £3416 All other multi-way sensitively analysis results were ICERs ranging from £25,483 to dominated (strategy was more costly and less effective than no phrophylaxis).
	Probabilistic sensitivity analysis	Not conducted

Bibliographic reference	**National Institute for Health and Clinical Excellence (2008) NICE clinical guideline 64 Prophylaxis against infective endocarditis: antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures.**
Applicability	**Directly Applicable**
Limitations	**Minor Limitations** No probabilistic sensitivity analysis No reasonable evidence was identified to support the assumptions that individual dental procedures can lead directly to the development of infective endocarditis or that antibiotic prophylaxis reduces that risk. **Conflicts** Refer to 2008 guideline documentation

Acronyms
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; AHA: American Heart Association; BE: bacterial endocarditis; IE: infective endocarditis; RR: relative risk; NYHA: New York Heart Association
(a) ICERs converted to 2015 UK pounds by using the Campbell and Cochrane Economics Methods Group EPPI Cost Converter available at http://www.c-cemg.org/, accessed 21-22 January 2015

L.26 Full economic evidence for non-dental procedures

Bibliographic reference	**Caviness AC, Cantor SB, Coburn HA, Ward MA (2004) A cost-effectiveness analysis of bacterial endocarditis prophylaxis for febrile children who have cardiac lesions and undergo urinary catheterization in the emergency department. Pediatrics, 113 (5), 1291-1296.**
Evaluation design	

Interventions	1. Amoxicillin 500 mg 2. Vancomycin 200 mg
Comparator	No prophylaxis
Base-line cohort characteristics	• Aged 0 to 24 months, have moderate-risk cardiac lesions, present to the ED with fever, and require urine collection to evaluate the possibility of an underlying urinary tract infection • Moderate-risk cardiac lesions were based on the American Heart Association guidelines at the time and included most congenital cardiac malformations such as ventricular septal defects, acquired valvular dysfunction such as rheumatic heart disease, hypertrophic cardiomyopathy, and mitral valve prolapse with valvular regurgitation and/or thickened leaflets.
Type of Analysis	Cost-utility analysis
Structure	Decision tree
Cycle length	Not applicable

Bibliographic reference	Caviness AC, Cantor SB, Coburn HA, Ward MA (2004) A cost-effectiveness analysis of bacterial endocarditis prophylaxis for febrile children who have cardiac lesions and undergo urinary catheterization in the emergency department. Pediatrics, 113 (5), 1291-1296.	
	Time horizon	Lifetime
	Perspective	Societal
	Country	United States
	Currency unit	$
	Cost year	2000
	Discounting	3%
	Other comments	Clinical assumptions: • Prophylaxis before urinary catheterisation prevents all bacterial endocarditis by preventing bacteraemia. • Amoxicillin and vancomycin are equally effective in preventing bacteraemia. • In the presence of bacteraemia with organisms that cause endocarditis, the incidence of bacterial endocarditis, no matter the cause for the bacteraemia or the type of moderate-risk cardia lesion. • In the absence of bacteraemia or in the presence of organisms not typically associated with endocarditis, bacterial endocarditis does not occur. • There is no increased risk of bacteraemia or bacterial endocarditis with contaminated urine specimens. • Bacteraemia occurs immediately after instrumentation and is followed immediately by bacterial seeding of the endocardium.

Bibliographic reference	**Caviness AC, Cantor SB, Coburn HA, Ward MA (2004) A cost-effectiveness analysis of bacterial endocarditis prophylaxis for febrile children who have cardiac lesions and undergo urinary catheterization in the emergency department. Pediatrics, 113 (5), 1291-1296.**

Results

Comparison	**Amoxicillin** vs. no prophylaxis
Incremental cost	US$495.30 (2000)
Incremental effects	-0.00045
Incremental cost effectiveness ratio	Dominated
Conclusion	"Antiobiotic prophylaxis for urinary catheterisation of febrile children who are aged 0 to 2 years and have moderate-risk cardiac lesions is not a cost-effective use of health care resources. This is true for the regimen using amoxicillin and for the regimen using vancomycin."

Comparison	**Vancomycin** vs. no prophylaxis
Incremental cost	US$666.16 (2000)
Incremental effects	0.00005
Incremental cost effectiveness ratio	US$13,323,200 (2000) or £12,213,677 (2015) [a]
Conclusion	"Antiobiotic prophylaxis for urinary catheterisation of febrile children who are aged 0 to 2 years and have moderate-risk cardiac lesions is not a cost-effective use of health care resources. This is true for the regimen using amoxicillin and for the regimen using vancomycin."

Data sources

Base-line data	• Prevalence of urinary tract infection in febrile children from 3 studies from the literature, base case 3.9%, range 3.3% to 5.3% • Prevalence of bacterial endocarditis causing organisms among urinary tract infection causing organisms from 2 studies from the literature, base case 3.4%, range 0% to 100% • Incidence of bacteraemia after urinary catheterisation from 2 adult studies, base case 23.1%, range 14.3% to 26.3% • Incidence of endocarditis in children with rheumatic heart disease after bacteraemia from tooth extractions from two studies, 1.1% and 2.2%
Effectiveness data	• Prophylactic efficacy of antibiotics in preventing bacteraemia from 1 clinical trial and 2 decision analyses, base case 89%, range 0% to 100% • Mortality from bacterial endocarditis from 4 studies from the literature, base case 11.6%, range 0% to 13.5% • Rate of decompensation requiring surgery for survivors from 4 studies from the literature, base case 18.6%, range 0% to 25% • Incidence of CHF attributable to bacterial endocarditis from 1 study from the literature, base case 27.1% (95% CI 14.5 to 39.7%)

Bibliographic reference	Caviness AC, Cantor SB, Coburn HA, Ward MA (2004) A cost-effectiveness analysis of bacterial endocarditis prophylaxis for febrile children who have cardiac lesions and undergo urinary catheterization in the emergency department. Pediatrics, 113 (5), 1291-1296.	
		• Average survival in children who recover from bacterial endocarditis with congestive heart failure from 1 adult study from the literature, 6.2 years • Mild reactions due to amoxicillin from 1 study from the literature, base case 1%, range 0.7% to 10% • Anaphylaxis due to amoxicillin estimated, base case 0.03%, range 0.02% to 0.04% • Mortality due to penicillin estimated, base case 0.002%, range 0% to 0.004% • Allergic or anaphylactic reactions due to vancomycin nil from 2 study from the literature
	Cost data	• Antibiotics from 2001 Drug Topics Red Book • Nursing labour for delivery from national data sets • Parental time from work missed based on average wages from national data sets • Mild anaphylactic reactions in the emergency department taken one study from the literature • Medical care preceding death from anaphylaxis assumed to be $2000 • Endocarditis, mitral valve replacement, congestive heart failure from one study from the literature • Outpatient visits from Medicaid charges for 2000
	Utility data	• Endocarditis utility score from the Years of Healthy Life Measure, base case 0.58, range 0.29 to 0.84 • Patients recovering fully from endocarditis return to their baseline quality of life, represented by mitral valve disorder with a utility score of 0.81, range 0.72 to 0.92 (range derived from other moderate-risk lesions) (Years of Healthy Life Measure) • Utility score for congestive heart failure from the Years of Healthy Life Measure, base case 0.40, range 0.17 to 0.55
Uncertainty		
	One-way sensitivity analysis	• When all antibiotic-related deaths due to amoxicillin were excluded, the ICER was US$9,875,800 (2000) or £9,053,368 (2015). • When the prevalence of urinary tract infections is increased to 100% (from 3.9%), the ICER for amoxicillin was $311,507 and $427,966 for vancomycin. • The conclusions were robust to all other sensitivity analyses.
	Probabilistic sensitivity analysis	Not undertaken

Bibliographic reference	**Caviness AC, Cantor SB, Coburn HA, Ward MA (2004) A cost-effectiveness analysis of bacterial endocarditis prophylaxis for febrile children who have cardiac lesions and undergo urinary catheterization in the emergency department. Pediatrics, 113 (5), 1291-1296.**
Applicability	**Partially Applicable** • Study based on the US healthcare system • Societal perspective taken for costs • Discount rate of 3% used • Years of Healthy Life Measure used for utilities to derive quality adjusted life years
Limitations	**Minor Limitations** • Decision tree used for model structure whereas a Markov model may have been more appropriate to model long term consequences • Parameters used for effectiveness were based on the limited evidence available in the literature • Full range of sensitivity analyses not reported • Probabilistic sensitivity analysis not done **Conflicts** No declaration provided

Acronyms
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; AHA: American Heart Association; BE: bacterial endocarditis; IE: infective endocarditis; CI: confidence interval
(a) ICERs converted to 2015 UK pounds by using the Campbell and Cochrane Economics Methods Group EPPI Cost Converter available at http://www.c-cemg.org/, accessed 21-22 January 2015

Appendix M: Quality assessment

Q3

Quality criteria for prognostic/clinical prediction question (Hayden's checklist)

Author	Criteria						Quality
	1	2	3	4	5	6	
Mohee (2014)	Y	U	Y	Y	Y	N	LRB
Chen (2013)	Y	U	Y	Y	N	Y	LRB
Ammar (2013)	Y	U	N	Y	U	N	HRB
Duval (2006)	Y	U	Y	Y	N	N	HRB
Lacassin (1995)	Y	U	Y	N	U	Y	HRB
Strom (2000)	Y	U	Y	Y	U	N	HRB

Y = Yes; N = No; U = Unclear

Hayden's checklist for prognostic/clinical prediction studies

	Criteria	Circle or highlight one option for each question		
1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes	No	Unclear
2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Yes	No	Unclear
3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Yes	No	Unclear
4	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias	Yes	No	Unclear
5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes	No	Unclear
6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes	No	Unclear

Q4

Quality criteria for controlled before and after (CBA) designs

Author	Criteria							Quality
	A	B	C	D	E	F	G	
Tuna (2012)	D	D	NC	ND	ND	N/A	D	HRB
DuVall (2013)	D	D	NC	ND	ND	N/A	D	HRB
Lockhart (2008)	D	D	D	ND	ND	N/A	D	LRB
Cherry (2007)	D	D	NC	ND	ND	N/A	D	HRB
Morozumi (2010)	D	D	ND	ND	ND	N/A	D	HRB
Pineiro (2010)	D	D	NC	ND	ND	N/A	D	HRB
Sonbol (2009)	D	D	NC	ND	ND	N/A	D	HRB
Lucas (2002)	D	D	NC	NC	ND	N/A	D	HRB
Roberts (2000)	D	D	NC	ND	ND	N/A	D	HRB

Roberts (2006)	D	D	NC	ND	ND	N/A	D	HRB
Roberts (1998)	D	D	ND	ND	ND	N/A	D	HRB
Tomas (2007)	D	D	NC	ND	ND	N/A	D	HRB
Yokoyama (2014)	D	D	ND	ND	ND	N/A	D	HRB
Zuccaro (1998)	D	D	NC	ND	ND	N/A	D	HRB
Assaf (2007)	D	D	NC	D	ND	N/A	D	LRB
Yagci (2013)	D	ND	NC	ND	ND	N/A	D	HRB
Zhang (2013)	D	ND	NC	ND	ND	N/A	D	HRB
Sharif-Kashani (2010)	D	ND	NC	ND	ND	N/A	D	HRB
El Batrawy (2014)	D	ND	NC	ND	ND	N/A	D	HRB
Saayman (2009)	D	ND	NC	ND	ND	N/A	D	HRB
Ho (1991)	D	NC	NC	NC	ND	N/A	D	HRB
London (1986)	D	ND	NC	ND	ND	N/A	D	HRB
Melendez (1991)	D	ND	NC	ND	ND	N/A	D	HRB
Roudaut (1993)	D	D	NC	NC	ND	N/A	D	HRB
Shyu (1992)	D	ND	NC	ND	ND	N/A	D	HRB
Yildirim (2003)	D	NC	NC	NC	ND	N/A	D	HRB
Min (2008)	D	D	NC	NC	ND	N/A	D	HRB
Chun (2012)	D	ND	NC	ND	ND	N/A	D	HRB
Weickert (2006)	D	D	NC	NC	ND	N/A	D	HRB
Kullman (1992)	D	ND	NC	ND	ND	N/A	D	HRB

D = Done; NC= Not clear; ND = Not done; NRB = No risk of bias; LRB = Low risk of bias; HRB = High risk of bias

Cochrane Effective Practice and Organisation of Care Review Group (EPOC)

Quality Checklist for before-and-after study (as suggested in Appendix H, Developing NICE guidelines - the Manual, NICE 2014)

(Reference)

http://epoc.cochrane.org/sites/epoc.cochrane.org/files/uploads/datacollectionchecklist.pdf

Quality criteria for controlled before and after (CBA) designs

Seven standard criteria are used for CBAs included in EPOC reviews:

A) Baseline measurement

Score DONE if performance or patient outcomes were measured prior to the intervention, and no substantial differences were present across study groups (e.g. where multiple pre intervention measures describe similar trends in intervention and control groups);

Score NOT CLEAR if baseline measures are not reported, or if it is unclear whether baseline measures are substantially different across study groups;

Score NOT DONE if there are differences at baseline in main outcome measures likely to undermine the post intervention differences (e.g. are differences between the groups before the intervention similar to those found post intervention).

b) Characteristics for studies using second site as control

Score DONE if characteristics of study and control providers are reported and similar;

Score NOT CLEAR if it is not clear in the paper e.g. characteristics are mentioned in the text but no data are presented;

Score NOT DONE if there is no report of characteristics either in the text or a table OR if baseline characteristics are reported and there are differences between study and control providers.

c) Blinded assessment of primary outcome(s) (protection against detection bias)*

Score DONE if the authors state explicitly that the primary outcome variables were assessed blindly OR the outcome variables are objective e.g. length of hospital stay, drug levels as assessed by a standardised test;

Score NOT CLEAR if not specified in the paper;

Score NOT DONE if the outcomes were not assessed blindly.

Primary outcome(s) are those variables that correspond to the primary hypothesis or question as defined by the authors. In the event that some of the primary outcome variables were assessed in a blind fashion and others were not, score each separately and label each outcome variable clearly.

d) Protection against contamination

Studies using second site as control

Score DONE if allocation was by community, institution, or practice and is unlikely that the control group received the intervention;

Score NOT CLEAR if providers were allocated within a clinic or practice and communication between experimental and group providers was likely to occur;

Score NOT DONE if it is likely that the control group received the intervention (e.g. cross-over studies or if patients rather than providers were randomised).

e) Reliable primary outcome measure(s)

Score DONE if two or more raters with at least 90% agreement or kappa greater than or equal to 0.8 OR the outcome is obtained from some automated system e.g. length of hospital stay, drug levels as assessed by a standardised test;

Score NOT CLEAR if reliability is not reported for outcome measures that are obtained by chart extraction or collected by an individual;

Score NOT DONE if agreement is less than 90% or kappa is less than 0.8.

In the event that some outcome variables were assessed in a reliable fashion and others were not, score each separately and label each outcome variable clearly.

f) Follow-up of professionals (protection against exclusion bias)

Score DONE if outcome measures obtained 80-100% subjects allocated to groups. (Do not assume 100% follow-up unless stated explicitly.);

Score NOT CLEAR if not specified in the paper;

Score NOT DONE if outcome measures obtained for less than 80% of patients allocated to groups.

g) Follow-up of patients

Score DONE if outcome measures obtained 80-100% of patients allocated to groups or for patients who entered the study. (Do not assume 100% follow-up unless stated explicitly.);

Score NOT CLEAR if not specified in the paper;

Score NOT DONE if outcome measures obtained for less than 80% of patients allocated to groups or for less than 80% of patients who entered the study.

Appendix N: Supporting information

N.1 Incidence of bacteraemia over time in those receiving antibiotics vs no prophylaxis/placebo

Study	Timepoints and incidence of bacteraemia				Trend
Sanchez-Carrion 2006	B: NR	30 secs: 3.9%	20 mins: 3.9%	-	
	B: NR	30 secs: 32.7%	20 mins: 14.3%	-	↓
Diz 2006	B: 5%	30 secs: 46.4%	15 mins: 10.7%	1 hr: 3.7%	↓ (Amoxicillin)
	B: 12.5%	30 secs: 85.1%	15 mins: 70.4%	1hr: 22.2%	↓ (Clindamycin)
	B: 7.5%	30 secs: 56.9%	15 mins: 24.1%	1hr: 7.1%	↓ (Moxifloxacin)
	B: 9.4%	30 secs: 96.2%	15 mins: 64.2%	1 hr: 20%	↓
Hall 1993	B: 0%	During extraction: 90%	10 mins after: 70%	-	↓ (Penicillin V)
	B: 0%	During extraction: 85%	10 mins after: 60%	-	↓ (Amoxicillin)
	B: 0%	During extraction: 90%	10 mins after: 80%	-	↓
Hall 1996	B: 0%	During extraction: 79%	10 mins after: 53%	-	↓
	B: 0%	During extraction: 85%	10 mins after: 47%	-	↓
Wahlman 1999	B: NR	10 mins after surgery: 23%	30 mins after surgery: 20%	-	↓
	B: NR	10 mins after surgery: 79%	10 mins after surgery: 69%	-	↓
Selby 1994	B: 0%	5 mins: 5.3%	4 hrs: 0%	24 hrs: 0%	↓
	B: 0%	5 mins:	4 hrs: 5%	24 hrs: 0%	↓

		31.6%			
Lockhart 2004	B after intubation: 4%	15mins: 2%	30mins: 0%	45mins: 0%	↓
	B after intubation: 18%	15mins: 18%	30mins: 16%	45mins: 14%	↓
Lockhart 2008	B: 0%	5 mins: 33%	20 mins: 1%	-	↓
	B: 0%	5 mins: 58%	20 mins: 10%	-	↓

1 NR: not reported

2 B: baseline

3 Antibiotic prophylaxis

4 No prophylaxis/placebo

N.2 5 Incidence of bacteraemia over time in those receiving 6 chlorhexidine compared to no prophylaxis/placebo

Study	Timepoints and incidence of bacteraemia				Trend
Pineiro 2010	B: 0%	30 secs: 0%	15 mins: 0%	-	-
	B: 3%	30 secs: 7%	15 mins: 3%	-	↓
Tuna 2012	B: 0%	1 mins: 25%	15 mins: 17%	-	↓
	B: 0%	1 mins: 40%	15 mins: 30%	-	↓
Tomas 2007	B: 9%	30 secs: 79%	15 mins: 30%	1 hr: 2%	↓
	B: 8%	30 secs: 96%	15 mins: 64%	1 hr: 20%	↓

7 B: baseline

8 Chlorhexidine prohylaxis

9 No prophylaxis/placebo

10

11

12

13

14

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Appendix O: Critique of Dayer et al. (2014) study by Ramsay (2015)

Methods Critique

Incidence of infective endocarditis in England, 2000–13: a secular trend, interrupted time-series analysis by Dayer *et al*

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Date completed: **4th February 2015**

Declared competing interests of the author

The author is statistical editor for the Cochrane Effective Practice and Organisation of Care Group and as such was involved in developing the risk of bias assessment tool for interrupted time series used in this report.

Rider on responsibility for report

The Health Services Research Unit is supported by a core grant from the Chief Scientist Office of the Scottish Government Health and Social Care Directorates. The views and opinions expressed herein are those of the author and do not necessarily reflect those of the Chief Scientist Office or the Department of Health.

This report contains a summary, description, critique and quality assessment of the methods used in Dayer MJ *et al*. Incidence of infective endocarditis in England, 2000–13: a secular trend, interrupted time-series (ITS) analysis. *Lancet* http://dx.doi.org/10.1016/S0140-6736(14)62007-9.

1. Summary

A brief summary of the critique is given below:

- There was no factual error with modelling approach undertaken in paper
- Data for incidence of endocarditis (Figure 2 in original paper) and incidence of high and low risk cases (Figure 3 in original paper) were abstracted from the graph and original paper analysis confirmed
- Exploratory investigation of data suggested that two straightlines might not be an adequate description of the series, implying that the change in slope in original paper is likely biased

- Multiple change-points seem possible rather than only one at the point of guideline introduction
- Reanalysis of series suggests the change in slope estimate is primarily driven by whether the post-intervention data is a straightline (as in the original paper) or not
- If an additional interruption is incorporated at June 2011, the change in slope at guideline introduction is reduced to zero, suggesting no effect of guidance on trends
- Applying the Cochrane Effective Practice and Organisation of Care risk of bias assessment for interrupted time series suggests the study is at high risk of bias
- Taking all evidence into account, I believe the effect of change in slope is biased and the published estimates are likely too high

2. Description of methods used by Dayer paper

2.1 Interrupted time series

Dayer *et al* applied a segmented regression time series model to monthly data points from January 2000 until end March 2013 (159 data points in total). The interruption was assumed to have occurred at end of March 2008, therefore 99 data points were assumed in the pre-intervention data and 60 data points in the post-intervention data. No other interruptions were assumed to have occurred. The regression lines before and after the interruption were assumed to be linear (straight lines). Recognising that the data may contain serial correlation (also known as autocorrelation) (i.e. that points closer in time may be more correlated with each other than points further away), investigation of autocorrelation functions and partial autocorrelation functions was undertaken. If serial correlation was identified, it could be adjusted for in the regression model though it was not stated in the paper exactly how this was performed.

Two effect sizes were produced by the regression model. A *change in level* and a *change in slope*. A change in level relates to an instantaneous change (or "interruption") in the time series at March 2008. If the effect is positive, then there is predicted to have been more cases of endocarditis in March 2008 than would have been predicted by the trend in the pre-intervention data. If the effect is negative then there are fewer cases than would have been expected. The change in slope relates to the difference in the monthly trend pre-intervention versus the monthly trend post-intervention (after the interruption). If the change in slope effect is positive then there is predicted to have been more cases of endocarditis per month than would have been predicted by the trend in the pre-intervention data.

Figure 2 in Dayer et al provides the main finding from the interrupted time series analysis. The change in slope was +0.11 (95% CI 0.05, 0.16; p<0.0001) and the change in level was -0.45 (95% CI -2.54, 1.63; p=0.670). These effects were interpreted as providing no statistically significant evidence for an instantaneous change in level in March 2008, but there was strong evidence for a change in the slope that suggested there was an increase in the incidence of endocarditis by 0.11 per ten million per month than would have been expected by chance.

2.2 Change-point analysis

In an attempt to confirm the robustness of the segmented regression, Dayer *et al* used change-point analysis to calculate the optimum positioning and number of data changepoints using the R change-point package that implements the Hinkley algorithm. In simple terms, the Hinkley algorithm is a form of binary segmentation whereby a single changepoint test-statistic is applied to the whole series and then if one is identified the data set is then split into two at that changepoint and each portion before and after the changepoint is then searched individually for further changepoints and the analysis recursively cuts the data set up into increasingly smaller chunks searching for significant changes in

mean levels before and after the cuts. The method is distribution-free and assumes that the datapoints are identical and independent. Given the chance of spuriously picking up changepoints because the entire sample space is being recursively searched, a variety of "penalties" can be applied to the data. It is not clear which, if any, approach was used in the Dayer *et al* model.

3. Critique of the methods used by Dayer *et al* paper

3.1 Critique of Interrupted time series

Abstracting Dayer et al data

The robustness of the interrupted time series analysis rests on how well one believes that the data are represented by the trends before and after the interruption. As part of the critique, the raw data from Dayer *et al* Figure 2 (incidence of infective endocarditis) and Figure 3 (incidence by risk group) was abstracted using Plot Digitizer software (http://plotdigitizer.sourceforge.net/). The accuracy of the abstraction can be seen in Table 1, where the Dayer *et al* result and the application of the Dayer *et al* model to the abstracted data can be compared.

Table 1 Comparison of Dayer *et al* estimates and abstracted data

Estimate	Dayer et al Estimate (95% CI)	Abstracted data Estimate (95% CI)
Fig 2 – incidence of endocarditis		
Change in level	-0.45 (-2.54, 1.63)	-0.45 (-2.69, 1.78)
Change in slope	+0.11 (0.05, 0.16)	+0.11 (0.05, 0.16)
Fig 3 – incidence of endocarditis (high risk)		
Change in level	-0.04 (-1.35, 1.27)	-0.09 (-1.67, 1.49)
Change in slope	+0.04 (0.01, 0.07)	+0.04 (0.00, 0.08)
Fig 3 – incidence of endocarditis (low risk)		
Change in level	-0.46 (-1.86, 1.09)	-0.47 (-2.08, 1.14)
Change in slope	+0.07 (0.03, 0.10)	+0.07 (0.02, 0.11)

Notwithstanding abstraction variability because of the resolution of Figures 2 and 3, the very slight discrepancy in the confidence intervals relates primarily to the method used to derive the trend lines. In the Dayer *et al* paper, the authors do not describe the actual model they fitted to the data in terms of any autocorrelation found, the paper only describes the approach they used to identify the autocorrelation. For the model I fitted to the data in Table 1, I assumed first order autocorrelation (see autocorrelation section below) and adjusted the data using the Cochran-Orcutt method and fitted the lines exactly as described by the Dayer *et al* paper (i.e. using the Wagner *et al* approach to model fitting). Note, however, this approach was an attempt to illustrate that the abstracted data was good enough to do further robust analysis on, it was not (in my opinion) the suboptimal model to fit to the data. In my opinion given the statistical estimates are accurate to within 2 decimal places for most of the estimates, the abstracted data is robust. Appendix 1 contains the abstracted data from each timepoint that is used in subsequent analyses.

Autocorrelation

The level of autocorrelation in a series is identified, as the Dayer *et al* paper suggests, by interpretation of autocorrelation function (ACF) and partial autocorrelation function (PACF). These functions are applied to the pre-intervention data only. The one method stipulation in using these functions is that the series should be "stationary". This means that any trend in the data should be removed before using. A trend can be removed by "differencing" and is a standard approach when using these functions. Figures 1a and 1b show the results of applying the functions to the differenced incidence data.

Figure 1a ACF of incidence

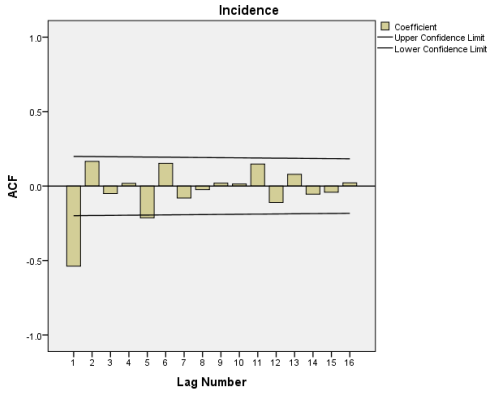
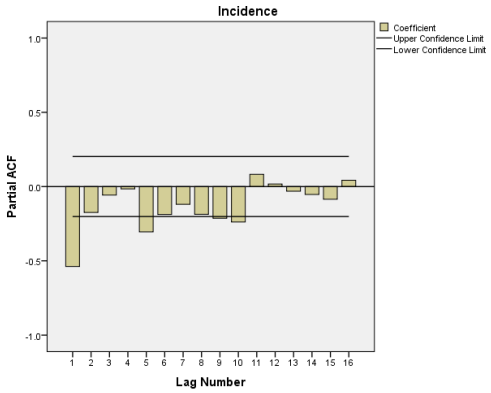


Figure 1b PACF of incidence



The above graphs are highly suggestive (monotonically decreasing ACF and PACF with one significant lag close to low lag numbers) that the series have what is known as **first order autocorrelation**. As Dayer *et al* suggested, there is no evidence of seasonality in the data (lag 12 would be significant if seasonality was present). I have assumed in subsequent analyses that the data have first order autocorrelation, but Dayer *et al* paper did not state what they found.

Time series modelling

Given it has been possible to replicate the Dayer *et al* results, I am confident that the model as they developed it, has been successfully implemented. The approach Dayer *et al* used fitted a straight line to the data pre-intervention and a straight line post-intervention. All their reported results are therefore robust to that model. Although I cannot be 100% confident, it does appear that Dayer *et al* have also correctly adjusted for autocorrelation in their series. So, the main distributional assumption in the modelling is that the residual error term is first order autocorrelated.

Where I have real uncertainty however is the assumption that a straight-line fits the pre-and post-intervention data. It is crucial that assumption is correct because the main finding of the Dayer study is for a change in slope at March 2008.

Shape of pre-intervention line

Visual interpretation of the incidence data would suggest that the pattern up to around point 60 (December 2003) looks different to points after December 2003. Prior to December 2003 the points appear to be quite flat (no trend or maybe even slightly downward) and then after 2003 increasing. Instead of fitting a straight line it is possible to test whether a curve fits the data better. The simplest curve to fit is a parabolic shape where

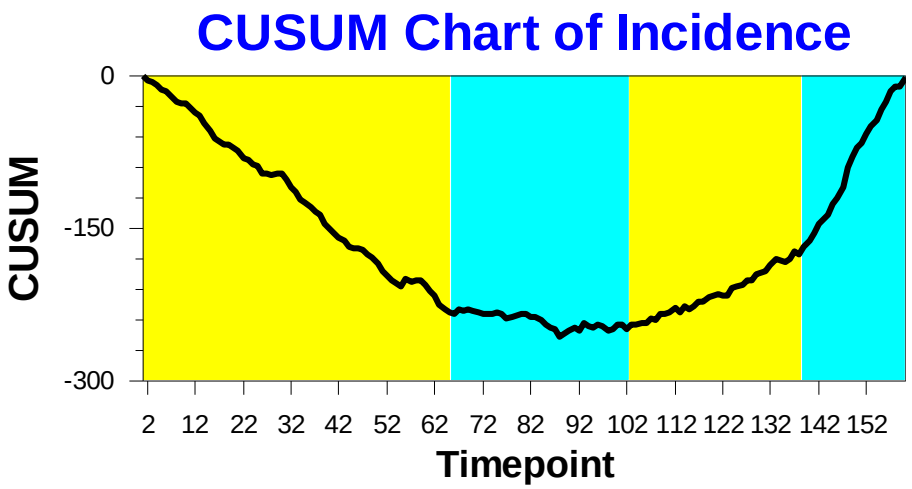
$$\text{Incidence} = \text{constant} + \text{time} + (\text{time})^2$$

When applying the above model to the pre-intervention data the $(\text{time})^2$ parameter was highly

significant (p<0.001) and positive thereby suggesting a 'U' shape fitted better. There was therefore strong evidence that the pre-intervention data was not linear.

An alternative way to look for patterns in time series data is to plot the CUSUM chart. In the CUSUM chart each observation is sequentially compared to the series mean. If the CUSUM chart is going downwards the data are trending to below the series mean, if flat they are at the series mean and if increasing they are above the series mean. If the data were increasing straight lines (as Dayer *et al* have assumed) we would expect the CUSUM chart to go in one direction before and after the guidelines were introduced. The CUSUM plot for the Incidence data is shown in Figure 2.

Figure 2 – CUSUM chart for Incidence data



The CUSUM plot demonstrates that the pre-intervention phase is not linear. There is a flattening out of the CUSUM curve around point 65.

So two approaches for investigating a non-linear relationship both provide strong evidence that a straightline relationship is not appropriate. The implications are that the reported change in slope is biased. I provide alternative estimates of the likely change in slope in the *Revised estimates of effect* section below.

There are other time series methods available that may provide a better test of the intervention effect compared to simple time series regression such as autoregressive integrated moving average models, which are particularly amenable to longer time series such as is found in this paper. Dayer *et al* have not discussed using any other interrupted time series method to crosscheck their time series regression findings. Instead, they chose to look for any changes in the series using a change-point technique, which is discussed below.

3.2 Critique of change-point analysis

Dayer *et al* used change-point analysis to calculate the optimum positioning and number of data changepoints using the R change-point package that implements the Hinkley algorithm. As described earlier the Hinkley algorithm is a form of binary segmentation whereby a single change-point test-statistic is applied to the whole series and then if one is identified the data set is then split into two at that changepoint and each portion before and after the changepoint is then searched individually for further changepoints and the analysis recursively cuts the data set up into increasingly smaller chunks searching for significant changes in mean levels before and after the cuts. The method is distribution-free and assumes that the datapoints are identical and independent. I have not had access to the R change-point package and therefore cannot replicate the analysis they performed. There are a variety of algorithms that could be used within the change-point package (Killick, R., Eckley, I.A. (2014) changepoint: An R package for changepoint analysis. *Journal of Statistical Software* 58(3) 1-19.), but there are insufficient details in the Dayer *et al* paper to determine which one they used. However, because they have referred to the Hinkley method it seems plausible that they have opted for the simplest of mean change models. I ran the data

through an alternative multiple change-point programme (Taylor, Wayne (2000a), Change-Point Analyzer 2.0 shareware program, Taylor Enterprises, Libertyville, Illinois. Web: http://www.variation.com/cpa) that performs distribution free change-point methodology akin to the Hinkley method. The results are shown in Table 2 and Figure 3.

Table 2 Results of change-point analysis on incidence data

Table of Significant Changes for Incidence

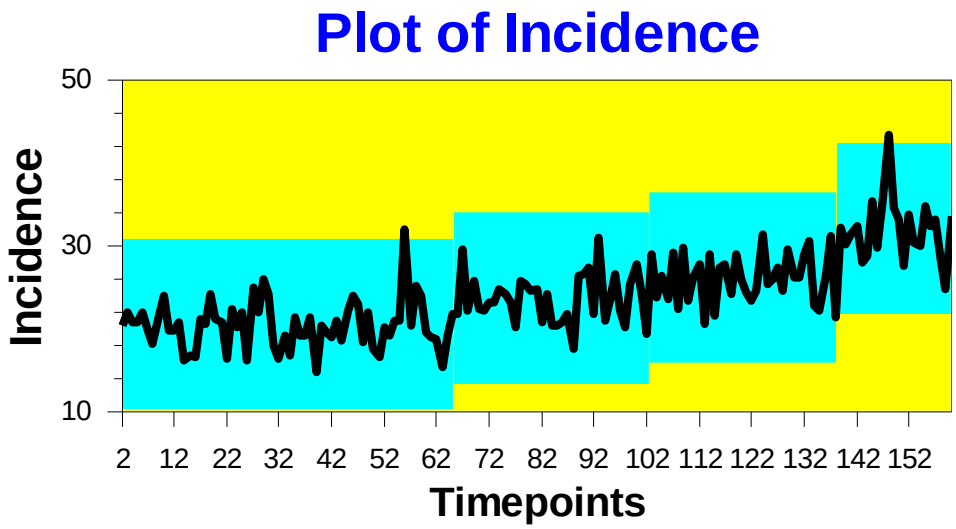
Confidence Level for Candidate Changes = 50%, Confidence Level for Inclusion in Table = 90%, Confidence Interval = 95%, Bootstraps = 1000, Without Replacement, MSE Estimates

Row	Confidence Interval	Conf. Level	From	To	Level
66	(54, 75)	99%	20.543	23.695	2
103	(88, 121)	99%	23.695	26.208	4
139	(136, 142)	100%	26.208	32.118	2

Table 2 illustrates that there is strong evidence of a change in the mean level of the data at data point 103 (this is 4 months after the guidelines were introduced) – this corresponds very closely with the Dayer *et al* result. However, the change-point analysis also identified two other significant change-points. One at point 66 and one at point 103. Graphically the data can be considered in four separate chunks as displayed in the shaded areas in Figure 3.

Dayer *et al* are unclear on number of change-points in their paper. Whilst they stated that a change-point occurred at 3 months post guideline introduction, they have not explicitly stated whether they did or did not identify any other change-points. According to my reanalysis, it is likely that there were other potential change-points in the series and these also seem to correspond with my earlier findings that a linear relationship was not appropriate. One is left to conjecture on what "events" occurred at these points in time to increase the incidence of endocarditis.

Figure 3 – Plot of incidence with change-points in shaded areas



3.3 Critique of Study Quality

The Cochrane Effective Practice and Organisational Care (EPOC) Group have developed seven risk of bias criteria for interrupted time series studies (https://epoc.cochrane.org/epoc-specific-

resources-review-authors). A description of the tool is given in Appendix 2. Applying the tool to Dayer *et al* (Table 2), the study has two criteria at high risk of bias (pre-specification of the intervention effect and biased statistical analysis). The study findings therefore are at a high risk of bias.

Table 2 – Risk of bias assessment

Was the intervention independent of other changes? YES
Reasonably convincing evidence that nothing else occurred at time of guideline introduction Eg "..dental statistics for England show that dental extractions have remained fairly constant.." or "a sudden large increase in the number of individuals at risk of infective endocarditis might have occurred. However, for many of the factors that put an individual at high risk of infective endocarditis, we have shown that this situation is unlikely to be the case…"
Was the shape of the intervention effect pre-specified? NO
A linear trend before and after the intervention was conducted, but no rationale was given or tested that this was the correct, pre-specified shape.
Was the intervention unlikely to affect data collection? YES
Unlikely intervention affected routine data collection e.g. "…because the coding was done independently of our study, it was not subject to study related bias or affected in any other way by the introduction of the NICE guidelines…"
Was knowledge of the allocated interventions adequately prevented during the study? YES
The routine data collection could not have been affected by knowledge of the guidelines
Were incomplete outcome data adequately addressed? YES
Whilst some cases may be missing, it is likely that they are random error e.g. "…the size of the dataset and the consistency of the underlying coding process are likely to negate the effect of any systematic error…"
Was the study free from selective outcome reporting? YES
The outcome has included all known reported cases of endocarditis and it is unlikely there were any other outcomes that could have been used.
Was the study free from other risks of bias? NO

The statistical analysis does not correctly model the trends in the data and likely biases the estimates.

4 Revised estimates of effect section

Taking all of the above evidence into account there is, in my opinion, a strong case for revising the model proposed by Dayer *et al*. The simplest amendment to make, would be to use the same methodology as Dayer *et al* (linear time series regression with first order autocorrelation), but to fit an additional interruption at an earlier time point. To maximise the data points pre-intervention I selected the lower bound from the confidence interval around point 66 interruption so this meant the time point for the first interruption was point 54 (June 2004). So the model fits a straightline to the first 54 datapoints, a straightline from point 54 to 99 and makes no change to the post-intervention data. A second analysis incorporated an additional interruption at time point 139 (June 2011). The results are displayed in Table 3.

Table 3 Comparison of Dayer *et al* estimates and "reviewer sensitivity analyses"

Incidence	**Dayer et al**	**Abstracted data Two change-points[1]**	**Abstracted data Three change-points[2]**
	Estimate (95% CI); p	**Estimate (95% CI); p**	**Estimate (95% CI); p**
All cases			
Change in level	-0.45 (-2.54, 1.63);0.670	-0.81 (-3.30, 1.71);0.562	+0.68 (-1.94, 3.31);0.606
Change in slope	+0.11 (0.05, 0.16);0.000	+0.10 (0.01, 0.19);0.021	-0.00 (-0.11, 0.11);0.970
high risk			
Change in level	-0.04 (-1.35, 1.27);0.951	-0.27 (-2.10,1.60);0.777	+0.17 (-1.87,2.21);0.870
Change in slope	+0.04 (0.01, 0.07);0.025	+0.03 (-0.04,0.09);0.373	-0.00 (-0.09, 0.08);0.938
low risk			
Change in level	-0.46 (-1.86, 1.09);0.547	-0.71 (-2.45,1.02);0.419	+0.35 (-1.50,2.21);0.705
Change in slope	+0.07 (0.03, 0.10);0.000	+0.07 (0.01,0.13);0.02	-0.00 (-0.08, 0.07);0.941

[1] change-points considered at point 54 and 99

[2] change-points considered at point 54, point 99 and point 139

The results in Table 3 suggest that the impact of the interruption at the point of guideline introduction is highly sensitive to whether there are multiple change-points. If three changes are modelled, the effects show no significant change in slope or level. The data suggests that the more datapoints are collected in the future, the more the model will move away from a single straightline describing it adequately. There is likely to be some minor change around the time of the guideline intervention, but there are also other substantive changes in the series that remain unexplained (i.e. what happened around June 2011?). It is worth considering these results in light of Dayer et al earlier published paper with fewer data points. At that point (2 years follow-up) they did not observe any change in incidence. The results above would also be in line with that original finding because much of the new data is possibly from a different shape of effect and unlikely to be due to the guideline introduction per se.

My final conclusion on the methods is that the methodology in the paper is relatively robust, but the size of the change in slopes are highly sensitive to whether you believe a single straightline describes the post-guideline data. My personal opinion based upon the reanalysed data is that it is likely that the Dayer *et al* change in slopes is biased too high, and that the real change is likely to be smaller. Due consideration must be given to whether it is plausible that the trends observed 3 or 4 years after the guideline introduction could be considered to be influenced by the guideline rather than some other external event(s).

Appendix 1 – Abstracted data from Dayer *et al*

Year/Month	Incidence	Incidence High risk	Incidence Low risk
2000m1	20.595856	2.04969	18.4206
2000m2	22.10708	1.35759	20.8696
2000m3	20.811745	2.44898	18.5271
2000m4	20.854921	2.84827	18.0479
2000m5	22.193438	4.9512	17.4623
2000m6	20.034542	3.96628	16.85
2000m7	18.393782	1.75688	16.6371
2000m8	21.675303	4.89796	16.8234
2000m9	24.136442	4.65839	19.5918
2000m10	19.861832	3.00799	16.8767
2000m11	19.905008	2.79503	17.3558
2000m12	20.811745	4.92458	16.3975

2001m1	16.321243	2.12955	14.2147
2001m2	16.968912	2.63531	14.3744
2001m3	16.753023	2.20941	14.5608
2001m4	21.373056	4.73824	16.9033
2001m5	20.768566	3.56699	17.1695
2001m6	24.309155	5.29725	19.3256
2001m7	21.243523	3.83319	17.5688
2001m8	20.984455	3.1677	17.835
2001m9	16.58031	3.4339	13.15
2001m10	22.582039	2.95475	19.6451
2001m11	20.336788	4.15262	16.4241
2001m12	22.193438	6.68146	15.6256
2002m1	16.234888	2.79503	13.4428
2002m2	25	6.70807	18.4206
2002m3	22.020725	5.61668	16.8234
2002m4	26.165804	13.5226	13.0701
2002m5	24.309155	6.78793	16.9299
2002m6	18.048359	3.96628	14.2413
2002m7	16.450777	2.4756	13.8421
2002m8	19.386873	4.25909	15.4126
2002m9	16.925734	3.75333	13.2298
2002m10	21.459414	5.08429	16.4508

2002m11	19.343697	4.15262	15.3061
2002m12	19.343697	4.60515	14.827
2003m1	21.416235	7.2937	14.268
2003m2	14.896373	2.12955	12.8305
2003m3	20.595856	5.48358	15.2795
2003m4	19.732298	5.66992	14.268
2003m5	19.170984	4.17924	15.2795
2003m6	21.027634	3.4339	17.7019
2003m7	18.609673	2.76841	16.0248
2003m8	22.366148	4.685	17.7019
2003m9	24.17962	8.06566	16.2644
2003m10	23.18653	6.38864	16.8767
2003m11	18.43696	3.80657	14.7471
2003m12	22.150259	4.84472	17.4623
2004m1	17.746115	4.79148	13.3097
2004m2	16.62349	5.43035	11.3132
2004m3	20.207254	3.93966	16.2112
2004m4	19.343697	4.73824	14.6673
2004m5	21.027634	4.36557	16.7968
2004m6	21.070812	3.51375	17.5155
2004m7	32.038	8.62467	23.5847
2004m8	20.595856	5.72316	14.9068

2004m9	25.388601	7.77285	17.7019
2004m10	24.136442	6.54836	17.8882
2004m11	19.602764	3.88642	15.8385
2004m12	19.08463	5.85626	13.496
2005m1	18.998272	3.67347	15.3327
2005m2	15.457685	3.75333	11.8722
2005m3	19.343697	4.20586	15.0665
2005m4	21.804836	4.79148	17.0364
2005m5	21.891191	4.25909	17.5954
2005m6	29.792746	8.14552	21.7746
2005m7	22.322971	4.49867	17.7551
2005m8	25.82038	7.53327	18.4472
2005m9	22.582039	6.25555	16.504
2005m10	22.366148	6.28217	16.1579
2005m11	23.35924	7.2937	16.2112
2005m12	23.272884	6.44188	16.9033
2006m1	24.913645	6.44188	18.5537
2006m2	24.352331	8.27862	16.0515
2006m3	23.229706	5.11091	18.3141
2006m4	20.29361	6.20231	14.2946
2006m5	25.863558	7.50665	18.5271
2006m6	25.474957	7.66637	17.8083

2006m7	24.611399	6.28217	18.4738
2006m8	24.827288	6.4685	18.4206
2006m9	20.941278	6.4685	14.7205
2006m10	24.352331	6.30878	18.2609
2006m11	20.552677	5.08429	15.4392
2006m12	20.552677	5.21739	15.4392
2007m1	20.8981	6.44188	14.5874
2007m2	21.891191	5.85626	15.9982
2007m3	17.702936	4.126	13.6291
2007m4	26.468048	5.19077	21.2689
2007m5	26.770294	6.86779	20.2839
2007m6	27.504318	9.95563	17.622
2007m7	21.891191	7.74623	14.268
2007m8	31.088083	14.0816	17.1695
2007m9	21.070812	5.7764	15.2795
2007m10	23.704662	5.27063	18.8731
2007m11	26.64076	7.40018	19.4587
2007m12	22.322971	4.8181	17.7019
2008m1	20.250431	5.82964	14.5342
2008m2	25.561312	9.74268	15.8917
2008m3	27.806562	8.62467	19.4587
2008m4	24.265976	7.10736	17.3292

2008m5	19.516407	5.98935	13.6823
2008m6	29.058722	5.7764	23.425
2008m7	23.834196	6.76131	17.1961
2008m8	26.468048	6.76131	19.9645
2008m9	23.704662	8.46495	15.0133
2008m10	29.231434	10.0887	19.299
2008m11	22.53886	6.89441	15.6788
2008m12	29.965458	8.73114	21.402
2009m1	23.57513	8.86424	14.8004
2009m2	26.20898	9.92902	15.8651
2009m3	27.979275	11.7657	16.3177
2009m4	20.639032	6.14907	14.5342
2009m5	29.145079	9.50311	19.8314
2009m6	21.718481	6.49512	15.2795
2009m7	27.590673	8.83762	18.6335
2009m8	27.936096	10.7276	17.1961
2009m9	24.265976	6.89441	17.3824
2009m10	29.015545	10.9405	18.1012
2009m11	26.079447	9.87578	16.2378
2009m12	24.438688	9.18367	15.1464
2010m1	23.445597	9.13043	14.3478
2010m2	24.654577	9.79592	14.8536

2010m3	31.433506	13.4161	18.0745
2010m4	25.43178	8.33185	17.1961
2010m5	26.122625	7.21384	19.0328
2010m6	27.417961	7.66637	20.0177
2010m7	24.654577	8.9441	15.732
2010m8	29.792746	7.74623	22.3336
2010m9	26.295338	6.57498	19.7249
2010m10	26.25216	7.4268	18.8731
2010m11	29.1019	9.55634	18.7933
2010m12	30.74266	12.9104	17.9947
2011m1	22.970638	7.50665	15.7054
2011m2	22.366148	6.04259	16.5839
2011m3	26.597582	8.33185	17.7551
2011m4	31.303972	14.0018	17.3558
2011m5	21.50259	7.32032	14.2147
2011m6	32.38342	9.44987	23.0524
2011m7	30.35406	8.70452	21.6948
2011m8	31.56304	11.1269	20.4969
2011m9	32.599308	11.2866	21.4818
2011m10	28.108809	9.9024	18.181
2011m11	28.842833	10.488	18.394
2011m12	35.405872	15.7853	19.6983

2012m1	29.92228	11.6859	18.394
2012m2	35.060448	13.3363	20.6832
2012m3	43.566494	18.2875	25.5013
2012m4	34.715027	17.3026	17.5688
2012m5	33.333332	12.1118	21.5617
2012m6	27.677029	9.13043	18.6868
2012m7	33.981003	10.6477	23.4516
2012m8	30.52677	11.3665	19.1925
2012m9	30.138168	9.87578	20.3372
2012m10	34.974094	11.606	23.5315
2012m11	32.599308	8.9441	23.7178
2012m12	33.37651	14.7205	18.8465
2013m1	28.972366	10.2484	19.0062
2013m2	24.827288	9.66282	15.2263
2013m3	33.678757	10.2218	23.6912

Appendix 2 - Risk of bias for interrupted time series (ITS) studies

Seven standard criteria are used for all ITS studies. Further information can be obtained from the Cochrane handbook section on Risk of Bias and from the draft methods paper on risk of bias under the EPOC specific resources section of the EPOC website.

Note: If the ITS study has ignored secular (trend) changes and performed a simple t-test of the pre versus post intervention periods without further justification, the study should not be included in the review unless reanalysis is possible.

Was the intervention independent of other changes?
Score “Yes” if there are compelling arguments that the intervention occurred independently of other changes over time and the outcome was not influenced by other confounding variables/historic events during study period. *If Events/variables identified, note what they are.* Score “NO” if reported that intervention was not independent of other

changes in time.
Was the shape of the intervention effect pre-specified?
Score ”Yes” if point of analysis is the point of intervention OR a rational explanation for the shape of intervention effect was given by the author(s). Where appropriate, this should include an explanation if the point of analysis is NOT the point of intervention;Score “No” if it is clear that the condition above is not met
Was the intervention unlikely to affect data collection?
Score “Yes” if reported that intervention itself was unlikely to affect data collection (for example, sources and methods of data collection were the same before and after the intervention); Score “No” if the intervention itself was likely to affect data collection (for example, any change in source or method of data collection reported).
Was knowledge of the allocated interventions adequately prevented during the study?[3]
Score “Yes” if the authors state explicitly that the primary outcome variables were assessed blindly, or the outcomes are objective, e.g. length of hospital stay. Primary outcomes are those variables that correspond to the primary hypothesis or question as defined by the authors. Score “No” if the outcomes were not assessed blindly. Score “unclear” if not specified in the paper.
Were incomplete outcome data adequately addressed?
Score “Yes” if missing outcome measures were unlikely to bias the results (e.g. the proportion of missing data was similar in the pre- and post-intervention periods or the proportion of missing data was less than the effect size i.e. unlikely to overturn the study result). Score “No” if missing outcome data was likely to bias the results. Score “Unclear” if not specified in the paper (Do not assume 100% follow up unless stated explicitly).
Was the study free from selective outcome reporting?
Score “Yes” if there is no evidence that outcomes were selectively reported (e.g. all relevant outcomes in the methods section are reported in the results section). Score “No” if some important outcomes are subsequently omitted from the results. Score “unclear” if not specified in the paper.
Was the study free from other risks of bias?
Score “Yes” if there is no evidence of other risk of biases. e.g. should consider if seasonality is an issue (i.e. if January to June comprises the preintervention period and July to December the post, could the “seasons’ have caused a spurious effect).

1

Appendix P: University of Sheffield's 2015 update of the 2008 NICE economic model

P.1 Background

A team at the University of Sheffield conducted an economic analysis independtly of the guideline update and kindly provided the initial results of this analysis to the Committee. A presentation was provided along with a report containing the full details of the analysis. The full details of this analysis cannot be disclosed in the present document because it has not yet been published and is considered academic in confidence. The investigators have provided the following summary of their analysis.

P.2 The findings of this analysis in the final published version may differ to what is reported here.Abstract: the cost effectiveness of prophylactic antibiotics for patients at risk of infective endocarditis

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P.2.1 Introduction

2008 guidance issued for the health services of England and Wales recommended that antibiotic prophylaxis before dental procedures for those considered at risk of infective endocarditis (IE) should cease. This study reports an economic evaluation of amoxicillin or clindamycin compared to no prophylaxis in this setting based on up-to-date estimates of their efficacy, adverse event profiles and the resource implications of infective endocarditis.

P.2.2 Methods

Costs, from a health service perspective, and health benefits measured in terms of Quality Adjusted Life Years, were estimated using a decision analytic model run over a time horizon spanning patients' whole lifetime. Observed rates of IE pre and for up to 5 years post the 2008 guidance were used to estimate prophylactic efficacy. Adverse event rates came from recent analyses of UK datasets. Updated resource implications were based on HES data.

P.2.3 Results

The base case analysis suggests clindamycin is unlikely to be cost effective due to the relatively high probability of fatal adverse events which may outweigh the health benefits of reduced risk of IE. The incremental cost effectiveness ratio (ICER) for amoxicillin is £31k in the base case. This is sensitive to the drug acquisition cost, efficacy, and the rate of fatal adverse events. The ICER increases to £53k using less optimistic estimates of prophylactic

efficacy. Both drugs are more cost effective if the baseline risk of IE is higher. Using a baseline risk for patients with prosthetic heart valves leads to estimates of £6.5k and £13k for amoxicillin and clindamycin respectively.

P.2.4 Conclusions

This study presents updated estimates of the cost effectiveness of two candidate antibiotics for prophylaxis in dental procedures in the UK health service. Base case estimates suggest amoxicillin may be cost effective whilst there is concern than clindamycin may generate more harms than health benefits for patients and is therefore dominated in terms of cost effectiveness. There does remain considerable uncertainty around these findings, driven in large part by the fact that there is no randomised controlled trial evidence on which to base estimates of antibiotic effectiveness or adverse event rates.

Appendix Q: CG64 original scope

1 Guideline title

Antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures

1.1 Short title

Prophylaxis against infective endocarditis

2 Background

a) The Department of Health has asked the National Institute for Health and Clinical Excellence ('NICE' or 'the Institute') to prepare guidance on 'antimicrobial prophylaxis against endocarditis for adults and children undergoing an interventional procedure (including dentistry)'. The guideline will provide recommendations for good practice that are based on the best available evidence of clinical and cost effectiveness.

b) The Institute's clinical guidelines will support the implementation of National Service Frameworks (NSFs) in those aspects of care where a Framework has been published. The statements in each NSF reflect the evidence that was used at the time the Framework was prepared. The clinical guidelines and technology appraisal guidance published by the Institute after an NSF has been issued will have the effect of updating the Framework.

c) NICE clinical guidelines support the role of healthcare professionals in providing care in partnership with patients, taking account of their individual needs and preferences, and ensuring that patients (and their carers and families, where appropriate) can make informed decisions about their care and treatment.

3 Clinical need for the guideline

a) Infective endocarditis (IE) is an inflammation of the inner lining of the heart, particularly affecting the heart valves, caused by bacterial or other

infections. It is a rare condition, with an annual incidence of less than 10 per 100,000 population. It is, however, a life-threatening disease with significant mortality (approximately 20%) and morbidity. IE predominantly affects people with underlying structural cardiac defects, both congenital and acquired, who develop bacteraemia (presence of bacteria in the blood) with organisms likely to cause IE. People with underlying structural cardiac defects constitute an important patient group 'at risk' of developing IE.

b) The prevention of IE has focused on the need to reduce bacteraemia in people at risk. This approach has three components: promotion of good oral health, timely treatment of sepsis and giving antimicrobial prophylaxis to at-risk people undergoing an interventional procedure that is considered likely to cause bacteraemia. The frequency of bacteraemia after healthcare procedures varies depending on type and site of the procedure. There is, however, controversy about whether procedure-based bacteraemia causes IE. There is a view that cumulative bacteraemia, caused by everyday activities like eating and tooth brushing, is more likely to cause IE, particularly in the case of dental procedures (including dentogingival manipulation).

c) It is considered biologically plausible that antimicrobial prophylaxis can reduce the risk of developing IE in people at risk. There is support for this position from laboratory animal models, although there is controversy about whether laboratory animal models can explain the pathophysiology of spontaneous IE in humans. The rarity of IE means that it is difficult to undertake controlled clinical trials, so evidence about the effectiveness of antimicrobial prophylaxis in reducing the risk of developing IE is likely to come from well conducted observational studies. Potential risks of inappropriate use of antibiotics include serious adverse events (such as anaphylaxis) and development of antimicrobial resistance.

d) There is currently conflicting UK guidance relating to prophylaxis for IE. The chief area of controversy relates to the need for antibiotic prophylaxis for dental procedures, where there is concern that the likelihood of

preventing IE by using antibiotics is less than the risk of the antibiotics causing serious adverse events.

4 The guideline

a) This document is the scope. It defines exactly what this guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

b) The areas that will be addressed by the guideline are described in the following sections.

4.1 Population

4.1.1 Groups that will be covered

a) Adults and children with known underlying structural cardiac defects, including those who have previously had IE.

b) Adults and children who have previously had IE (irrespective of whether they have a known underlying cardiac defect).

c) There are no additional subgroups of patients who may need specific consideration in their treatment or care.

4.1.2 Groups that will not be covered

a) People at increased risk of IE who do not have structural cardiac defects (such as intravenous drug users).

4.2 Healthcare setting

a) Primary dental care, primary medical care and community settings.

b) Secondary care.

4.3 Clinical management

a) Definition of people with structural heart lesions at risk of developing IE. This will include classifying structural heart lesions into those at risk and those not at risk of IE.

b) Definition of interventional procedures considered to need antimicrobial prophylaxis for IE for specific at-risk groups. This will include:

- Dental procedures.
- Other interventional procedures if there is considered to be an increased risk of IE in at-risk people. The following sites will be covered.
  - Upper and lower gastrointestinal (GI) tract.
  - Genitourinary tract. This includes urological, gynaecological and obstetric procedures (including childbirth).
  - Upper and lower respiratory tract. This includes ear nose and throat and bronchoscopy procedures.

c) Antimicrobial regimen to be used. This will include:

- specifying antibiotics that may be used
- the role of chlorhexidine mouthwash.

d) The guideline will not offer detailed recommendations on the route of administration, timing and duration of antibiotic and antimicrobial regimen(s). It is anticipated that the GDG and technical team will liaise with the 'British National Formulary' to ensure that the March 2008 'British National Formulary' publication will provide advice for clinicians that complements this guideline.

e) The information needs of patients regarding the benefits and risks of antimicrobial prophylaxis for IE. This will specifically include advice regarding body piercing and tattooing that involves damage to mucosal tissue.

f) The guideline defines IE as bacterial endocarditis. Non-infective, fungal and atypical bacterial causes of IE will not be considered.

g) The Guideline Development Group will take reasonable steps to identify ineffective interventions and approaches to care. If robust and credible recommendations for re-positioning the intervention for optimal use, including the identification of appropriate patient subgroups, or changing the approach to care to make more efficient use of resources, can be

made, they will be clearly stated. If the resources released are substantial, consideration will be given to listing such recommendations in the 'Key priorities for implementation' section of the guideline.

4.4 Key outcome measures

Key outcomes that will be considered when reviewing the evidence include:

- risk of dental and other interventional procedures causing IE
- risk of antibiotics prescribed for prophylaxis causing serious adverse events, for example anaphylaxis, in 'at risk' population
- mortality and/or morbidity (for example congestive cardiac failure)
- health-related quality of life
- resource use and costs.

4.5 Economic aspects

The developers will take into account the cost-effectiveness of antimicrobial (principally antibiotic) prophylaxis against infective bacterial endocarditis in people undergoing the interventional procedures described in section 4.3b. .

4.6 Status

4.6.1 Scope

This is the final version of the scope.

4.6.2 Guideline

The development of the guideline recommendations will begin in July 2007.

5 Further information

Information on the guideline development process is provided in:

- 'The guideline development process: an overview for stakeholders, the public and the NHS'
- 'Developing NICE guidelines - the Manual 2014'.

These booklets are available as PDF files from the NICE website (www.nice.org.uk/guidelinesmanual). Information on the progress of the guideline will also be available from the website.

The Guideline Development Group will work in accordance with the methods set out in the documents above. The short clinical guidelines programme is in development and will be consulted on.