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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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Contents

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

6 Appendices

6.1 Appendix 1 – The scope

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SHORT CLINICAL GUIDELINE

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'
- 'The guidelines manual'.

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.

6.2 Appendix 2 – Key clinical questions

Topic areas and structured clinical questions

Topic area 1: Risk of developing infective endocarditis

Clinical questions:
SCQ 1a) What pre-existing cardiac conditions, in adults and children increase the risk of developing IE?

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

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

Topic area 2: Interventional procedures:

- *which increase the risk of those at risk developing IE*
- *which cause significant bacteraemia*

Clinical questions:
SCQ 3) Which dental and other interventional procedures are associated with increased incidence of IE in those considered at risk of IE?
SCQ 4) What levels of bacteraemia are associated with interventional procedures, both pre and post-procedure (including consideration of what is considered significant bacteraemia?)

SCQ 5) What levels of bacteraemia are associated with everyday activities (toothbrushing/chewing/urination/defecation)?

Topic area 3: Prophylaxis regimen to be used

Clinical questions:
SCQ 6a) Does antibiotic prophylaxis in those at risk of developing IE reduce the incidence of IE when given before a defined Interventional Procedure?

SCQ 6b) Does oral chlorhexidine prophylaxis in those at risk of developing IE reduce the risk of developing IE when given before a defined Interventional Procedure?

SCQ 7a) Does antibiotic prophylaxis given to those undergoing Interventional Procedures reduce the level and duration of bacteraemia?

SCQ 7b) Does oral chlorhexidine prophylaxis given to those undergoing Interventional Procedures reduce the level and duration of bacteraemia?

SCQ 8) What rates of adverse events (in particular, anaphylaxis) have been found in those taking antibiotic prophylaxis?

Topic area 4: Patient perspectives

Clinical question:
SCQ 9) What are the issues that individuals, who are considered at risk of IE regarding prophylaxis against infective endocarditis, report as important?

6.3 Appendix 3 – Search strategies

Medline search strategies for PIE guideline

Search strategies

Scoping searches

Scoping searches were undertaken on the following websites and databases in January 2007 to provide information for scope development and project planning. Browsing or simple search strategies were employed.

Guidance/guidelines	Systematic reviews/economic evaluations
• British Cardiovascular Society • British Dental Association • British Society for Antimicrobial Chemotherapy • British Society of Gastroenterology • British Thoracic Society • Canadian Medical Association Infobase • Department of Health • Guidelines International Network (GIN) • National Guideline Clearing House (US) • National Health and Medical Research Council (Australia) • National Institute for Health and Clinical Excellence (NICE) - published & in development • National Institute for Health and Clinical Excellence (NICE) - Topic Selection • National Library for Health (NLH) Guidelines Finder • National Library for Health (NLH) Protocols and Care Pathways Database • National Library for Health (NLH) Specialist Libraries • New Zealand Guidelines Group • Prodigy • Royal College of General Practitioners • Royal College of Radiologists • Royal College of Surgeons • Scottish Intercollegiate Guidelines Network (SIGN)	• Cochrane Database of Systematic Reviews (CDSR) • Database of Abstracts of Reviews of Effects (DARE) • Health Economic Evaluations Database (HEED) • Health Technology Assessment (HTA) Database • National Coordinating Centre for Health Technology Assessment (NCCHTA) • NHS Economic Evaluation Database (NHS EED) • TRIP Database

Simple, exploratory scoping searches were also undertaken on primary literature bibliographic databases and clinical trials sources to provide information for scope development and project planning.

Primary literature	Clinical Trials
• CINAHL • EMBASE • MEDLINE • MEDLINE IN PROCESS	• Cochrane Central Register of Controlled Trials (CENTRAL) • ClinicalTrials.gov • Current Controlled Trials (mRCT) • National Research Register (NRR) • Research Findings Electronic Register (ReFeR)

Main searches

The following sources were searched for the topics presented in the sections below.

- Cochrane Database of Systematic Reviews – CDSR (Wiley)
- Cochrane Central Register of Controlled Trials – CENTRAL (Wiley)
- Database of Abstracts of Reviews of Effects – DARE (Wiley)
- Health Technology Assessment Database – HTA (Wiley)
- CINAHL (Ovid)
- EMBASE (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)
- PsycINFO (Ovid)
- Science Citation Index (Dialog DataStar)

Identification of evidence on infective endocarditis

The searches were conducted on 29 May 2007. The aim of the searches was to identify papers on infective endocarditis to provide evidence on risk factors associated with the condition and evidence on the effectiveness of antibiotic prophylaxis in preventing the condition. Search filters for systematic reviews, randomised controlled trials and observational studies were appended to the search strategies to retrieve high quality papers (see **Identification of**

systematic reviews, randomised controlled trials and observational studies).

The MEDLINE search strategy is presented below. It was translated for use in all of the other databases.

Ovid MEDLINE(R) <1950 to May Week 3 2007>

1. exp Endocarditis/
2. endocardit$.tw.
3. 1 or 2

Identification of evidence on bacteraemia levels associated with defined interventional procedures

The searches were conducted on 31 August 2007. Search filters for systematic reviews, randomised controlled trials and observational studies were appended to the search strategies to retrieve high quality papers (see below for **Identification of systematic reviews, randomised controlled trials and observational studies**).

The MEDLINE search strategy is presented below. It was translated for use in all of the other databases.

Ovid MEDLINE(R) <1950 to July Week 3 2007>

---

1 exp Dentistry, Operative/

2 exp Dental Prophylaxis/

3 ((dent$ or tooth$ or teeth or peridont$ or orthodont$) adj prophyla$).tw.

4 (crown adj3 length$).tw.

5 exp Endodontics/

6 endodontic$.tw.

7 apicoectom$.tw.

8 (pulp$ adj3 cap$).tw.

9 pulpectom$.tw.

10 pulpotom$.tw.

11 exp Oral Surgical Procedures/

12 gingivectom$.tw.

13 gingivoplast$.tw.

14 glossectom$.tw.

15 mucoperio$ flap$.tw.

16 (tartar adj3 remov$).tw.

17 Sialography/

18 sialograph$.tw.

19 (root adj2 canal adj3 (therap$ or treat$)).tw.

20 ((dent$ or oral$ or tooth$ or teeth or peridont$ or orthodont$ or root$) adj3 (restorat$ 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

21 ((dent$ or oral$ or tooth$ or teeth$ or peridont$ or orthodont$ or root$ canal$) adj3 (surg$ or procedure$ or endoscop$ or operat$ or incis$ or excis$ or intervention$ or invasiv$ or biops$ or inject$)).tw.

22 or/1-21

23 exp Digestive System Surgical Procedures/

24 roux-en-y.tw.

25 appendectom$.tw.

26 (bili$ adj3 (bypas$ or divers$)).tw.

27 cholecystectom$.tw.

28 (gallbladder adj3 remov$).tw.

29 cholecystostom$.tw.

30 portoenterostom$.tw.

31 sphincterotom$.tw.

32 papillotom$.tw.

33 colectom$.tw.

34 proctocolectom$.tw.

35 coloproctectom$.tw.

36 laparotom$.tw.

37 endoscop$.tw.

38 colonoscop$.tw.

39 duodenoscop$.tw.

40 gastroscop$.tw.

41 proctoscop$.tw.

42 cholangiopancreatograph$.tw.

43 ercp.tw.

44 esophagoscop$.tw.

45 esophagogastroduodenoscop$.tw.

46 oesophagoscop$.tw.

47 oesophagogastroduodenoscop$.tw.

48 (oesophag$ adj3 dilat$).tw.

49 (esophag$ adj3 dilat$).tw.

50 Echocardiography, Transesophageal/

51 Echocardiography/

52 (transesophag$ adj3 echo$).tw.

53 (trans-esophag$ adj3 echo$).tw.

54 (esophag$ adj3 echo$).tw.

55 (transoesophag$ adj3 echo$).tw.

56 (trans-oesophag$ adj3 echo$).tw.

57 (oesophag$ adj3 echo$).tw.

58 tee.tw.

59 toe.tw.

60 exp Lithotripsy/

61 lithotrip$.tw.

62 litholapax$.tw.

63 enterostom$.tw.

64 cecostom$.tw.

65 colostom$.tw.

66 duodenostom$.tw.

67 Ileostom$.tw.

68 jejunostom$.tw.

69 esophagectom$.tw.

70 oesophagectom$.tw.

71 esophagoplast$.tw.

72 oesophagoplast$.tw.

73 esophagostom$.tw.

74 oesophagostom$.tw.

75 fundoplicat$.tw.

76 nissen.tw.

77 gastrectom$.tw.

78 gastroenterostom$.tw.

79 billroth.tw.

80 gastrojejunostom$.tw.

81 (gast$ adj3 bypass).tw.

82 gastroplast$.tw.

83 gastrostom$.tw.

84 hepatectom$.tw.

85 (jejunoileal adj3 bypass).tw.

86 (ileojejunal adj3 bypass).tw.

87 (intestin$ adj3 bypass).tw.

88 ((liver or hepat$) adj3 (transplant$ or graft$)).tw.

89 (pancrea$ adj3 (transplant$ or graft$)).tw.

90 pancreatectom$.tw.

91 (pancrea$ adj3 remov$).tw.

92 pancreaticoduodenectom$.tw.

93 duodenopancreatectom$.tw.

94 pancreatoduodenectom$.tw.

95 pancreaticojejunostom$.tw.

96 (periton$ adj3 shunt$).tw.

97 (leveen adj3 shunt$).tw.

98 ((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$) adj3 (surg$ or procedure$ or operat$ or incis$ or excis$ or intervention$ or invasiv$ or biops$ or endoscop$ or sclerotherap$)).tw.

99 or/23-98

100 exp Urogenital Surgical Procedures/

101 colposcop$.tw.

102 colpotom$.tw.

103 culdoscop$.tw.

104 (dilatation adj3 curettage).tw.

105 (vacuum adj3 curettage).tw.

106 hysterectom$.tw.

107 hysteroscop$.tw.

108 (uter$ adj3 endoscop$).tw.

109 ovariectom$.tw.

110 oophorectom$.tw.

111 salpingostom$.tw.

112 (reproduct$ adj3 sterili$).tw.

113 (tub$ adj3 sterili$).tw.

114 (tub$ adj3 ligat$).tw.

115 aldridge.tw.

116 (tub$ adj3 occlu$).tw.

117 cooke.tw.

118 (cornual adj3 coagulat$).tw.

119 fimbriectom$.tw.

120 irving.tw.

121 kroener.tw.

122 madlener.tw.

123 pomeroy.tw.

124 (tub$ adj3 excis$).tw.

125 (tub$ adj3 ring$).tw.

126 uchida.tw.

127 vasectom$.tw.

128 cystectom$.tw.

129 cystoscop$.tw.

130 cystostom$.tw.

131 cystotom$.tw.

132 (kidney$ adj3 transplant$).tw.

133 (kidney$ adj3 graft$).tw.

134 nephrectom$.tw.

135 vesicotom$.tw.

136 ureteroscop$.tw.

137 (urin$ adj3 diver$).tw.

138 nephrostom$.tw.

139 nephroli$.tw.

140 ureterostom$.tw.

141 orchiectom$.tw.

142 (pen$ adj3 implant$).tw.

143 prostatectom$.tw.

144 trans?uret$.tw.

145 trans?rect$.tw.

146 vasovasostom$.tw.

147 castrat$.tw.

148 circumci$.tw.

149 (uret$ adj3 catheter$).tw.

150 (uret$ adj3 dilatat$).tw.

151 exp Obstetric Surgical Procedures/

152 abortion$.tw.

153 embryotom$.tw.

154 cerclage.tw.

155 (obstetr$ adj3 deliver$).tw.

156 (abdom$ adj3 deliver$).tw.

157 cesarean.tw.

158 caesarean.tw.

159 episiotom$.tw.

160 (obstetr$ adj3 extract$).tw.

161 (induc$ adj3 (labor$ or labour$)).tw.

162 Parturition/

163 parturit$.tw.

164 childbirth$.tw.

165 birth$.tw.

166 (vagina$ adj3 deliver$).tw.

167 ((fet$ or cepha$) adj3 version$).tw.

168 fetoscop$.tw.

169 Intrauterine Devices/

170 (intra?uterine adj3 device$).tw.

171 iud.tw.

172 Vaginal Smears/

173 ((vagina$ or cervi$ or papanicolaou) adj3 smear$).tw.

174 ((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$) adj3 (surg$ or procedure$ or operat$ or incis$ or excis$ or intervention$ or invasiv$ or biops$ or endoscop$)).tw.

175 or/100-174

176 exp Pulmonary Surgical Procedures/

177 (collapse adj3 therap$).tw.

178 pneumonolys$.tw.

179 pneumothora$.tw.

180 Bronchoscopy/

181 bronchoscop$.tw.

182 thyroidectomy/ or adenoidectomy/ or laryngectomy/ or laryngoscopy/ or neck dissection/ or pharyngectomy/ or pharyngostomy/ or rhinoplasty/ or tonsillectomy/ or tracheostomy/ or tracheotomy/

183 thyroidectom$.tw.

184 adenoidectom$.tw.

185 laryngectom$.tw.

186 laryngoscop$.tw.

187 neck dissect$.tw.

188 pharyngectom$.tw.

189 pharyngostom$.tw.

190 rhinoplast$.tw.

191 tonsillectom$.tw.

192 tracheostom$.tw.

193 tracheotom$.tw.

194 (nasal adj3 pack$).tw.

195 Pneumonectomy/

196 pneumonectom$.tw.

197 (lung$ adj3 transplant$).tw.

198 (lung$ adj3 graft$).tw.

199 ((nasal or sinus$ or rhino$ or rhina$ or pharyn$ or laryn$ or trache$ or bronch$ or lung$ or pulmonar$ or respirat$) adj3 (surg$ or procedure$ or endoscop$ or operat$ or incis$ or excis$ or intervention$ or invasiv$ or biops$)).tw.

200 or/176-199

201 22 or 99 or 175 or 200

202 (bacter$ adj5 (level$ or rate$ or incidence$ or prevalence$ or duration$ or cumulat$ or transient or translocat$ or trans-locat$ or transfer$)).tw.

203 (streptococ$ adj5 (level$ or rate$ or incidence$ or prevalence$ or duration$ or cumulat$ or transient or translocat$ or trans-locat$ or transfer$)).tw.

204 (staphylococ$ adj5 (level$ or rate$ or incidence$ or prevalence$ or duration$ or cumulat$ or transient or translocat$ or trans-locat$ or transfer$)).tw.

205 (enterococ$ adj5 (level$ or rate$ or incidence$ or prevalence$ or duration$ or cumulat$ or transient or translocat$ or trans-locat$ or transfer$)).tw.

206 or/202-205

207 201 and 206

Identification of evidence on bacteraemia levels associated with defined activities of daily living

The searches were conducted on 9 August 2007. Search filters for systematic reviews, randomised controlled trials and observational studies were appended to the search strategies to retrieve high quality papers (see below for **Identification of systematic reviews, randomised controlled trials and observational studies**).

The MEDLINE search strategy is presented below. It was translated for use in all of the other databases.

Database: Ovid MEDLINE(R) <1950 to July Week 3 2007>

---

1. Oral Hygiene/
2. ((oral$ or dent$ or mouth$) adj3 hyg$).tw.
3. Toothbrushing/
4. toothbrush$.tw.
5. tooth-brush$.tw.
6. ((tooth$ or teeth) adj3 brush$).tw.
7. ((tooth$ or teeth) adj3 clean$).tw.
8. (tongue$ adj3 (brush$ or scrap$ or clean$)).tw.
9. Dental Devices, Home Care/
10. floss$.tw.
11. ((tooth$ or teeth) adj3 pick$).tw.
12. Mastication/

13. masticat$.tw.
14. chew$.tw.
15. or/1-14
16. Exercise/
17. exercise.tw.
18. exercising.tw.
19. physical$ activit$.tw.
20. exp Sports/
21. sport$.tw.
22. (workout$ or work$ out$).tw.
23. Exertion/
24. exertion$.tw.
25. physical effort$.tw.
26. Physical Fitness/
27. fit$.tw.
28. or/16-27
29. Defecation/
30. defecat$.tw.
31. defaecat$.tw.
32. ((void$ or pass$ or excret$ or evac$ or discharg$ or empt$ or mov$ or motion$ or open$) adj3 bowel$).tw.
33. laxation.tw.

34. ((void$ or pass$ or discharg$ or excret$) adj3 (excreta or stool$ or feces or fecal or faec$)).tw.

35. or/29-34

36. Urination/

37. (urinat$ or micturit$).tw.

38. ((void$ or pass$ or excret$ or evac$ or discharg$ or empt$) adj3 (bladder or urin$)).tw.

39. ((pass$ or mak$) adj2 water$).tw.

40. or/36-39

41. 15 or 28 or 35 or 40

42. (bacter$ adj5 (level$ or rate$ or incidence$ or prevalence$ or duration$ or cumulat$ or transient or translocat$ or trans-locat$ or transfer$)).tw.

43. (streptococ$ adj5 (level$ or rate$ or incidence$ or prevalence$ or duration$ or cumulat$ or transient or translocat$ or trans-locat$ or transfer$)).tw.

44. (staphylococ$ adj5 (level$ or rate$ or incidence$ or prevalence$ or duration$ or cumulat$ or transient or translocat$ or trans-locat$ or transfer$)).tw.

45. (enterococ$ adj5 (level$ or rate$ or incidence$ or prevalence$ or duration$ or cumulat$ or transient or translocat$ or trans-locat$ or transfer$)).tw.

46. or/42-45

47. 41 and 46

Identification of evidence on the effectiveness of antibiotic prophylaxis in reducing bacteraemia levels associated with defined interventional procedures

The searches were conducted on 7 September 2007. Search filters for systematic reviews, randomised controlled trials and observational studies were appended to the search strategies to retrieve high quality papers (see below for **Identification of systematic reviews, randomised controlled trials and observational studies**).

The MEDLINE search strategy is presented below. It was translated for use in all of the other databases.

Ovid MEDLINE(R) <1950 to August Week 5 2007>

1 exp Dentistry, Operative/

2 exp Dental Prophylaxis/

3 ((dent$ or tooth$ or teeth$ or peridont$ or orthodont$) adj prophyla$).tw.

4 (crown adj3 length$).tw.

5 exp Endodontics/

6 endodontic$.tw.

7 apicoectom$.tw.

8 (pulp$ adj3 cap$).tw.

9 pulpectom$.tw.

10 pulpotom$.tw.

11 exp Oral Surgical Procedures/

12 gingivectom$.tw.

13 gingivoplast$.tw.

14 glossectom$.tw.

15 mucoperio$ flap$.tw.

16 (tartar adj3 remov$).tw.

17 Sialography/

18 sialograph$.tw.

19 (root adj2 canal adj3 (therap$ or treat$)).tw.

20 ((dent$ or oral$ or tooth$ or teeth or peridont$ or orthodont$ or root$) adj3 (restorat$ 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.

21 ((dent$ or oral$ or tooth$ or teeth$ or peridont$ or orthodont$ or root$ canal$) adj3 (surg$ or procedure$ or endoscop$ or operat$ or incis$ or excis$ or intervention$ or invasiv$ or biops$ or inject$)).tw.

22 or/1-21

23 exp Digestive System Surgical Procedures/

24 roux-en-y.tw.

25 appendectom$.tw.

26 (bili$ adj3 (bypas$ or divers$)).tw.

27 cholecystectom$.tw.

28 (gallbladder adj3 remov$).tw.

29 cholecystostom$.tw.

30 portoenterostom$.tw.

31 sphincterotom$.tw.

32 papillotom$.tw.

33 colectom$.tw.

34 proctocolectom$.tw.

35 coloproctectom$.tw.

36 laparotom$.tw.

37 endoscop$.tw.

38 colonoscop$.tw.

39 duodenoscop$.tw.

40 gastroscop$.tw.

41 proctoscop$.tw.

42 cholangiopancreatograph$.tw.

43 ercp.tw.

44 esophagoscop$.tw.

45 esophagogastroduodenoscop$.tw.

46 oesophagoscop$.tw.

47 oesophagogastroduodenoscop$.tw.

48 Echocardiography, Transesophageal/

49 Echocardiography/

50 (transesophag$ adj3 echo$).tw.

51 (trans-esophag$ adj3 echo$).tw.

52 (esophag$ adj3 echo$).tw.

53 (transoesophag$ adj3 echo$).tw.

54 (trans-oesophag$ adj3 echo$).tw.

55 (oesophag$ adj3 echo$).tw.

56 tee.tw.

57 toe.tw.

58 (oesophag$ adj3 dilat$).tw.

59 (esophag$ adj3 dilat$).tw.

60 exp Lithotripsy/

61 lithotrip$.tw.

62 litholapax$.tw.

63 enterostom$.tw.

64 cecostom$.tw.

65 colostom$.tw.

66 duodenostom$.tw.

67 ileostom$.tw.

68 jejunostom$.tw.

69 esophagectom$.tw.

70 oesophagectom$.tw.

71 esophagoplast$.tw.

72 oesophagoplast$.tw.

73 esophagostom$.tw.

74 oesophagostom$.tw.

75 fundoplicat$.tw.

76 nissen.tw.

77 gastrectom$.tw.

78 gastroenterostom$.tw.

79 billroth.tw.

80 gastrojejunostom$.tw.

81 (gast$ adj3 bypass).tw.

82 gastroplast$.tw.

83 gastrostom$.tw.

84 hepatectom$.tw.

85 (jejunoileal adj3 bypass).tw.

86 (ileojejunal adj3 bypass).tw.

87 (intestin$ adj3 bypass).tw.

88 ((liver or hepat$) adj3 (transplant$ or graft$)).tw.

89 (pancrea$ adj3 (transplant$ or graft$)).tw.

90 pancreatectom$.tw.

91 (pancrea$ adj3 remov$).tw.

92 pancreaticoduodenectom$.tw.

93 duodenopancreatectom$.tw.

94 pancreatoduodenectom$.tw.

95 pancreaticojejunostom$.tw.

96 (periton$ adj3 shunt$).tw.

97 (leveen adj3 shunt$).tw.

98 ((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$) adj3 (surg$ or procedure$ or operat$ or incis$ or excis$ or intervention$ or invasiv$ or biops$ or endoscop$ or sclerotherap$)).tw.

99 or/23-98

100 exp Urogenital Surgical Procedures/

101 colposcop$.tw.

102 colpotom$.tw.

103 culdoscop$.tw.

104 (dilatation adj3 curettage).tw.

105 (vacuum adj3 curettage).tw.

106 hysterectom$.tw.

107 hysteroscop$.tw.

108 (uter$ adj3 endoscop$).tw.

109 ovariectom$.tw.

110 oophorectom$.tw.

111 salpingostom$.tw.

112 (reproduct$ adj3 sterili$).tw.

113 (tub$ adj3 Sterili$).tw.

114 (tub$ adj3 ligat$).tw.

115 aldridge.tw.

116 (tub$ adj3 occlu$).tw.

117 cooke.tw.

118 (cornual adj3 coagulat$).tw.

119 fimbriectom$.tw.

120 irving.tw.

121 kroener.tw.

122 madlener.tw.

123 pomeroy.tw.

124 (tub$ adj3 excis$).tw.

125 (tub$ adj3 ring$).tw.

126 uchida.tw.

127 vasectom$.tw.

128 cystectom$.tw.

129 cystoscop$.tw.

130 cystostom$.tw.

131 cystotom$.tw.

132 (kidney$ adj3 transplant$).tw.

133 (kidney$ adj3 graft$).tw.

134 nephrectom$.tw.

135 vesicotom$.tw.

136 ureteroscop$.tw.

137 (urin$ adj3 diver$).tw.

138 nephrostom$.tw.

139 nephroli$.tw.

140 ureterostom$.tw.

141 orchiectom$.tw.

142 (pen$ adj3 implant$).tw.

143 prostatectom$.tw.

144 trans?uret$.tw.

145 trans?rect$.tw.

146 vasovasostom$.tw.

147 castrat$.tw.

148 circumci$.tw.

149 (uret$ adj3 catheter$).tw.

150 (uret$ adj3 dilatat$).tw.

151 exp Obstetric Surgical Procedures/

152 abortion$.tw.

153 embryotom$.tw.

154 cerclage.tw.

155 (obstetr$ adj3 deliver$).tw.

156 (abdom$ adj3 deliver$).tw.

157 cesarean.tw.

158 caesarean.tw.

159 episiotom$.tw.

160 (obstetr$ adj3 extract$).tw.

161 (induc$ adj3 (labor$ or labour$)).tw.

162 Parturition/

163 parturit$.tw.

164 childbirth$.tw.

165 birth$.tw.

166 (vagina$ adj3 deliver$).tw.

167 ((fet$ or cepha$) adj3 version$).tw.

168 fetoscop$.tw.

169 Intrauterine Devices/

170 (intra?uterine adj3 device$).tw.

171 iud.tw.

172 Vaginal Smears/

173 ((vagina$ or cervi$ or papanicolaou) adj3 smear$).tw.

174 ((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$) adj3 (surg$ or procedure$ or operat$ or incis$ or excis$ or intervention$ or invasiv$ or biops$ or endoscop$)).tw.

175 or/100-174

176 exp Pulmonary Surgical Procedures/

177 (collapse adj3 therap$).tw.

178 pneumonolys$.tw.

179 pneumothora$.tw.

180 Bronchoscopy/

181 bronchoscop$.tw.

182 thyroidectomy/ or adenoidectomy/ or laryngectomy/ or laryngoscopy/ or neck dissection/ or pharyngectomy/ or pharyngostomy/ or rhinoplasty/ or tonsillectomy/ or tracheostomy/ or tracheotomy/

183 thyroidectom$.tw.

184 adenoidectom$.tw.

185 laryngectom$.tw.

186 laryngoscop$.tw.

187 neck dissect$.tw.

188 pharyngectom$.tw.

189 pharyngostom$.tw.

190 rhinoplast$.tw.

191 tonsillectom$.tw.

192 tracheostom$.tw.

193 tracheotom$.tw.

194 (nasal adj3 pack$).tw.

195 Pneumonectomy/

196 pneumonectom$.tw.

197 (lung$ adj3 transplant$).tw.

198 (lung$ adj3 graft$).tw.

199 ((nasal or sinus$ or rhino$ or rhina$ or pharyn$ or laryn$ or trache$ or bronch$ or lung$ or pulmonar$ or respirat$) adj3 (surg$ or procedure$ or endoscop$ or operat$ or incis$ or excis$ or intervention$ or invasiv$ or biops$)).tw.

200 or/176-199

201 22 or 99 or 175 or 200

202 exp Chemoprevention/

203 chemoprevent$.tw.

204 chemo-prevent$.tw.

205 prophyla$.tw.

206 chemoprophyla$.tw.

207 chemo-prophyla$.tw.

208 exp anti-infective agents/

209 exp Penicillins/

210 penicillin$.tw.

211 "pen v".tw.

212 "pen g".tw.

213 antibiot$.tw.

214 anti-biot$.tw.

215 antibacter$.tw.

216 anti-bacter$.tw.

217 antimycobacter$.tw.

218 anti-mycobacter$.tw.

219 bacteriocid$.tw.

220 microbicid$.tw.

221 antimicrob$.tw.

222 anti-microb$.tw.

223 anti-infect$.tw.

224 antiinfect$.tw.

225 gentamicin$.tw.

226 gentamycin$.tw.

227 cidomycin$.tw.

228 garamycin$.tw.

229 garamicin$.tw.

230 gentacycol.tw.

231 gentavet.tw.

232 genticin$.tw.

233 Glycopeptides/

234 teicoplanin$.tw.

235 teichomycin$.tw.

236 teichomicin$.tw.

237 targocid$.tw.

238 clindamycin$.tw.

239 clindamicin$.tw.

240 dalacin c.tw.

241 deoxylincomycin$.tw.

242 chlolincocin$.tw.

243 chlorlincocin$.tw.

244 cleocin.tw.

245 ceftriaxon$.tw.

246 rocephin.tw.

247 cefatriaxon$.tw.

248 cephalexin$.tw.

249 cefalexin$.tw.

250 ceporex.tw.

251 keflex.tw.

252 azithromycin$.tw.

253 azithromicin$.tw.

254 azythromycin$.tw.

255 azythromicin$.tw.

256 zithromax.tw.

257 clarithromycin$.tw.

258 clarithromicin$.tw.

259 clarothromycin$.tw.

260 clarothromicin$.tw.

261 clarosip.tw.

262 klaricid.tw.

263 vancomycin$.tw.

264 vancomicin$.tw.

265 vancocin$.tw.

266 cefuroxime.tw.

267 cephuroxime.tw.

268 zinacef.tw.

269 zinnat.tw.

270 ampicillin$.tw.

271 penbritin.tw.

272 amcill.tw.

273 aminobenzylpenicillin$.tw.

274 aminobenzyl-penicillin$.tw.

275 benzylpenicillin$.tw.

276 benzyl-penicillin$.tw.

277 omnipen.tw.

278 pentrexyl.tw.

279 polycillin$.tw.

280 ukapen.tw.

281 augmentin$.tw.

282 amoxicillin$.tw.

283 amoxycillin$.tw.

284 co-amox$.tw.

285 coamox$.tw.

286 hydroxyampicillin$.tw.

287 actimoxi.tw.

288 amoxil$.tw.

289 amoyl$.tw.

290 clamoxyl.tw.

291 penamox.tw.

292 polymox.tw.

293 trimox.tw.

294 wymox.tw.

295 flucloxacillin$.tw.

296 fluorochloroxacillin$.tw.

297 floxapen.tw.

298 cefazolin$.tw.

299 cephazolin$.tw.

300 cefamedin$.tw.

301 cefamezine$.tw.

302 gramaxin$.tw.

303 or/202-302

304 ((bacter$ or staphylococ$ or streptococ$ or enterococ$) adj5 (eliminat$ or prevent$ or reduc$ or decreas$ or lower$)).tw.

305 201 and 303 and 304

306 chemoprevent$.ti.

307 chemo-prevent$.ti.

308 chemoprophyla$.ti.

309 chemo-prophyla$.ti.

310 (antibiot$ and prophyla$).ti.

311 (anti-biot$ and prophyla$).ti.

312 (antimicrob$ and prophyla$).ti.

313 (anti-microb$ and prophyla$).ti.

314 (antibacter$ and prophyla$).ti.

315 (anti-bacter$ and prophyla$).ti.

316 (antibiot$ and premedi$).ti.

317 (anti-biot$ and premedi$).ti.

318 (antimicrob$ and premedi$).ti.

319 (anti-microb$ and premedi$).ti.

320 (antibacter$ and premedi$).ti.

321 (anti-bacter$ and premedi$).ti.

322 (antibiot$ and prevent$).ti.

323 (anti-biot$ and prevent$).ti.

324 (antimicrob$ and prevent$).ti.

325 (anti-microb$ and prevent$).ti.

326 (antibacter$ and prevent$).ti.

327 (anti-bacter$ and prevent$).ti.

328 or/306-327

329 201 and 328

330 305 or 329

Identification of evidence on the effectiveness of oral chlorhexidine prophylaxis in reducing bacteraemia levels associated with dental interventional procedures

The searches were conducted on 4 September 2007. Search filters for systematic reviews, randomised controlled trials and observational studies were appended to the search strategies to retrieve high quality papers (see below for **Identification of systematic reviews, randomised controlled trials and observational studies**).

The MEDLINE search strategy is presented below. It was translated for use in all of the other databases.

Ovid MEDLINE(R) <1950 to August Week 4 2007>

1 exp Dentistry, Operative/

2 exp Dental Prophylaxis/

3 ((dent$ or tooth$ or teeth or peridont$ or orthodont$) adj prophyla$).tw.

4 (crown adj3 length$).tw.

5 exp Endodontics/

6 endodontic$.tw.

7 apicoectom$.tw.

8 (pulp$ adj3 cap$).tw.

9 pulpectom$.tw.

10 pulpotom$.tw.

11 exp Oral Surgical Procedures/

12 gingivectom$.tw.

13 gingivoplast$.tw.

14 glossectom$.tw.

15 mucoperio$ flap$.tw.

16 (tartar adj3 remov$).tw.

17 Sialography/

18 sialograph$.tw.

19 (root adj2 canal adj3 (therap$ or treat$)).tw.

20 ((dent$ or oral$ or tooth$ or teeth or peridont$ or orthodont$ or root$) adj3 (restorat$ 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.

21 ((dent$ or oral$ or tooth$ or teeth$ or peridont$ or orthodont$ or root$ canal$) adj3 (surg$ or procedure$ or endoscop$ or operat$ or incis$ or excis$ or intervention$ or invasiv$ or biops$ or inject$)).tw.

22 or/1-21

23 Mouthwashes/

24 mouthwash$.tw.

25 mouth wash$.tw.

26 Chlorobenzenes/

27 Biguanides/

28 Chlorhexidine/

29 chlorhex$.tw.

30 chlorohex$.tw.

31 corsodyl.tw.

32 eludril.tw.

33 tubulicid.tw.

34 ((cavit$ or oral or dent$ or mouth$ or endodontic$ or orthodontic$ or peridont$) adj3 (antibiot$ 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.

35 or/23-34

36 exp Bacteria/

37 Bacterial Infections/

38 exp Bacteremia/

39 bacter$.tw.

40 enterococ$.tw.

41 streptococ$.tw.

42 staphylococ$.tw.

43 or/36-42

44 22 and 35 and 43

Identification of systematic reviews, randomised controlled trials and observational studies

Search filters for systematic reviews, randomised controlled trials and observational studies were appended to the search strategies above to retrieve high quality evidence.

The MEDLINE search filters are presented below. They were translated for use in all of the other databases.

Systematic Reviews

1. meta-analysis.pt.
2. review.pt.
3. exp review literature/
4. meta-analysis/
5. (metaanaly$ or metanaly$ or (meta adj2 analy$)).tw.
6. (review$ or overview$).ti.
7. (systematic$ adj4 (review$ or overview$)).tw.
8. ((quantitative$ or qualitative$) adj4 (review$ or overview$)).tw.
9. ((studies or trial$) adj1 (review$ or overview$)).tw.
10. (integrat$ adj2 (research or review$ or literature)).tw.
11. (pool$ adj1 (analy$ or data)).tw.
12. (handsearch$ or (hand adj2 search$)).tw.
13. (manual$ adj2 search$).tw.
14. or/1-13

Randomised Controlled Trials

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. clinical trial.pt.
4. exp clinical trials/
5. placebos/
6. random allocation/
7. double-blind method/
8. single-blind method/
9. cross-over studies/
10. ((random$ or control$ or clinical$) adj2 (trial$ or stud$)).tw.
11. (random$ adj2 allocat$).tw.
12. placebo$.tw.
13. ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.
14. (crossover$ or (cross adj over$)).tw.
15. or/1-14

Observational Studies

1. Epidemiologic Studies/
2. exp Case-Control Studies/

3. exp Cohort Studies/
4. Cross-Sectional Studies/
5. Comparative Study.pt.
6. case control$.tw.
7. case series.tw.
8. (cohort adj (study or studies)).tw.
9. cohort analy$.tw.
10. (follow up adj (study or studies)).tw.
11. (observational adj (study or studies)).tw.
12. longitudinal.tw.
13. prospective.tw.
14. retrospective.tw.
15. cross sectional.tw.
16. or/1-15

Identification of evidence on patient views about antibiotic prophylaxis for infective endocarditis

The searches were conducted on 21 September 2007.

The MEDLINE search strategy is presented below. It was translated for use in all of the other databases.

Ovid MEDLINE(R) <1950 to September Week 2 2007>

---

1 Qualitative Research/

2 Nursing Methodology Research/

3 exp Interviews/

4 Questionnaires/

5 Narration/

6 Health Care Surveys/

7 (qualitative$ or interview$ or focus group$ or questionnaire$ or narrative$ or narration$ or survey$).tw.

8 (ethno$ or emic or etic or phenomenolog$ or grounded theory or constant compar$ or (thematic$ adj3 analys$) or theoretical sampl$ or purposive sampl$).tw.

9 (hermeneutic$ or heidegger$ or husser$ or colaizzi$ or van kaam$ or van manen$ or giorgi$ or glaser$ or strauss$ or ricoeur$ or spiegelberg$ or merleau$).tw.

10 (metasynthes$ or meta-synthes$ or metasummar$ or meta-summar$ or metastud$ or meta-stud$).tw.

11 or/1-10

12 exp Patients/px

13 exp Parents/px

14 exp Family/px

15 Caregivers/px

16 Stress, Psychological/

17 Emotions/

18 Anxiety/

19 Fear/

20 exp Consumer Satisfaction/

21 ((patient$ or parent$ or famil$ or carer$ or caregiver$ or care-giver$ or inpatient$ or in-patient$) adj2 (experience$ or belief$ or stress$ or emotion$ or anx$ or fear$ or concern$ or uncertain$ or unsure or thought$ or feeling$ or felt$ or view$ or opinion$ or perception$ or perspective$ or attitud$ or satisfact$ or know$ or understand$ or aware$)).tw.

22 or/12-21

23 11 or 22

24 exp Endocarditis/

25 endocardit$.tw.

26 24 or 25

27 exp Chemoprevention/

28 chemoprevent$.tw.

29 chemo-prevent$.tw.

30 prophyla$.tw.

31 chemoprophyla$.tw.

32 chemo-prophyla$.tw.

33 exp anti-infective agents/

34 exp Penicillins/

35 penicillin$.tw.

36 "pen v".tw.

37 "pen g".tw.

38 antibiot$.tw.

39 anti-biot$.tw.

40 antibacter$.tw.

41 anti-bacter$.tw.

42 antimycobacter$.tw.

43 anti-mycobacter$.tw.

44 bacteriocid$.tw.

45 microbicid$.tw.

46 antimicrob$.tw.

47 anti-microb$.tw.

48 antiinfect$.tw.

49 anti-infect$.tw.

50 or/27-49

51 26 and 50

52 23 and 51

Health economics

Sources

The following sources were searched to identify economic evaluations:

- NHS Economic Evaluation Database – NHS EED (via Cochrane Library, Wiley)
- Health Economic Evaluations Database – HEED (OHE interface)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)

Strategies

The searches were undertaken on 21 September 2007. The MEDLINE search strategy presented in the section - **Identification of evidence on infective endocarditis** was used and translated for use in NHS EED and HEED. Filters to retrieve economic evaluations and quality of life papers were appended to the MEDLINE search to identify relevant evidence.

The MEDLINE economic evaluations and quality of life search filters are presented below. They were translated for use in the MEDLINE In-Process database.

Ovid MEDLINE(R) <1950 to September Week 2 2007>

Economic Evaluations

1 Economics/

2 exp "Costs and Cost Analysis"/

3 Economics, Dental/

4 exp Economics, Hospital/

5 exp Economics, Medical/

6 Economics, Nursing/

7 Economics, Pharmaceutical/

8 Budgets/

9 "Quality of Life"/

10 "Value of Life"/

11 quality-adjusted life years/

12 exp models, economic/

13 markov chains/

14 monte carlo method/

15 Decision Trees/

16 economic$.tw.

17 quality of life.tw.

18 qol?.tw.

19 hrqol?.tw.

20 quality adjusted life year?.tw.

21 qaly?.tw.

22 cba.tw.

23 cea.tw.

24 cua.tw.

25 markov$.tw.

26 (monte adj carlo).tw.

27 (decision adj2 (tree? or analys$)).tw.

28 utilit$.tw.

29 pathway?.tw.

30 ((critical or clinical or patient) adj (path? or protocol?)).tw.

31 (cost? or costing? or costly or costed).tw.

32 (price? or pricing?).tw.

33 fiscal$.tw.

34 (fund? or funding or funded).tw.

35 financ$.tw.

36 budget$.tw.

37 expenditure?.tw.

38 (fee or fees).tw.

39 saving?.tw.

40 (value adj2 (money or monetary)).tw.

41 (pharmacoeconomic? or (pharmaco adj economic?)).tw.

42 ration$.tw.

43 (resource? adj2 allocat$).tw.

44 or/1-43

Ovid MEDLINE(R) <1950 to September Week 2 2007>

Quality of life

1 value of life/

2 quality adjusted life year/

3 quality adjusted life.tw.

4 (qaly$ or qald$ or qale$ or qtime$).tw.

5 disability adjusted life.tw.

6 daly$.tw.

7 health status indicators/

8 (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.

9 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.

10 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.

11 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.

12 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.

13 (euroqol or euro qol or eq5d or eq 5d).tw.

14 (hql or hqol or h qol or hrqol or hr qol).tw.

15 (hye or hyes).tw.

16 health$ year$ equivalent$.tw.

17 health utilit$.tw.

18 (hui or hui1 or hui2 or hui3).tw.

19 disutili$.tw.

20 rosser.tw.

21 quality of wellbeing.tw.

22 quality of well-being.tw.

23 qwb.tw.

24 willingness to pay.tw.

25 standard gamble$.tw.

26 time trade off.tw.

27 time tradeoff.tw.

28 tto.tw.

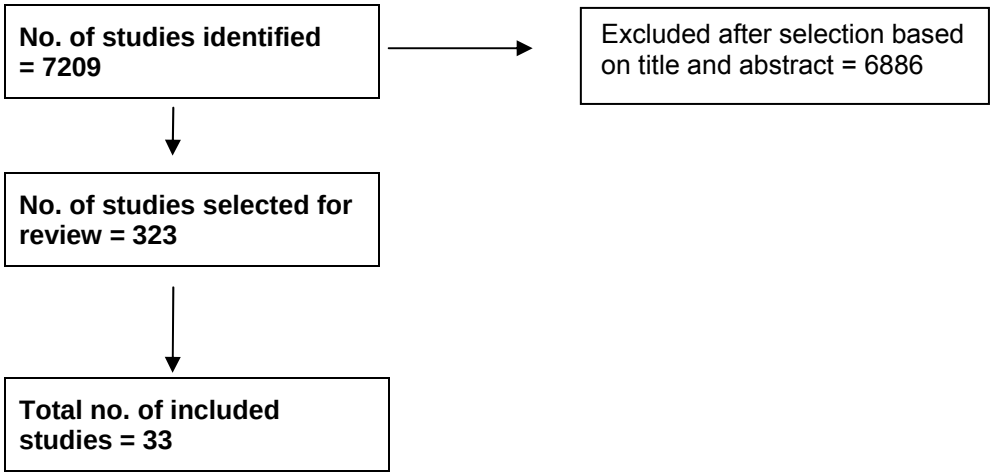
29 or/1-28

6.4 Appendix 4 – Evidence flow charts and evidence tables

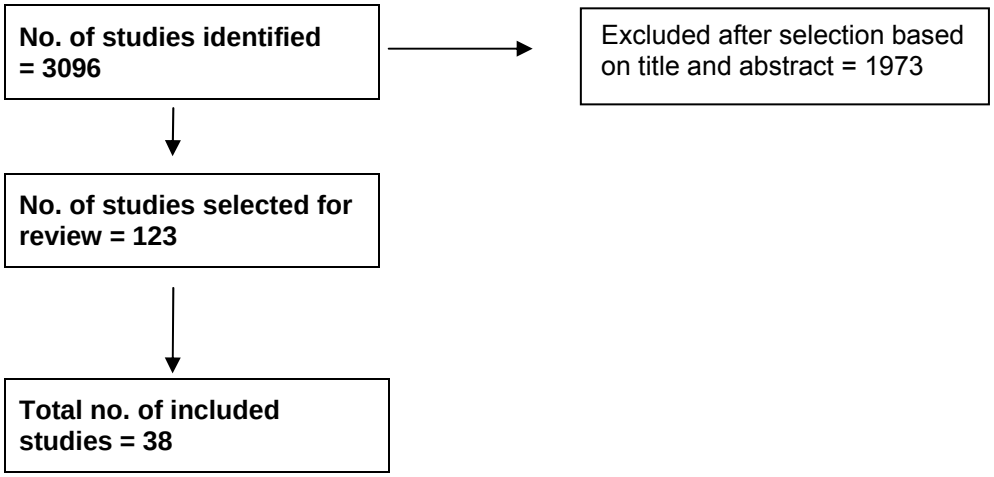
Flow chart figures

This initial search was a very broad search which used infective endocarditis as the main search term. The consideration of the titles and abstracts from this search yielded a large number of papers which included those which would be relevant to the consideration of the risk/outcomes of developing IE with cardiac conditions but also included papers which it was identified would be appropriate for other sections under consideration in this guideline.

Initial search – infective endocarditis search and including risk and outcomes

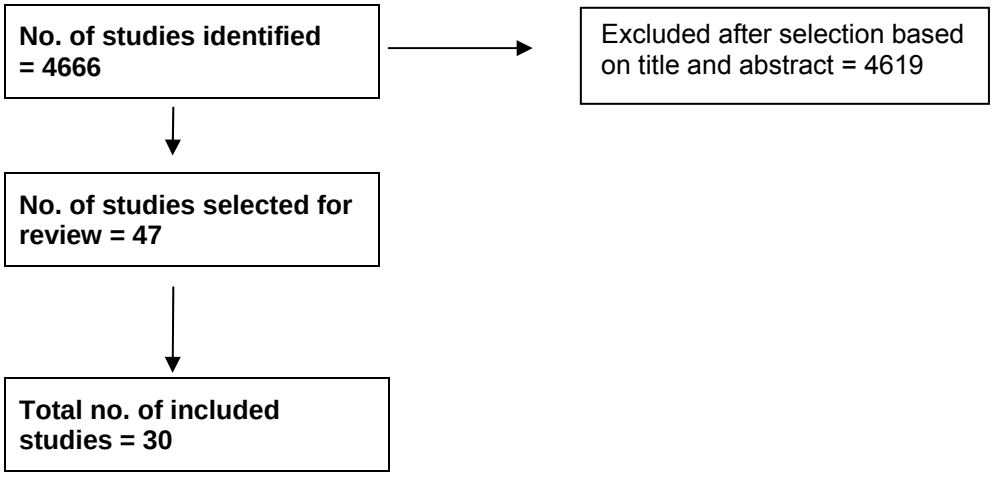


Bacteraemia and interventional procedures.



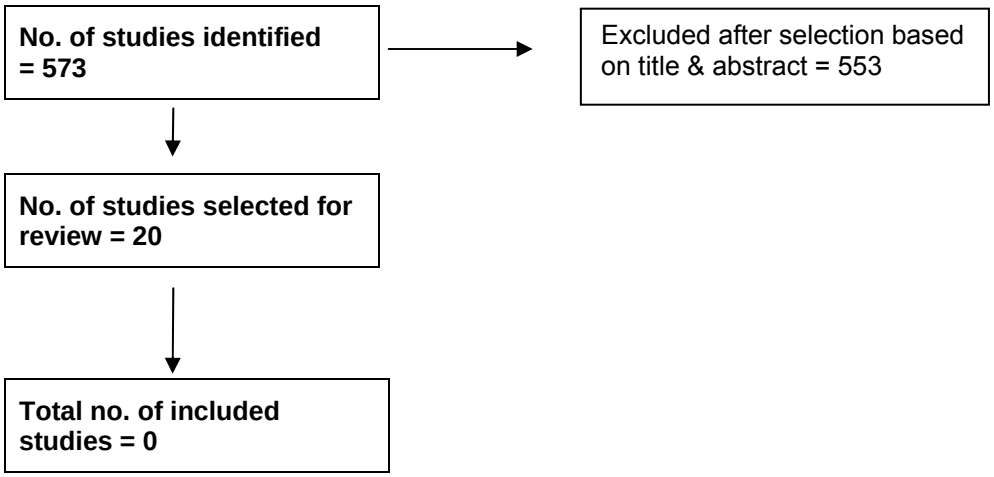
The third search was devised in consideration of antibiotic prophylaxis against IE.

Antibiotic prophylaxis



The final search was devised to consider patient perspectives on prophylaxis against IE.

Patient perspectives



Evidence Tables

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Al Karaawi ZM, Lucas VS, Gelbier M, Roberts GJ (2001) Dental procedures in children with severe congenital heart disease: A theoretical analysis of prophylaxis and non-prophylaxis procedures. *Heart* 85: 66–68. Ref ID: 3435	retrospective theoretical analysis	Between June 1993 to June 1998 at GOSH and from January to June 1998 at Eastman Dental Hospital n = 136 (n = 133 GOSH and n = 3 EDH) UK	Records of children with severe congenital disease and from the case records of a dento-gingival manipulative procedure	Prophylaxis procedures[1]	Non-prophylaxis procedures[2]	5 yrs from GSOH and 6 mths at EDH	Cumulative exposure derived from the equation: intensity x tally x prevalence x duration = cumulative exposure in cfu/ml/procedure/yr Intensity is the number of colony forming units (cfu)/ml blood[3] Tally is the average number of a given dento-gingival manipulative procedure performed annually[4]	Not stated

[1] According to the guidelines of the endocarditis working party of the British Society of Antimicrobial Chemotherapy (1993) and the American Heart Association (1997)
[2] According to the guidelines of the endocarditis working party of the British Society of Antimicrobial Chemotherapy (1993) and the American Heart Association (1997)
[3] Derived from several sources
[4] Derived solely from this study

							Prevalence is the number of positive cultures expressed as a proportion[5], for purposes of calculation, a percentage prevalence is converted to a proportion (eg. 38% = 0.38) Duration is the length of bacteraemia, which is 15 mins	

[5] Derived from several sources

Effect size:

Cumulative exposure
The theoretical cumulative exposure was expressed as the number of colony forming units/ml blood/minute in the standardised year[6]
The greatest cumulative exposure was for the placement of a rubber dam and the smallest was from a single primary tooth extraction

Prophylaxis procedures		***Non-prophylaxis procedures***	
Scaling	1.685	Dental examination	1.999
Single extraction primary tooth	0.059	Polishing teeth	16.410
Single extraction permanent tooth	0.685	Local anaesthetic infiltration	4.925
Multiple extractions – primary & permanent	51.775	Rubber dam placement with clamps	8210.970
Mucoperiosteal surgery	18.428	Slow drill	0.993
		Fast drill	1.904
		Matrix band placement	2.7648

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Allan WR, Kumar A (1985) Prophylactic mezlocillin for transurethral prostatectomy. British Journal of Urology 57: 46–49.	RCT [7]	n = 100 UK	Inclusion: undergoing transurethral prostatectomy Exclusion: allergy to penicillin, known UTI, had received antibiotics in the week before surgery There was NS difference between the groups	n = 50 mezlocillin Blood samples: immediately after the operation, first post-operative day, at removal of urethral catheter	n = 50 placebo Blood samples: immediately after the operation, first post-operative day, at removal of urethral catheter		Bacteraemia	Bayer Company

[6] As some individual's records covered less than a year or several years the number of times a dento-gingival manipulative procedure was carried out was standardised on a year
[7] Allocated by coded sealed letter from Bayer Co, opened by the anaesthetist when the patient came to the theatre

Effect size:

Bacteraemia
After completion of operation n = 2, 4% mezlocillin, n = 16, 36% control, p<0.001
First day post-op and after removal of catheter NS difference between the groups
Progressed to septicaemia in n = 4 patients, but in no cases where prophylactic cover was given

Catheter
n = 8 mezlocillin and n = 15 control had a pre-op catheter, 12% (n = 1/8) mezlocillin and 33% (n = 5/15) control had a positive blood culture

If there was a pre-op infected urine bacteraemia was likely to follow the operation, in n = 7/8 in the control group and n = 1/2 in the mezlocillin group
Of those who developed bacteraemia 94% also developed infection in the urine

Organisms isolated
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*)

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Anderson DJ, Olaison L, Mcdonald J et al. (2005) Enterococcal prosthetic valve infective endocarditis: report of 45 episodes from the	Case series	n = 159	Inclusion: data collected by the International Collaboration on Endocarditis-Merged Endocarditis Database (ICE-MD)[8], a large multinational study of IE; IE was defined according to the Duke Criteria	n = 45 prosthetic valve endocarditis	n = 114 native valve endocarditis		Patient characteristics, complications of IE, outcomes of IE due to enterococci	Not stated

[8] Databases originated in locations in the USA (2 locations) and Europe (Spain, France, Sweden, UK)

International Collaboration on Endocarditis-merged database. Eur J Clin Microbiol Infect Dis 24: 665–70								

Effect size:

Characteristics
n = 159 (7.2%) cases with definite enterococcal IE occurred among the n = 2212 patients with definite IE in the merged database, *Enterococcus faecalis* accounted for 94%
n = 45 involved a prosthetic valve; n = 114 involved native valves

Outcomes
Those with enterococcal PVE were more likely to have intracardiac abscesses vs. NVE, p=0.009
Those with enterococcal NVE were more likely to have detectable vegetations vs. PVE, p<0.001
There was NS difference between the groups with respect to valvular location of infection

Rates of complications/outcomes were NS different between the groups:
- heart failure; PVE n = 17/45 (38%); NVE n = 54/114 (47%)
- all embolisation; PVE n = 9/45 (20%); NVE n = 31/114 (27%)
- central nervous system; PVE n = 5/42 (12%); NVE n = 12/100 (12%)
- stroke; PVE n = 3/41 (7%); NVE n = 9/102 (9%)
- valvular surgery this episode; PVE n = 14/45 (31%); NVE n = 35/114 (31%)
- death (during hospitalisation); PVE n = 6/43 (14%); NVE n = 14/114 (12%)

n = 46/296 (16%) cases of PVE were definite nonenterococcal
Those with enterococcal PVE were similar to those with nonenterococcal PVE for clinical characteristics, rates of complications and echocardiographic characteristics
Mortality was NS higher in those with nonenterococcal PVE

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Barawi M, Gottlieb K, Cunha B, Portis M, Gress F (2001) A prospective evaluation of the incidence of bacteremia associated with EUS-guided fine-needle aspiration. Gastrointestinal Endoscopy 53: 189–92. Ref ID: 411	Pilot study, case series USA	n = 100 (n = 108 sites aspirated)	Inclusion: those undergoing endoscopic ultrasound (EUS)- guided fine needle aspiration (FNA), mean age 65.5 yrs (range 34 to 94 yrs), most common reason was for evaluation of pancreatic mass Exclusion: conditions for which the American Society for Gastrointestinal Endoscopy or AHA guidelines recommend antibiotic prophylaxis , antibiotic use within 1 week before procedure, a requirement for dilation of a stricture or stenosis of the GI tract within 24 to 48hrs or immediately before EUS-guided FNA, the presence of a cystic lesion, advanced liver disease or HIV/AIDS	EUS-guided FNA 200 sets of blood cultures Blood samples: 30 and 60 mins after the last EUS-guided FNA		1wk	Blood cultures Microbiological techniques: 10 ml of blood drawn at each sample time point and were injected into commercially available aerobic/anaerobic blood culture bottles, cultures were incubated for 7days and 37.5˚C	Not stated
Effect size: **Blood cultures** In the 200 sets of blood cultures, in these incubated blood cultures there was no significant bacterial growth except in n = 6 patients in whom coagulase negative Staphylococcus grew in 1 of 2 bottles (these 6 positive blood cultures were considered due to contaminants) There was no infectious complication reported by any subjects or the referring physicians at 1 week after the procedure								

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Barragan Casas JM, Hernandez Hernandez JM, Garcinuno Jimenez MA, et al. (1999) Bacteremia cased by digestive system endoscopy. Revista Espanola de Enfermedades Digestivas 91: 111–16. Ref ID: 1680	Randomised, prospective study	n = 102 Single hospital site, Spain	Inclusion: random selection from all patients scheduled for endoscopic examination (gastroscopy, sigmoidoscopy or colonoscopy, or ERCP) in a hospital in Spain, regardless of reason for admission, n = 55 male, n = 47 female, mean age 59.6±16yrs (range 16 to 87yrs) Exclusion: febrile syndrome before the endoscope, prior treatment with antibiotics, bacterial growth in the blood sample obtained before the examination, incomplete blood sampling, emergency endoscopic examination	n = 44 gastroscopy n = 30 colonoscopy n = 28 ERCP	Blood samples: baseline and 5 and 30min after the start of the procedure, in most cases this meant that blood samples were obtained while the examination was still in progress	16mths	Blood cultures Microbiology: Blood samples were incubated in aerobic (ESP 80A) and anaerobic blood culture bottles (ESP 80N, Difco) and processed with habitually used techniques, cultures were considered negative with no signs of growth at 6 days	Not stated
Effect size: **Gastroscopy** Blood cultures were positive in n = 11/44 (25%) with *Staphylococcus* spp and *Streptococcus* spp isolated, in n = 8 (72.7%) the 5min sample was positive, n = 6 (54.5%) the 30 min was positive, n = 2 (18.1%) both cultures were positive, n = 1 patient had polymicrobial growth in one sample The most frequent endoscopic findings were hiatus hernia with varying degrees of oesophagitis (n = 4) and peptic ulcer (n = 4) **Lower digestive tract endoscopy** Blood cultures were positive in n = 3/30 (10%) all in the 5 min samples, n = 1 was also positive in the 30 min sample								

ERCP
Blood cultures were positive in n = 11/28 (39.2%) with *E. coli, Morganella morganii*, *Staphylococcus* spp and *Streptococcus* spp were isolated, in n = 4 (36.3%) the 5 min sample was positive, n = 9 (81.8%) the 30min was positive, n = 2 (18.1%) both cultures were positive, n = 1 culture was positive for more than one microorganism
The most frequent endoscopic finding was biliary-pancreatic tree disease (n = 8)

(endoscopic examination frequently causes bacteraemia, generally due to saprophytic gram-positive microorganisms of the skin and mucosa)

Antimicrobial sensitivity
The microorganisms found most frequently were *Staphylococcus* spp and *Streptococcus* spp, antimicrobial sensitivity of these pathogens was; vancomycin 100%, rifampicin and amikacin 96.5%, gentamicin 93.1%, cefotaxime 89.6%, etercyclines 79.3%, ciprofloxacin, erythromycin, clindamycin and trimethoprim 75.8%, amoxicillin-clavulanic acid 68.9%, ampicillin 55.1%
Enterobacteria and Gram-negative microorganisms were sensitive to amikacin, gentamicin and ciprofloxacin in all n = 3 patients

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Benn M, Hagelskjer LH, Tvede M (1997) Infective endocarditis, 1984 through 1993: A clinical and microbiological survey. Journal of Internal Medicine 242:15–22	Retrospective review	n = 59 patients n = 62 episodes of IE Denmark	Patients were identified from hospital discharge statistics, the study used von Reyn's diagnostic criteria Mean age 55.4 yrs, median age 60.7 yrs (range 14.5–82.9) The mean age was 50.8yrs for males and 65.9 yrs for females Male/female ratio was 1:4			10-yr review, between 1 January 1984 and 31 December 1993	Incidence, predisposing factors, complications	Not stated

Effect size:

Incidence
62 episodes in n = 59 patients (40 definite, 16 probable, 6 possible)
The overall incidence was 27 episodes per million per year, for native valve IE was 23.5 episodes per million per year.
The overall incidence increased from 17.4 to 36.5 episodes per million per year from the first part to the second part of the decade ($p<0.001$)
(The authors identified concerns about the quality of the data with a retrospective study and also noted that the main reason for increased incidence is probably due to the unmasking of more episodes of IE)

Predisposing factors
From n = 62 total number of episodes, n = 41 (66.1%) had identified predisposing factors, with n = 21 episodes without predisposing factors

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 & mitral valve prosthesis	1
Fistula in septum	1	Aortic regurgitation	5
Ebstein's anomaly	1	Aortic stenosis	6
Transposition of great arteries & VSD	1	Mitral stenosis	8
		Mitral stenosis, rheumatic	3
		Aortic stenosis, rheumatic	3

For n = 11 already known portals of entry were found (an intravenous catheter; impetigo; erysipelas; bursitis; two episodes of septic arthritis; UTI; GI tract infection)

n = 2 patients had recorded surgical treatment in the 3 mths before admission

None of the episodes had recorded dental treatment as the portal of entry (The authors noted that there is a high level of dental hygiene and a high focus on prophylaxis in Denmark)

Complications
There was no difference in the relative risk of embolism between the aortic and mitral valve IE and between the native and prosthetic valve IE.
Mortality was n = 22/62 episodes, 35.5% overall.

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
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. Ref ID: 829	RCT Not blinded	n = 50 children Children's hospital & regional medical centre, USA	Inclusion: 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: positive blood cultures before toothbrushing	n = 25 Teeth brushed for a timed one-minute interval manually Blood cultures taken 30 seconds after toothbrushing	n = 25 Teeth brushed for a timed one-minute interval with the Sonicare electric toothbrush (high frequency brushing, 31,000 brush strokes per minute) Blood cultures taken 30 seconds after toothbrushing		Gingival health and plaque scores were determined for participants Positive blood cultures Microbiology: 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	Washington Dental Service Foundation, Phillips Oral Healthcare Corporation

Effect size:

Positive blood cultures
Toothbrushing resulted in positive blood cultures in n = 11/24 (46%, 26 to 66%, 95% CI) of manual and n = 18/23 (78%, 62 to 95%, 95% CI) of Sonicare participants, p=0.022

Gingival score
There was no significant difference in gingival health and plaque scores between the 2 groups. Analysis which controlled for plaque and gingival scores indicated that bacteraemia levels were higher in the Sonicare group (OR 6.6, p = 0.013)
There was NS difference in the rate of bacteraemia in those with normal gingiva and those with mild inflammation and there was no relationship between plaque scores and bacteraemia

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
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	RCT [9] [10]	n = 116 ITT analysis UK	Inclusion: women with menorrhagia undergoing either transcervical resection (TCRE) or laser ablation of the endometrium (ELA)	n = 55 1.2 g augmentin IV at the induction of anaesthesia Blood samples: immediately after the routine TCRE or ELA	n = 61 No antibiotic	Discharged same or following day, given a diary to record events over the next 2 wks	Blood cultures, infectious morbidity Blood culture bottles incubated in a non-radiometric Bactec 860 analyser at 37˚C for 5 days	Chief Scientists Office of the Scottish Office

[9] Randomised by the opening of sealed opaque envelopes
[10] Study had 80% power to detect a difference of 15%, from 1% to 16% at the 5% significance level

Effect size:

Blood cultures
n = 6/61 ELA compared with n = 5/55 TCRE
n = 10 (16%) positive blood cultures in the no antibiotic group compared with n = 1 (2%) in the antibiotic group, p<0.02

Infectious morbidity
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

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Boggess KA, Watts DH, Hillier SL, Krohn MA, Benedetti TJ, Eschenbach DA et al. (1996) Bacteremia shortly after placental separation during cesarean delivery. Obstetrics &	Case series	n = 93 USA	Inclusion: women undergoing caesarean delivery, included if they had rupture of membranes and/or labour for at least 4 hrs Exclusion: antibiotic use within 7 days before delivery, medical conditions requiring antibiotic treatment during labour, temperature greater than 38˚C	Blood samples: within 15 mins of delivery of the placenta in women undergoing caesarean without labour; within 5mins in women undergoing caesarean after labour		30 July 1985 to 31 July 1986 and 1 October 1993 to 30 September 1994	Blood cultures Microbiology: 10 ml per sample, stored at room temperature, inoculated into trypticase-soy yeast broths that were incubated aerobically and anaerobically. Cultures were incubated at 37˚C, blind cultures were performed from the trypticase-soy	Not stated

Gynecology 87: 779–84. Ref ID: 6337							yeast bottle at 24 hrs and 5 days and from the anaerobic bottles at 48 hrs and 7 days	

Effect size:

Blood cultures
Bacteraemia occurred in n = 13/93 (14%) of women after labour or rupture of membranes, n = 6/13 also had positive chorioamnionic membrane cultures, n = 5 of these were at ≤32 weeks gestation or less, gestational age of 32 weeks or less was strongly associated with a positive chorioamnionic placental culture

A positive blood culture was associated with earlier median gestational age at delivery (<32 weeks, OR 13.9; 3.5 to 54.8, 95% CI); lower median birth weight (less than 2500g, OR 10.5; 2.8 to 39, 95% CI) and positive chorioamnionic membrane culture (OR 6.4; 1.7 to 24.7, 95% CI)

After adjustment for hours of membrane rupture, hours of labour and intrauterine monitoring; median gestational age and positive chorioamnionic membrane culture remained significantly associated with bacteraemia

After adjustment for gestational age, intrauterine monitor use (OR 9.7; 6.5 to 40.8, 95% CI) and positive chorioamnionic membrane culture (OR 4.4; 1.6 to 26.7 95% CI) were significant predictors of bacteraemia

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Bouza E, Menasalvas A, Oz P, et al. (2001) Infective endocarditis: a prospective study at the end of the twentieth century: New	Prospectiv e case series	n = 101 (n = 109 episodes of IE) Spain	All cases followed by an infectious diseases consultant All cases fulfilled 1 or more of criteria of: clinical suspicion; echocardiographic evidence of IE; bloodstream infections caused by specific organisms; histologic findings n = 80 (73%) were male, n = 29 (27%) female, male:female ratio was 2.76; mean age 50 yrs (range, 19-89)			March 1994 to October 1996	Epidemiology	Not stated

predisposing conditions, new etiologic agents, and still a high mortality. *Medicine* 80: 298–307								

Effect size:

Epidemiology
The incidence was 6.4 cases per 100,000 inhabitants per year, 0.8 cases per 1,000 admissions and 3.5% of all cases of significant bacteraemia

Underlying conditions
n = 109 episodes of IE (n = 39, IVDU), all but n = 5 had underlying conditions

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%)		

Outcome
Related mortality was 25.7%, there was 100% mortality with early PVE (n = 6), 25% mortality with late PVE (n = 3) and 25% with NVE (n = 13)
With multivariate analysis early PVE, the presence of congestive heart failure and acute renal impairment were significantly related to mortality

Valve replacement was required in n = 25, n = 16(30.7%) of NVE, n = 2(33%) with early PVE and n = 6(50%) with late PVE.

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Brewster SFM (1995) Antimicrobial prophylaxis for transrectal prostatic biopsy: a prospective randomized trial of cefuroxime versus piperacillin/tazobactam. British Journal of Urology: 351–54	RCT	n = 111 UK	Inclusion: men undergoing ultrasonically transrectal prostatic biopsy to diagnose or stage carcinoma of the prostate Exclusion: history of penicillin hypersensitivity, prosthetic heart valve, heart murmur, rectal stenosis, concurrent antimicrobial therapy, bleeding diathesis, anticoagulant therapy	n = 56 1.5g cefuroxime IV over 1–2 mins, 20 mins before TPB Blood samples; baseline, 48 hr after TRP	n = 55 4.5 g piperacillin/tazobactam IV over 1–2 mins, 20 mins before TPB	8hrlt temperature for 4days	Blood cultures, temperature	Not stated

Effect size:

n = 109 evaluable

Clinically unsuccessful outcome
Defined as the presence of symptoms to indicate urinary or systemic sepsis, or pyrexia ≥37.5C after TRB was observed in n = 3/56 with cefuroxime and n = 5/55 piperacillin/tazobactam

Blood culture positive
n = 1 with cefuroxime considered to be septic, urine and blood both grew E coli

Adverse events
n = 61/111, n = 48 (45%) considered to be drug related, GI events the most common (n = 2 cefuroxime and =16 piperacillin/tazobactam mild transient diarrhoea; n = 8 piperacillin/tazobactam nausea/vomited once)

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Brown AR, Papasian CJ, Shultz P, et al (1998) Bacteremia and intraoral suture removal: can an antimicrobial rinse help? Journal of the	RCT [11]	n = 71 (n = 10 lost to follow-up) USA	Inclusion: requiring the removal of a third molar which would require at least 8 sutures, n = 37 female, aged 15 to 35 yrs Exclusion: systemic disease, taking steroids, had used antibiotics or oral rinses within the previous 4wks, moderate-to-severe peridontitis or residual pericoronitis, required preoperative prophylactic antibiotics All used similar flap designs and 3–0 black silk suture placement, used no medication in the sockets, nor did they	Group I n = 31 30 cubic centimetres of 0.12% chlorhexidine preprocedural rinse for 1 min Blood samples: baseline, 90 sec after suture removal	Group II n = 24 no-treatment control		oral hygiene All plates were examined for 7 days before negative results were reported, colony counts were performed on media showing growth and organisms identified using morphological	Not stated

[11] the doctor performing suture removal was unaware of whether or nor a patient had used a rinse; power calculation completed

American Dental Association 129: 1455–61.			use preoperative irrigation or rinses, subjects returned for suture removal seven days after the extraction and were randomly assigned to one of two groups				criteria and routine bacteriologic methods	
Effect size: **Bacteraemia** Pre-treatment blood samples were all negative Post-treatment n = 4/31 chlorhexidine and n = 2/24 control group had positive cultures, total incidence 10.9% (organisms identified: Staphylococcus coagulase negative, Propionibacterium, Staphylococcus aureus, Corynebacterium, Streptococcus sanguis, Bifidobacterium, S. viridans, Micrococcus, S. mitis, Prevotella sp, Peptostreptococcus) There was NS difference in the proportion of bacteraemia with experimental vs. control groups Bleeding on suture removal occurred in n = 47/55 patients, none of those in whom bleeding did not occur developed bacteraemia, there was NS relationship between the presence of bleeding after suture removal and the incidence of bacteraemia								

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Calderwood SB, Swinski LA, Karchmer AW et al. (1986) Prosthetic valve endocarditis. Analysis of factors affecting outcome of therapy. Journal of Thoracic & Cardiovascular Surgery 92: 776–83	Case series	n = 116 USA	Inclusion: diagnosis of PVE based on a strict case definition, mean age 59.6±10.7, median 60.5 yrs (range (21 to 79 yrs), [12]			Study period 1 January 1975 to 31 December 1982 Mean follow-up 20.2 mths (range 0.5 –79 mths)	Factors associated with complicated PVE, medical-surgical therapy, mortality	Not stated

[12] 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 doe 10days or more days during appropriate antibiotic therapy; new or progressive abnormalities of cardiac condition
Relapse – if infection occurred in the 12mths after hospital discharge and either was caused by the same organism or else no pathogen was identified

Effect size:

Factors associated with complicated PVE
n = 74/116 (64%) had complicated PVE
Logistic regression models of complicated PVE in a single vale recipient showed aortic valve infection, early onset of IE to be factor associated with complicated infection

Factors associated with medical-surgical therapy for PVE[13]
n = 45/115 (39%) received medical-surgical therapy
Logistic regression identified three factors as associated with a decision foe medical-surgical therapy; complicated PVE, infection with coagulase negative staphylococci, infection of a single prosthesis (may reflect bias against operating on those with multiple prosthesis

Factors associated with mortality of PVE
n = 27/116 (23%) died during initial hospitalisation for the treatment of PVE
Logistic regression showed complicated PVE to be the best predictor of mortality
The mortality rate was significantly lower in those with coagulase-negative staphylococci (OR<1)
None of the other variables exerted an independent effect on mortality from PVE

Follow-up
n = 89 survived hospitalisation, on discharge n = 71 had no or mild CHF, n = 13 moderate and n = 5 severe
The presence of moderate to severe CHF on discharge affected survival after therapy compared to no or mild CHF (p=0.03)
NS effect on mortality after discharge; position of the infected valve, porcine vs. mechanical prosthesis, patient sex, medical vs. medical-surgical therapy

n = 11/89 (12%) relapsed; NS difference in medical vs. medical-surgical treatment
Valve site originally infected or infecting organism did not affect relapse rate

n = 14/56 (25%) who had had medical therapy vs. n = 2/33 (6%), p=0.04, who had had medical-surgical therapy required an operation for late sequelae of infection (other than relapse)

Including death, relapse of PVE and subsequent cardiac operation for late sequelae of infection as bad outcomes of initial therapy; the medical group showed

[13] Medical-surgical therapy was considered to be where patient underwent repair or replacement of the infected prosthesis during the initial hospitalisation for treatment of PVE

significantly worse outcome than those who had medical-surgical therapy (p = 0.02)
NS influence were patient sex, position of infected valve, porcine vs. mechanical prosthesis, infecting organism and early vs. late onset

Analysis of outcome of complicated PVE
Survival of patient with complicated PVE without the need for additional therapy was more frequently found with initial medical-surgical vs. medical therapy (p = 0.008)

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Cecchi E, Forno D, Imazio M, Migliardi et al. (2004) New trends in the epidemiological and clinical features of infective endocarditis: results of a multicenter prospective study. Italian Heart Journal 5: 249–56	Prospective multicentre survey	n = 147 cases Italy	Patients with a definite diagnosis of IE in a region of Italy, diagnosis was based on Duke University criteria and 3-mth follow-up data These cases constituted the samples population for the purposes of this study			January 2000 to December 2001	Predisposing heart disease	Not stated

Effect size:

Predisposing heart disease

n = 104/147 considered to be related to predisposing heart disease

Prosthetic valves	**37(25%)**	Aortic insufficiency	6
Native valves	**67(45%)**	Mitral insufficiency	3
Mitral valve prolapse	25	Mitral & aortic insufficiency	5
Aortic stenosis	5	Bicuspid aortic valve	8
Aortic stenosis & insufficiency	6	Interventricular septal defect	1
Mitral stenosis	2	Previous mitral valvuloplasty	2
Mitral stenosis & insufficiency	3	Aortic valve sclerosis	2

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Choudhury R, Grover A, Varma J, et al. (1992) Active infective endocarditis observed in an Indian hospital 1981-1991. Am J Cardiol 70: 1453–58	Retrospective review	n = 186 patients (n = 190 episodes of IE) India	Data from patient records at a hospital in Northern India, diagnostic criteria: vegetation on echocardiography; ≥2 positive blood cultures growing the same organism with ≥2 specified clinical features n = 133 males, n = 53 females, mean age 25±12yrs SD (range 2–75 yrs)			January 1981 to July 1991	Underlying heart disease, outcomes	Not stated

Effect size:

Underlying heart disease

n = 190 episodes (n = 186 patients) of IE, underlying heart disease (rheumatic heart disease n = 79(42%), normal n = 17(9%))

Congenital heart disease - total	**62 (33%)**	**Uncertain aetiology**	**24 (13%)**
Bicuspid aortic valve	25	Aortic regurgitation	15
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		

Outcome

For those with congenital heart disease n = 11(23%) died and n = 53(38%) recovered

For those with mitral valve prolapse n = 2 recovered

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Chu J, Wilkins G, Williams M, Chu J, et al. (2004) Review of 65 cases of infective endocarditis in Dunedin Public Hospital. New Zealand Medical Journal 117:U1021	Case review	n = 62 patients n = 65 episodes	IE diagnosed using the Duke criteria, n = 42 male, n = 20 female; mean age 65.0±18.1 yrs (range 7–89 yrs)			5years November 1997 to October 2002	Underlying heart disease, outcome	Not stated

Effect size:

Underlying heart disease
n = 65 episodes (n = 62 patients) of IE, predisposing heart conditions (normal valves n = 25; 40.3%)

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 *	1 (1.6%)	Aortic stenosis	8 (12.9%)
Transposition of great arteries *	1 (1.6%)	Mitral valve prolapse	4 (6.5%)
Abnormal pulmonary valve	1 (1.6%)	Prosthetic valves	15 (24.2%)
		Automated implantable cardioverter defibrillator	1 (1.6%)

*post repair

Outcome
Mortality for those with NVE was n = 11/20(55.0%), n = 33/42 (78.5%) recovered
Mortality for those with PVE was n = 6/20 (30.0%), n = 6/42 (14.3%) recovered

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Clemens JD, Horwitz RI, Jaffe CC, et al. (1982) A controlled evaluation of the risk of	Case-control	n = 204	Inclusion: hospital inpatients 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[14]	n = 51 cases	n = 153 control group Similar for age, sex and prevalence of white patients	4yrs of cases Between 1 Nov 1976 and 1 Nov 1980	Mitral valve prolapse	Not stated

[14] 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

bacterial endocarditis in persons with mitral-valve prolapse. *N Engl J Med* 307: 776–81. Ref ID: 1272			Inclusion: cases: data extracted from medical records, who fulfilled the diagnostic and/or pathological criteria for bacterial endocarditis 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 Inclusion: 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) Exclusion: 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 2 groups 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					

[15] The eligibility of patients was determined by a 'blinded' researcher, without knowledge of the echocardiograph findings

			cardiovascular lesions that were unsuspected before echocardiography, adjustment was made for these inequalities [15]					

Effect size:

Mitral valve prolapse
n = 13 (25%) of the cases and n = 10 (7%) of the controls had mitral valve prolapse
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

Analysis was completed using only the echocardiographic criteria for MVP (the association was unaffected) 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).

(the authors consider that these results demonstrate a substantial association between MVP and BE)

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Danchin N, Voiriot P, Briancon S, Bairati I, Mathieu P, Deschamps JP *et al*. Mitral valve prolapse as a risk factor for infective endocarditis.	Case-control	n = 144 France	Inclusion: cases; records of all those with bacterial endocarditis admitted to cardiology and cardiovascular surgery Bacterial endocarditis considered present in those with pathological evidence of endocarditis at operation or necropsy; or if the patients had fever and 2 major diagnostic criteria; or fever with 1 major and 3 minor diagnostic criteria. All had ≥1 echocardiography, only those with echocardiographic evidence of mitral valve	n = 48 cases	n = 96 controls, matched for age and sex[16]	Between 1st Jan 1981 to 31st March 1986	Mitral valve prolapse, risk of BE	Not stated

[16] Mitral valve prolapse diagnosed by echocardiography

[see comment]. Lancet 1: 743–45. Ref ID: 7167			endocarditis were entered into the study Exclusion: cases; endocarditis of the aortic valve or of one of the right sided valves without mitral valve endocarditis or endocarditis on a mitral valve prosthesis Controls; 2 groups; a random sample of n = 71 under 60 yrs, who were examined echocardiographically during routine family screening who attended between 5 to 16 January 1987; and n = 25, over 60 yrs, randomly selected from patients admitted for surgery of the limbs					

Effect size:

Frequency of mitral valve prolapse[17]
Cases; n = 9 (19%) of the n = 48 with mitral valve endocarditis had mitral valve prolapse
(the characteristics of the patients with or without mitral valve prolapse identified that these groups did not differ significantly in the infective organism)
Controls; n = 6 (6%) of the n = 96 controls had echocardiographic evidence of mitral valve prolapse
Mitral valve prolapse identified in x3 in those with IE (19%) than those without (6%), this increased to x14 for those with mitral valve prolapse and a previously recognised systolic murmur

Risk of bacterial endocarditis
Whole group:
All MVP; cases n = 9, controls n = 6, OR 3.5 (1.1 to 10.5, 95%CI)
MVP with systolic murmur; cases n = 7, controls n = 1, OR 14.5 (1.7 to 125, 95%CI)
MVP without systolic murmur; cases n = 2, controls n = 5, OR 1.0 (0.2 to 5.5, 95%CI)

Excluding those with rheumatic heart disease:
All MVP; cases n = 9/48, controls n = 6/96, OR 5.7 (1.8 to 18.4, 95%CI)
MVP with systolic murmur; cases n = 7/41, controls n = 1/91, OR 27.4 (3.1 to 239, 95%CI)
MVP without systolic murmur; cases n = 2/41, controls n = 5/95, OR 1.6 (0.3 to 8.7, 95%CI)

(author conclusion: only those with mitral valve prolapse and systolic murmurs are at increased risk of IE and may need antibiotic prophylaxis)

[17] The authors note that the frequency of mitral valve prolapse in the general population varies according to the diagnostic criteria used

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
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.	RCT [18]	n = 221 Spain	Inclusion: patients who for behavioural reasons underwent dental extractions under GA, 57% male, 43% female, mean age 24.9±5.7yrs (range 18 to 57yrs) 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 There was NS difference in age, sex, oral health grade and number of dental extractions between the four groups	n = 56 2 g amoxicillin n = 54 600 mg clindamycin n = 58 400 mg moxifloxacin	n = 53 control Blood samples: baseline, 30 secs, 15 min and 1 hr after dental extraction	January 2003 to December 2004	Bacteraemia resistance 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	Xunta de Galicia of Spain

[18] randomisation not specified; power calculated

Effect size:

Oral health scale grades 0 and 1 (n = 46, 21%), grade 2 (n = 84, 38%), grade 3 (n = 91, 41%)
Median number of teeth extracted per patient n = 4

Bacteraemia
At baseline; control group (9.4%), amoxicillin (5%), clindamycin (12.5%), moxifloxacin (7.5%)

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)

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)

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)

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%)

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%)

Of the *Streptococcus* spp 1.5% were highly resistant to penicillin, 0.8% to ampicillin, 0.8% to amoxicillin, 45.9% to erythromycin, 22.6% to clindamycin

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
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. 4**2**: e102–07. Ref ID: 10629	Epidemiological study France	n = 2805 interviewed adults, n = 104 native valve PCC n = 24 prosthetic valve PCC	Included: 25-84 yrs from the French population	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)[19] (numerator)[20] and the annual number of at-risk dental procedures performed in adults with known PCCs (denominator)[21]		1-year study 1999	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	Programme hospitalier de recherché clinique, the federation francaise de cardiologie, Aventis and SmithKilne Beecham Labs

[19] PCC were defined according to the French recommendations for IE prophylaxis
[20] Data used was taken from a 1-yr French epidemiological study on IE in 1999
[21] Sample 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

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
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[22], 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

[22] 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

(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)

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Dyson C, Barnes RA, Harrison GA, et al. (1999) Infective endocarditis: an epidemiological review of 128 episodes.[see comment]. Journal of Infection 38: 87–93	Epidemiological review	n = 125 patients n = 128 episodes Wales	those within a hospital in Wales, including those transferred from other units for specialised medical/surgical treatment, episodes included where clinical and investigational criteria were met; mean age 53.1 yrs, n = 87 (69.6%) male and n = 38 (30.4%) female			9 years March 1987 to March 1996	Cardiac risk factors, outcome	Not stated

Effect size:

Frequencies of predisposing cardiac risk factors NVE episodes

n = 128 episodes (n = 125 patients) of IE, predisposing cardiac risk factors for NVE episodes (no identifiable risk factor n = 29(37.7%)

Congenital heart lesion	**21(26.9%)**	Mitral valve prolapse	9(11.5%)
Bicuspid 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%)		

Outcome
Mortality rate 17.2% (n = 21)
Mortality rate for PVE, 24.5 % (n = 12) and for NVE, 12.3% (n = 9)
For early PVE the mortality rate was 30.8%, for late PVE the mortality rate was 22.2%

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
El Baba M, Tolia V, Lin CH, Dajani A. Absence of bacteremia after gastrointestinal procedures in children. *Gastrointestinal Endoscopy* 1996;**44**:378-81. Ref ID: 627	Case series	n = 95 (n = 108 procedures) Children's Hospital of Michigan, Detroit	Inclusion: requiring gastrointestinal endoscopy, n = 43 females, n = 52 males Exclusion: receiving or had received antibiotics in the preceding week, none of the patients had fever, chills or clinical evidence of any intercurrent illness prior to endoscopic procedure Those with a specific need for prophylactic antibiotics prior to the procedures were excluded	n = 68 oesoagogastroduodenoscopies n = 29 colonoscopies n = 11 flexible sigmoidoscopies	Blood samples: just before endoscopy and within 5mins of withdrawal of the endoscope[23]	October 1992 to October 1993	Blood cultures Microbiology: 2ml per sample, injected into a sterile Dupont isolator 1.5 microbial tube, specimens were processed within 1hr. 0.3ml was inoculated on chocolate agar (4dyas in 5 to 10% Co2 at 37˚C) and 0.3ml on Columbian anaerobic blood agar (6days at 37˚C). All isolated were	Not stated

[23] An additional blood sample was obtained 5mins after ET intubation but before endoscopy in those who had a GA to assess if the endotracheal intubation may have resulted in bacteraemia

							identified using standard microbiologic techniques	

Effect size:

Blood cultures
Of the n = 236 samples obtained, n = 10 from n = 9 patients were positive (n = 4 pre-endoscopy, n = 2 post ET intubation which were negative after endoscopy)
A total of n = 4 post endoscopy blood cultures were positive, the organisms isolated were Micrococcus, S. epidermidis, Bacillus sp., diptheroids; all organisms were normal skin flora or environmental contaminants, none were indigenous oropharyngeal or GI flora (Micrococcus and Bacillus species were considered to be contaminants

All those with positive cultures remained afebrile and without any evidence of sepsis during the 72hrs following procedure

The risk of bacteraemia was not affected by the procedure, underlying GI pathology, method of bowel prep, duration of procedure, performance of endoscopic biopsies or ET intubation

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Gentry LO, Khoshdel A (1989) New approaches to the diagnosis and treatment of infective endocarditis. Review of 100 consecutive cases 1813. Texas Heart Institute Journal 16: 250-7	Retrospective review, case series	Between 1983 to 1989 n = 94 confirmed cases of IE	Medical records of the 100 most recent patients whose discharge diagnosis included IE. Diagnosis of endocarditis was made on the basis of positive blood cultures or other convincing evidence of systemic infection, as well as the lack of an obvious focus for the infection and the presence of significant underlying risk factors for endocarditis.				Special attention was paid to predisposing underlying conditions	Not stated
Effect size: **Valves** n = 54 (57%) had NVE, n = 40 (43%) had PVE, as the percentage of the population with prosthetic heart valves is much smaller than 43%, prosthetic valves appear to increase the risk of endocarditis								

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Gersony WM, Hayes CJ, Driscoll	Cohort	n = 2401 entered into	Those with aortic stenosis (AS), pulmonary stenosis (PS) or ventricular septum defect (VSD), most patients with	n = 462 aortic stenosis	n = 1,347 VSD with or without aortic	NHS-2 from 1983-1989	Prevalence and incidence,	Not stated

DJ, Keane JF, Kidd L, O'Fallon W *et al*. Bacterial endocarditis in patients with aortic stenosis, pulmonary stenosis, or ventricular septal defect. *Circulation* 1993;**87**:I-121-I-126. Ref ID: 539		NHS-1[24],this study reports on the extended follow-up, NHS-2[25]	severe defects were managed surgically and most with mild defects were managed medically NHS-1 the prevalence of a history of BE was determined, new occurrences were noted and confirmed. NHS-2 all participants were asked about occurrences of BE, all questionnaire items were reviewed by the examining physician and medical and surgical records were reviewed (full details O'Fallon et al, 1993)	n = 592 pulmonary stenosis	regurgitation	Overall; 40,855 person-years (average 17.4±8.3 person-years of follow-up per patient) Aortic stenosis; 8,115 person-years (17.9±8.0 person-years) Pulmonary stenosis; 10,688 person-years (18.1±7.8 person-years) VSD; 22,077 person-years (16.4±8.6 person-years)	outcome	
Effect size: (all CI 95%)								

[24] The First Natural History Study of Congenital Heart Defects between 1958-1965
[25] The Second Natural History Study between 1983-1989

Prevalence – on admission to NHS-1
Overall; n = 25/2401 had or either had or had experienced BE, prevalence of a history of BE was 104 per 10,000 patients (CI; 67.4 to 153.6)
AS; n = 1/462 had or either had or had experienced BE, prevalence of a history of BE was 21.6 per 10,000 patients (CI; 0.5 to 120.6)
PS; n = 1/592 had or either had or had experienced BE, prevalence of a history of BE was 16.9 per 10,000 patients (CI; 0.4 to 94.1)
VSD[26]; n = 23/1347 had or either had or had experienced BE, prevalence of a history of BE was 170.6 per 10,000 patients (CI; 108.2 to 256.0)

Incidence
Follow-up; n = 55 had BE, incidence rate of 13.5 per 10,000 person-years (CI; 10.1 to 17.5)

Aortic stenosis:
n = 22 had a diagnosis of BE, incidence rate of 27.1 per 10,000 person-years (CI; 17.0 to 41.0)
Medical management n = 7 had BE for an incidence rate of 15.7 per 10,000 person-years (CI; 6.3 to 32.4)
Surgical management n = 15 had BE for an incidence rate of 40.9 per 10,000 person-years (CI; 22.9 to 67.4)
Ratio (post-op to nonoperated) is 2.6 (CI; 1.1 to 6.6), this is significantly >1 (p=0.0150), BE is more than twice as likely to be experienced post-op than when medically managed for those with aortic stenosis

The ratio of severity of AS (≥50mmHg vs. <50mmHg, peak systolic gradient) is 12.0 (CI; 4.0 to 43.8), p<0.0001, those with more severe AS are more likely to experience an episode of BE

n = 8 cases of BE occurred before a diagnosis of aortic regurgitation and n = 14 after; a non-aortic regurgitation rate of 19.8 per 10,000 person-years and a post-aortic regurgitation of 34.3, the difference in these rates was NS

Pulmonary stenosis:
n = 1 experienced BE, an incidence rate of 0.9 per 10,000 (CI; 0.02 to 5.2), further analysis not possible due to low incidence.

Ventricular septum defect:
n = 32 experienced BE, for an overall incidence rate of 14.5 per 10,000 person-years of follow-up (CI; 9.9 to 20.5)
n = 564/1347 had surgical attempts to close the VSD, n = 6 developed BE (7.3 per 10,000 person-years CI; 2.7 to 15.9)
n = 26 of BE in the nonoperated patients (18.7 per 10,000 person-years CI; 12.2 to 27.5)
The ratio (nonoperated to post-op) is 2.6 (CI; 1.1to 6.7), significantly >1 (p=0.0122), BE is more than twice as likely to occur before attempts to surgically close the VSD

Using 5 categories of severity rates of VSD the development of BE were NS different

[26] VSD and VSD plus aortic regurgitation

n = 25 cases of BE with non-aortic regurgitation, incidence 12.5 per 10,000 person-years, n = 7 in post-aortic regurgitation, incidence 34.8, the difference in rates was significant (p=0.0002), suggesting that after AR, VSD patients are more likely to experience BE than before AR

Outcomes
AS complications n = 7 aortic regurgitation ruptured aorta sinus; n = 5 emboli; n = 1 shock, VF; n = 10 none
PS complications n = 1 none
VSD complications n = 7 aortic regurgitation ruptured aorta sinus; n = 6 emboli; n = 1 meningitis; n = 1 shock, VF; n = 15 none
n = 10 deaths, not analysed by underlying complication

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Griffin MR, Wilson WR, Edwards WD, Ofallon WM, Kurland LT. Infective endocarditis - Olmsted County, Minnesota, 1950 through 1981. *Journal of the American Medical Association* 1985;**254**:1199-202. Ref ID: 10723	Population based study	n = 78 patients n = 78 episodes USA	Records of all County residents with a diagnostic code of endocarditis, cases defined using Von Reyn criteria; mean age 58yrs (range <1yr to 90yrs), there was no change in the age distribution over the 32yrs of the study, n = 45 male, n = 33 female			32years 1950 to 1981	Incidence, underlying cardiac disease	National Institutes of Health

Effect size:

Incidence rate
Mean annual incidence rate 3.8 per 100,000 person-years (3.2 per 100,000person-years for definite and probable cases only)
Mean annual incidence rate 2.8 (women) and 5.2 (men) per 100,000 person-years

Underlying cardiac disease
n = 78 residents with IE identified

Rheumatic heart disease	20(26%)
Mitral valve prolapse	13(17%)
Congenital heart disease	11(14%)
Degenerative heart disease*	7(9%)
Aortic arch prosthesis	1(1%)
Prior systolic murmur	15(19%)

*calcific aortic stenosis, calcified mitral valve, papillary muscle dysfunction

Outcome
n = 13(17%) were diagnosed at autopsy, of the remaining n = 65(29%) died within 2mths of diagnosis

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Habib G, Tribouilloy C, Thuny F et al. (2005) Prosthetic valve endocarditis: Who needs surgery? A multicentre study of 104 cases. Heart 91: 954-9	Multicentre study	n = 104 France	Inclusion: consecutive from two centres who fulfilled the Duke criteria for PVE, n = 71 male, mean age 60 (SD 16), all patients underwent blood culture and systematic transthoracic and transoesophageal studies	All patients were scheduled for a 4 to 6week antibiotic regimen		Study from January 1991 to March 2003	Outcomes, mortality, influence of surgery	Not stated
Effect size: **Outcomes** Embolic events n = 35 (33%) patients, rates similar between early and late PVE[27] Early surgery was more often needed in the early group than in the late group (80% vs. 41%) n = 22/104 (21%) died in hospital (causes of death; n = 10 multiorgan failure; n = 3 uncontrolled infection; n = 6 congestive heart failure or cardiogenic shock, n = 3 cerebral haemorrhage n = 5 recurrent PVE n = 82 in-hospital survivors, n = 21 (26%) died during a mean 32mths follow-up Cumulative mortality was higher in early than in late PVE (65% vs. 36%, p=0.01)								

[27] Early PVE; PVE occurring during the first 12mths after surgery
Late PVE; PVE occurring after 12mths

After a mean 32mths follow-up, only n = 61 (58%) patients were still alive

Factors affecting in-hospital and long term mortality
Univariate analysis identified factors associated with in-hospital mortality were severe co-morbidity (p=0.05), renal failure (p=0.05), moderate-to-severe regurgitation (p=0.006), staphylococcal infection (p=0.001), severe heart failure (p=0.001), and occurrence of any complication (p=0.05)

Multivariate analysis identified severe heart failure (OR 5.5, 1.9 to 16.1, 95% CI) and S aureus infection (OR 6.1, 1.9 to 19.2, 95% CI) were the only predictors of in-hospital death

Influence of surgery
n = 51 (49%) underwent surgery during the active phase of endocarditis
In-hospital mortality was NS different between surgical and non-surgical patients
In those with staphylococcal PVE in-hospital mortality was lower in those treated surgically than non-surgically (27% vs. 73%, p=0.03)
Long-term mortality was lower in staphylococcal PVE treated surgically than in the medical group (p=0.03)

Among n = 69 with complicated PVE, in-hospital mortality was lower in n = 44 (n = 8 deaths, 18%) surgical patients compared with n = 25 (n = 12 deaths, 48%) non-surgical, p=0.05
In-hospital mortality was low in the remaining n = 35 with non-complicated PVE for both surgical and non-surgical patients

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
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	RCT [28]	n = 60 Sweden	Inclusion: 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 None of the patients were receiving any medication except analgesics	n = 20 penicillin V (2g) n = 20 amoxicillin (3g) Orally 1hr before dental extraction Blood samples: before, during and 10mins after dental extraction	n = 20 matched placebo		Bacteraemia Lysis filtration under anaerobic conditions	Not stated

[28] Randomisation not specified

Effect size:

Bacteraemia
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

10mins after dental extraction, the number of microorganisms had decreased in similar ways in all three patient groups from that found during extraction ($p<0.01$)

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
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 15: 646–49	RCT [29] Double-blind	n = 39 Sweden	Inclusion: those undergoing dental extraction	n = 19 1g cefaclor, 1 hr prior to dental extraction Blood samples before, during and 10 min after dental extraction	n = 20 placebo, 1 hr prior to dental extraction Blood samples before, during and 10 min after dental extraction		Processed by lysis filtration under anaerobic conditions, aerobic and anaerobic microorganisms were identified using standard methods	Swedish Medical Research Council

[29] Randomisation not specified

Effect size:

Bacteraemia
None of the patients were bacteraemic prior to dental extraction

Post-extraction bacteraemia had a dominance of gram-positive strains (>90%) in both groups

During dental extraction positive blood cultures; 79% cefaclor group; 85% placebo group
Viridans streptococci during extraction; 79% cefaclor; 50% placebo group

10mins after extraction positive blood cultures; 53% cefaclor group; 47% placebo group
Viridans streptococci 10mins after extraction; 26% cefaclor; 30% placebo group
Strains of streptococcus intermedius most frequently, followed by streptococcus sanguis and streptococcus mitis in both patient groups

Anaerobic bacteraemia during extraction; 74% cefaclor; 47% placebo group
Anaerobic bacteraemia during extraction; 75% cefaclor; 35% placebo group
Actinomyces spp. Most commonly identified (Veilloneela and Prevotella isolated from single patients)

Susceptibility
More than 99% of the viridans streptococci were classified as susceptible to cefaclor (≤8mg/l), penicillin V (≤0.125mg/l), clindamycin (≤0.5mg/l) and erythromycin (≤0.5mg/l); ampicillin (0.125 mg/l) inhibited 90% of the viridans strains

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Hall G, Nord CE, Heimdahl A (1996) Elimination of bacteraemia after dental	RCT Double-blind	n = 38 Sweden	Inclusion: referred to the department of oral surgery for dental extraction because of dental caries or chronic periradicular ostetis, n = 24 males, mean age 48.5 yrs (range 25 to 74 yrs), except for analgesics and oral contraceptives, none of the patients was on any medication	n = 19 x2 0.5g erythromycin stearate tablets 1.5hr before dental extraction Blood samples:	n = 19 x 2 0.3g clindamycin capsules 1.5 hr before dental extraction		Bacteraemia Vacuum filtration and the filters placed on brain heart infusion agar plates for anaerobic	Swedish Medical Research Council and the Swedish National Associati

extraction: comparison of erythromycin and clindamycin for prophylaxis of infective endocarditis. Journal of Antimicrobial Chemotherapy 37: 783–95			Exclusion: those with a history of allergic reaction or systemic symptoms following clindamycin or erythromycin therapy, those with cardiovascular, renal, hepatic or GI diseases	before, during and 10min after dental extraction			incubation at 37C for 10days. Aerobic and anaerobic microorganisms were identified using methods described by Lennette et al (1985)	on against heart and Chest Diseases

Effect size:
Bacteraemia
All pre-extraction blood samples showed no growth
Post-extraction bacteraemia; erythromycin (79%), clindamycin (84%)
10mins post-extraction bacteraemia; erythromycin (58%), clindamycin (53%)
Anaerobic bacteria dominated the findings of post-extraction bacteraemia, aerobic bacteria (other than viridans streptococci) were recovered infrequently

Overall incidence of viridans streptococcal bacteraemia; 79% erythromycin, 74% clindamycin
Anaerobic bacteraemia (Actinomyces, Eubacterium, Lactobacillus most commonly) during extraction was; 58% erythromycin, 74% clindamycin

n = 38, all samples obtained before dental extraction showed no growth (despite evidence of chronic dentoalveolar pathology in most cases)
Anaerobic bacteria dominated postextraction bacteraemia, gram-positive strains outnumbered gram-negative, aerobic bacteria other than viridans streptococci were infrequent

Incidence of bacteraemia during dental extraction was 79% in the erythromycin group and 84% in the clindamycin group
At 10mins; 58% erythromycin and 53% clindamycin

There was NS difference in the incidence or magnitude of total bacteraemia, bacteraemia with viridans streptococci or bacteraemia with anaerobic bacteria between the two groups at any sampling time

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Harris A, Chan AC, Torres-Viera C et al. (1999) Meta-analysis of antibiotic prophylaxis in endoscopic retrograde cholangiopancreatography (ERCP). Endoscopy 31: 718-24	Meta-analysis	n = 7 RCT, placebo controlled trials (2 double blinded)	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[30] Inclusion: RCTs, placebo controlled studies of the efficacy of antibiotic prophylaxis in ERCP using oral or intravenous antibiotics Exclusion: had received other antibiotics in addition to prophylaxis, were diagnosed with sepsis or cholangitis prior to ERCP	Antibiotic prophylaxis for ERCP			Required end points included bacteraemia, sepsis or cholangitis	
Effect size: **Bacteraemia** 4 studies reported bacteraemia, the RR in those receiving antibiotics compared with those receiving the placebo was NS [31] **Sepsis/cholangitis** The RR for sepsis/cholangitis for prophylaxis compared with no prophylaxis was NS								

[30] Titles or abstracts identified by the search were reviewed independently by two investigators regarding suitability for inclusion in the meta-analysis, if there was disagreement an assessment was made by a third investigator

[31] There was little heterogeneity between the results

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
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. Ref ID: 1242	Case-control	n = 224 Australia	Inclusion: cases ≥15yrs admitted to hospital, all who had echocardiography, met the criteria set for diagnosis for endocarditis Inclusion: controls 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	n = 56 cases[32] (n = 66 met the criteria, n = 10 excluded due to antecedent lesions)	n = 168 controls (n = 4620 met the criteria) matched for age, sex and date of echocardiography	Between Jan 1976 to Jan 1984	Prevalence of mitral valve prolapse, systolic murmur, probability of developing endocarditis	Not stated
Effect size: **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[33] OR for the association of MVP and BE was 5.3 (2.0 to 14.4, 95% CI)								

[32] 7 of the cases were on chronic haemodialysis and 6 were parenteral drug users
[33] In no set was MVP present in more than one of the 3 controls

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)

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[34], 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

(authors conclude that antibiotic prophylaxis is not warranted fro all patients with MVP, the risk of developing BE is slight; findings suggest that antibiotics prophylaxis is required for those patients with MVP who have systolic murmur)

[34] Taken from the New South Wales State hospital morbidity and mortality statistics for 1980

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
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	Case series	n = 72 (n = 126 endoscopies)	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 The emergency endoscopy and sclerotherapy groups were comparable in age and sex distribution	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) Blood samples: Before endoscopy, at 5min and 30min after the procedure	July 1985 to April 1987	Significant bacteraemia group[35] Nonsignificant bacteraemia group[36] 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	Not stated

[35] Any positive blood culture in which the isolated microorganism is one of the following: coliform bacteria (including Escherichi coli and Proteus) Bacteroides, Hemophilus, group A Streptococcus, and Streptococcus pneumoniae, or more than one blood culture, drawn at different times, positive for the same organism. Patients were not necessarily symptomatic

Effect size:

Blood cultures
Positive blood cultures were found in n = 30/378 cultures (7.9%), of these n = 11 were considered to be potentially significant

Emergency endoscopy group blood cultures
n = 5 positive[37], the incidence of endoscopy-related bacteraemia was considered to be 11% (n = 4) with a predominance of skin flora

Sclerotherapy groups
Elective EVS sclerotherapy;
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;
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
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%)

Differences in bacteraemia between groups
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

Analysis of significant bacteraemia
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

[36] A single positive blood culture in which the isolated microorganism is one of the following: Staphylococcus coag negative (including S. epidermidis anf S. warneri), Corynebacterium, Propionibacterium and Bacillus species, unless a patient has a prosthetic valve, graft or shunt, or a single blood culture for Clostridia (including C. perfringens and C. sordelli) without clinical correlation of active infection
[37] none of the blood culture results drawn before endoscopy were positive

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Horstkotte D, Rosin H, Friedrichs W, Loogen F (1987) Contribution for choosing the optimal prophylaxis of bacterial endocarditis. Eur Heart J. 8: 379–81.	Comparison of 2 patient groups	n = 533 Germany	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	Group A n = 229 in whom n = 287 diagnostic and therapeutic procedures were performed using a prophylactic antibiotic regime considered correctly administered[38]	Group B n = 304 (out of n = 1898 patients questioned) in whom n = 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		Cases of PVE	Not stated

[38] The prevention used was similar to that recommended earlier by the AHA

Effect size:

Prosthetic valve endocarditis[39]
In group A no PVE was observed, in group B n = 6 cases of PVE which corresponds to an incidence of 1.5 cases per 100 procedures. The highest incidence (n = 2/39 procedures, 5.1%) 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

n = 2 cases of PVE in n = 117 dental procedures, both of which occurred after tooth extraction, a case of enterococcal PVE after spontaneous passage of a renal calculus without having undergone any invasive intervention

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Hricak V, Kovacik J, Marx P et al. (1998) Etiology and risk factors of 180 cases of native Valve Endocarditis : Report from a 5-year national prospective survey in Slovak	National survey	n = 180 Slovakia	Inclusion: cases from 12 clinics/departments, Duke Endocarditis Service Criteria were used as inclusion criteria and to define the probability			Study from 1st January 1992 to 31st December 1996	Positive cultures, infected valves Blood culturing performed in all centres with a BACTEC blood culturing system	Not stated

[39] PVE was considered related to the diagnostic or therapeutic procedure only if symptoms of endocarditis occurred within 2weeks

Republic 3598. Diagnostic Microbiology & Infectious Disease 31: 431-5								
Effect size: n = 169 definitive and n = 11 probable/possible cases of IE n = 48 (26.7%) were culture negative **Positive cultures**; Staphylococci (n = 60, 33.3%), viridans Streptococci (n = 22, 12.2%), Enterococcus faecalis (n = 21, 11.7%), Haemophilus spp. (n = 11, 6.1%) **Infected valves**; aortic valve (46.7%), mitral valve (47.2%) Univariate analysis of the differences between deaths and surviving patients showed NS difference between the two groups; only age >60yrs (40% vs. 21.4%), p<0.05; staphylococcal aetiology (56% vs. 27.1%), p<0.04; antibiotic therapy <21days without surgery (65% vs. 3.6%), p<0.001 were significantly more often associated with deaths Therapy with antibiotics only (without surgery) was observed more in those who died than those who survived (92.5% vs. 59.3%), p<0.05								

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Ishiwada N, Niwa K, Tateno S, et al. (2005) Causative organism	Case series	n = 188 (n = 113 paediatric, n = 75	Inclusion: members of the Japanese Society of Paediatrics Cardiology and Cardiac Surgery in 66 institutions registered paediatric and adult patients with CHD and IE; n = 107 male, mean age 15.1±14.3yrs (range 14 days–63 yrs)			Study over a 5yr period 1997 to 2001	Causative organism Source of infection Complications	Japanese Society of Pediatric Cardiology and Cardiac

influences clinical profile and outcome of infective endocarditis in pediatric patients and adults with congenital heart disease. Circulation 69: 1266–70		adult) Japan						Surgery Joint Working Groups for Guidelines for Prophylaxis, Diagnosis and Management of Infective Endocarditis in Patients with Congenital Heart Disease

Effect size:

Streptococcus (n = 94, 50%) and Staphylococcus species (n = 68, 36.2%) were the commonest pathogens
n = 58/94 streptococcus mitis; n = 57/68 staphylococcus aureus

The likely source of infection was identified in n = 59 (31.4%);

- Streptococcal IE; dental procedure (n = 17/28, 60.7%), pneumonia (n = 4/28, 14.3%)
- Staphylococcal IE; cardiac surgery (n = 7/21, 33.3%), dental procedure (n = 3/21, 14.3%), atopic dermatitis (n = 2/21, 9.5%)

Complications

Total complications n = 126/188, 67.0%, NS difference in the incidence of complications among the different causative species;

- vegetation n = 109, 58.0%
- valvular regurgitation n = 58, 30.9%
- cardiac failure n = 38, 20.2%
- arrythmias n = 10, 5.3%
- CNS embolism n = 13, 6.9%
- Other embolism n = 17, 9.0%
- Abscess n = 9, 4.8%
- Aneurysm n = 3, 1.6%

Mortality

n = 20 (10.6%) died of IE, mean age of 10.5 yrs (2 mths to 25 yrs), mortality was highest in those <1yr (n = 5/16, 31.3%)
n = 14/20 (70%) had undergone cardiac surgery, n = 11 of whom had had prophylactic antibiotics before the onset of IE
S. aureus was isolated from n = 11/20, n = 7 with MRSA
Overall mortality was higher for S. aureus (n = 11.57, 19.3%) than for *Streptococcus* spp (n = 5/94, 5.3%), $p<0.05$
Candida mortality (n = 2/5, 40.0%), Pseudomonas mortality (n = 2/4, 50.0%)

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Jokinen MA. Prevention of postextraction bacteremia by local prophylaxis. *International Journal of Oral Surgery* 1978;**7**:450-2.	Controlled study [40]	n = 152 Finland	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 There were NS differences among the four groups in regard to sex or age	n = 38 mouth rinsing with 1% iodine solution n = 38 operative field isolation with cotton rolls and saliva ejector n = 38 operative field isolation and disinfection with 10% iodine solution	n = 38 operative field isolation and disinfection with 0.5% chlorhexidine			Not stated
Effect size: **Bacteraemia** Positive cultures; iodine mouth rinses n = 21/38, 55%; operative field in isolation n = 13/38, 34%; operative field isolation and disinfection with iodine n = 12/28, 32%; operative field isolation and disinfection with chlorhexidine n = 5/38, 13%, p=0.05 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								

[40] The bacteriologic determinations were made in the laboratory without the investigator having any knowledge of the nature of the individual samples

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Kullman E, Borch K, Lindstrom E, et al. (1992) Bacteremia following diagnostic and therapeutic ercp. Gastrointestinal Endoscopy 38: 444–49. Ref ID: 10028	Consecutive case series	n = 180 (n = 194 examinations) University Hospital, Sweden	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	Diagnostic ERCP n = 115 participants (n = 126 procedures) Therapeutic ERCP n = 65 participants (n = 68 procedures)	Blood samples: taken at 5min after cannulation and at 5 and 15 min after the end of examination	November 1988 to December 1990	Bacteraemia Microbiology: A 2-phase blood culture system, one aerobic and one anaerobic flask was inoculated with 4ml of blood and each incubated at 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	Not stated

Effect size:

Bacteraemia
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

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Kullman E, Jonsson KA, Lindstrom E, et al. (1992) Bacteremia associated with extracorporeal shockwave lithotripsy of gallbladder	Consecutive case series	n = 76 (n = 107 treatments) University hospital, Sweden	Inclusion: all patients undergoing extra corporeal shock wave lithotripsy (ESWL), median age 52yrs (range 21 to 87yrs), n = 55 female, n = 21 male, mean BMI 25.9±0.4kg/m2 Exclusion: those with signs of localised or general infection, antibiotic treatment within the preceding 7 days, history or signs of endocarditis or valvular heart disease, treatment with corticosteroids or other immunosuppressive drugs		Blood samples: prior to ESWL, immediately after stone fragmentation during treatment, at 5mins, 20 mins and 18 hrs after the end of treatment	Mean follow-up time was 29±1 (range 6 to 48 mths)	Blood cultures Microbiology: A 2-phase blood culture system, one aerobic and one anaerobic flask was inoculated with 4ml of blood and each incubated at 37˚C, the flasks	Not stated

stones. Hepato-Gastroenterology 42: 816–20. Ref ID: 669							were inspected for bacterial growth twice daily for 2 days and then once daily for an additional 8 days. 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	
Effect size: **Blood cultures** No patient had positive blood cultures at more than one treatment (repeat treatment was performed within 10days in n = 10 patients) Positive blood cultures: - during ESWL n = 16 (n = 15 S epidermidis; n = 1 S aureus) - after 5min n = 12 (n = 11 S epidermis; n = 1 Propionibacterium acnes) - after 20min n = 6 (n = 11 S epidermis; n = 1 Propionibacterium acnes; n = 1 Enterococcus) - after 18hrs n = 3 (all S epidermis) n = 24/107 (22%) of the EWSL sessions were associated with bacteraemia during and/or with 18hrs of the procedure, n = 3 of the 24 had polymicrobial bacteraemia with 4 detected groups of organisms. Staphylococcus epidermidis was the most common and was identified in n = 23 (96%) of the treatments associated with								

bacteraemia There was no difference between the patients with and without bacteraemia regarding age and sex distribution, or BMI, or regarding the duration of treatment, the number of shock waves, the energy index, the mean stone volume, or the occurrence of calcified gallstones During follow-up no patient developed sepsis or clinically overt endocarditis

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
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.	Prospective epidemiological study Case-control	n = 171 pairs Public and private medical facilities in 3 regions in France	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.	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	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	1st November 1990 to 31st October 1991	The relative risk of IE for each procedure, causative organisms, antibiotic prophylaxis	Several grants from medical societies in France and from the following companies: Baxter, Dideco-Shiley, Eli-Lily, Medtronic, St Jude Medical Companies

[41] 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

Ref ID: 1013			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)	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 [41]	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			

Effect size:

Procedures
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[42](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)

[42] 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

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:
Variables included; extraction, scaling, root canal treatment, urological, GI and surgical procedures, skin wound, infectious episode. Only infectious episodes (OR 3.9; 2.1 to 7.3, p<0.05, 95%CI) and skin wounds (OR 3.9; 1.6 to 9.6, p<0.05, 95%CI) significantly and independently contributed to the explanation of the risk of IE. The procedures were NS

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

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)

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Li W,.Somerville J. Infective endocarditis in the grown-up congenital heart (GUCH) population. *European Heart Journal* 1998;**19**:166-73. Ref ID: 3609	Retrospective and prospective cohort	n = 185 (n = 214 episodes of IE) London	Up to 1993 data were collected retrospectively from patient notes, from 1993 to 1996 data were collected prospectively from patients. Diagnosis by Duke criteria n = 111/185 male, n = 7 previous IE at age 6-11yrs Divided into 2 groups according to whether or not the definitive repair surgery had been performed on the main lesion The number of males was more than females in Group II compared to Group I ($p<0.05$)	Group I n = 128 (n = 155 episodes) unoperated or palliated (n = 25 palliative procedures, including systemic to pulmonary shunts or pulmonary artery banding)	Group II n = 57 (n = 59 episodes) after definitive and/or valve repair/replacement (including aortic, pulmonary, mitral and/or tricuspid valvotomy, repair or valve repair)	The grown-up congenital disease database (GUCH), 13yrs of data Between 1983 to 1996	Cardiac lesions, predisposing events, organisms, echocardiography/site of infection, delay in diagnosis, recurrence, specific problems, surgery during infective endocarditis, outcome	Not stated

Effect size:

Cardiac lesions
Left ventricular outflow tract lesions were the most frequent lesions, n = 42 patients (n = 45episodes), this significant incidence showed a similar incidence was found in those with and without previous surgery

The differences in the rates of IE for those with a ventricular septal defect are noted to raise the question about whether closing a small ventricular septal defect would improve prognosis

Lesions	Group I	Group II

	(episodes)	(episodes)
Left ventricular outflow tract	22 (24)	20 (21)*
VSD	31 (37)	6 (6)*
Fallot (shunt 6, valvotomy 1)	12 (13)	11 (11)
Corrected transposition	11 (18)	2 (2)
Mitral valve prolapse	17 (18)	(1)
Pulmonary atresia (shunt 7)	10 (13)	2 (2)
One ventricle (shunt 7, PA banding 1)	12 (15)	-
Classic transposition (shunt 2)	5 (9)	3 (3)
Atrioventricular defect	2 (2)	8 (8)
Coarctation	1 (1)	3 (3)
Common trunk	2 (2)	1 (1)
Infundibular pulmonary stenosis	2 (2)	-
Duct	1 (1)	-
Ebstein	-	1 (1)

* p<0.05

Recurrence
Recurrence occurred in n = 21(11%) of patients, n = 19 of whom were in Group I

Outcome

	Group |	Group II
Cured	106 (83%)	50 (88%)
Recurrent	19 (15%)	2 (3%)*
Death	3 (2%)	5 (9%)*

*p<0.05

The cardiac lesions of the n = 8 patients who died during endocarditis were: VSD; aortic stenosis/aortic regurgitation; pulmonary atresia/VSD (n = 2); aortic stenosis/aortic regurgitation/mitral regurgitation (n = 2); aortic stenosis/Coarctation; transposition of the great arteries/VSD/pulmonary stenosis

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Lindert KA, Kabalin JN, Terris MK. Bacteremia and bacteriuria after transrectal ultrasound guided prostate biopsy. *Journal of Urology* 2000;**164**:76-80. Ref ID: 447	RCT	n = 50 USA	Inclusion: men scheduled for prostate ultrasound and ultrasound guided biopsy to rule out prostate cancer Exclusion: patients with a history of prosthetic devices and/or valvular heart disease that mandated prophylactic antibiotics before biopsy	n = 25 preoperative enema[43] Blood culture was taken 15mins after biopsies No antibiotics were given before the procedure, immediately after all cultures were obtained patients were given oral antibiotics, including 500mg ciprofloxacin and 500mg metronidazole	n = 25 no preoperative enema		Blood cultures Microbiology: 10ml samples, inoculated into aerobic and anaerobic bottles, blood cultures were assayed colorimetrically every 15mins for 5days, when any bacterial growth was detected, colonies were harvested to identify further the organisms involved	Not stated

[43] usual procedure is to administer an enema with antibiotics before the procedure and a repeat dose of antibiotics 12hrs after the procedure

Effect size:

Blood cultures
n = 8 (16%) of blood cultures taken after biopsy had bacterial growth[44] (including enteric flora in n = 5 (62.5%)
n = 4 patients had pre-biopsy bacteriuria and post-biopsy bacteraemia, however the same organism was present in pre-biopsy urine culture and post-biopsy blood culture in only n = 1 man, and none had the same organism in post-biopsy urine and blood cultures

There was no correlation of bacterial growth in blood cultures with patient age, history of dysuria and/or UTI, PSA, number of biopsies, obstructive voiding symptoms, prostate volume, cancer, or post-biopsy haematuria or voiding symptoms

n = 7 (28%) who did not receive an enema before biopsy had positive blood cultures, n = 1 (4%) of those given an enema had a positive blood culture, p=0.0003 for the difference

n = 1 patient with a fever of >37.5C after the procedure, the remaining men were asymptomatic

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Lo GH, Lai KH, Shen MT, Chang CF. A comparison of the incidence of transient bacteremia and infectious sequelae after	Case series	n = 105 Veterans General Hospital, Kaohsiung, China	Inclusion: patients admitted with acute variceal bleeding, all underwent EIS or EVL not more than 24hrs after onset of bleeding Exclusion: signs of infection before treatment, blood or body fluid culture before endoscopy showed bacterial growth, antibiotics within 2 wks before admission, required balloon tamponade or placement of a central venous catheter or Foley catheter which can cause bacteraemia	n = 50 (n = 58 admissions) endoscopic injection sclerotherapy (EIS)	n = 55 (n = 60 admissions) endoscopic variceal ligation (EVL) Blood samples: before the procedure, 5mins, 30mins and 24hrs after completion of the procedure	July 1990 to June 1991	Blood cultures Microbiology: 10ml samples, 5ml inoculated into a trypic soy broth (Bactec 6B, aerobic) and pre-reduced tryptic soy broth (Bactec 7C, anaerobic), they were incubated at 37˚C	Not stated

[44] organisms identified; Staphylococcus, Streptococcus, Diptheroids, Bacteeroides fraglis, E coli, Proprionibacterium, Gemella morbillum (all N=1 patient), Enterobacter, Gram-pos rods (all N=2 patients)

sclerotherapy and rubber band ligation of bleeding esophageal-varices. *Gastrointestinal Endoscopy* 1994;**40**:-679. Ref ID: 4770			Both groups were comparable with regard to age, sex, underlying cause of liver disease, incidence of hepatocellular carcinoma, episodes of active bleeding and Pugh's grade				for 7days and monitored using Bactec 460	
Effect size: **Blood cultures** n = 10/58 (17.2%) EIS had positive blood cultures; n = 2/60 (3.3%) EVL had positive blood cultures, p<0.03 Organisms grown; Staph aureus (n = 3), Staph epidermidis (n = 1), Strep pneumoniae (n = 1), E coli (n = 3), Klebsiella pneumoniae (n = 2), Proteus vulgaris (N-=1), Clostridium fallax (n = 1) In the EIS group n = 5/10 episodes of bacteraemia were associated with fever and leukocytosis, with positive blood cultures in all at 24hrs In the EVL group n = 1/2 episodes of bacteraemia were associated with fever and leukocytosis, blood culture positive at 24hrs Infectious complications Spontaneous bacterial peritonitis (n = 4), empyema (n = 2), pneumonia (n = 1) The frequency of infectious complications (included sustained bacteraemia) after EIS (18%) was significantly higher than that after EVL (1.8%), p<0.01								

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Lockhart PB. An analysis of bacteremias during dental extractions. A double-blind, placebo-controlled study of chlorhexidine. [Review] [67 refs]. *Archives of Internal Medicine* 1996;**156**:513-20	RCT, double blind [45]	n = 70 USA	Inclusion: >18yrs, no valvular heart disease, no infectious disease, no poorly controlled systemic disease, facial cellulitis, n = 37 male, mean age 37yrs (range 21 to 72yrs) Exclusion: use of steroids or chlorhexidine during the previous 2mths, use of antibiotics during the previous 2wks, any manipulation of the gingival within 1hr of the extraction There was an equal distribution between maxillary and mandibular teeth	n = 35 10ml 0.2% chlorhexidine hydrochloride (peridex) rinse for 30sec, rinsing was repeated 1min later Blood samples: 1min following initiation of surgery, 3min mark	n = 35 10ml placebo rinse for 30sec, rinsing was repeated 1min later		Bacteraemia Blood bottles processed and tested on a blood culture system (BACTEC 660) for 5days or until yields were positive	Not stated
Effect size: 70% were multirooted, the majority were molars (87%) n = 57 (81%) of these teeth had peridontitis with a mean alveolar bone loss of 33% n = 16 (22%) had tooth mobilities of 2 or 3 due to peridontitis and alvelolar bone loss								

[45] study patients were selected consecutively from a large pool of outpatients who underwent dental extractions; randomised by a random number generator in the hospital pharmacy, unmarked identical bottles; power analysis

The mean greatest pocket depth was 6.4mm and the mean total pocket depth was 29mm

Bacteraemia
n = 62 (89%) had positive blood cultures at either the 1 or 3min point; at 1min n = 43 (61%); at 3min n = 56 (80%)

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

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 (94%); chlorhexidine group n = 31 (84%)

Chlorhexidine had NS difference on either the incidence of polymicrobial cultures or the incidence of blood cultures and the three surgeons in the incidence of positive blood cultures

The mean time for surgery was 4.7mins (range 1 to 48mins). Patients who had surgery times of less than 3mins showed significantly increased number of positive blood cultures vs. those with surgery >3mins (p=0.04); those with times >6mins had significantly increased positive blood cultures vs. those with surgery times of <6mins (p=0.04)

The degree or severity of odontogenic disease did not correlate with the results of the blood cultures

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Lockhart PB, Brennan MT, Kent ML, Norton HJ, Weinrib DA. Impact of amoxicillin prophylaxis	RCT [46]	n = 100	Inclusion: children who required dental treatment in the operating room setting because of behaviour, young age and/or the scope of treatment needs Exclusion: poorly controlled systemic illness, medical conditions requiring antibiotic prophylaxis, allergy to penicillin-	n = 49 amoxicillin Blood samples: 2mins after the initiation of intubation; dental	n = 51 placebo Blood samples: 2mins after the initiation of intubation; dental		Incidence, nature and duration of bacteraemia Aerobic and anaerobic were processed according to	Health Services Foundation Inc, Carolinas HealthCare System,

[46] A computer-generated random number system was used by our pharmacy to assign identically appearing syringes containing placebo or study drug. All investigators were blinded as to the assigned treatment

on the incidence, nature, and duration of bacteraemia in children after intubation and dental procedures. *Circulation* 2004;**109**:2878-84.			type drugs, weight <12kg, exposure to systemic antibiotics within the past 2wks There was NS difference in the baseline characteristics for all subjects, stratified by treatment group	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	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		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	Charlotte, NC

Effect size:

Bacteraemia was defined as the occurrence of a positive culture at any of the 8 blood draws, only bacteria considered as likely or possibly from the oral cavity were included in the analysis of draws 2 to 8[47].

Incidence bacteraemia
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 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

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)

Logistic regression analysis suggests that the incidence of bacteraemia associated with extraction draws increase with the age of the subject (p=0.025) and number of teeth extracted (p=0.002) and that the use of amoxicillin significantly reduced the incidence of bacteraemia (p<0.0001)

No subject had a positive culture at D6,7 or 8 who did not have a positive extraction blood draw

Logistic regression analysis demonstrated that amoxicillin significantly reduced the incidence of bacteraemia (p=0.03)

Nature
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

Duration
Positive draw 4/5 n = 38 placebo, n = 11 amoxicillin; D6 15mins n = 12 placebo, n = 1 amoxicillin; D7 30mins n = 9 placebo, n = 0 amoxicillin; D8 45mins n = 5 placebo, n = 0 amoxicillin

[47] All bacteria were considered in the analysis of the intubation blood draw, number 1, because the skin and nasopharynx are more likely to harbour other bacteria

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
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	Case series	n = 50 New Zealand	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		Blood samples: before colonoscopic insertion, 5mins after insertion,		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	Not stated

Effect size:

Blood cultures
n = 204 blood cultures from n = 5 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)

Positive blood cultures were in n = 4/45 patients who had whole gut lavage and in n = 1/5 who had an enema

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Low DE, Shoenut JP, Kennedy JK, Sharma GP, Harding GK, Den Boer B *et al*. Prospective assessment of risk of bacteraemia with colonoscopy and polypectomy. *Digestive Diseases & Sciences*	Prospective case series	n = 270 (n = 280 procedures) St. Boniface General hospital, Winnipeg, Canada	Inclusion: patients undergoing colonoscopy with or without polypectomy, a high saline enema was given prior to the colonoscopy Exclusion: none of the patients had received antimicrobial agents during the 2 weeks prior to the procedure	n = 165 colonoscopy-only (n = 169 procedures) n = 105 colonoscopy with polypectomy (n = 111 procedures)	Blood samples: colonoscopy-only group, postinsertion blood cultures at 10min in n = 86 procedures and at 15min in n = 83 procedures; Polypectomy group post-polypectomy blood cultures at 5min in n = 42 procedures, at 5 and 10min in n = 26	August 1983 to March 1985	Blood cultures, patients were observed for 24hrs after the procedure for evidence of sepsis Microbiology: 5ml samples, inoculated into 45ml of supplemented peptone broth (Becton-Dickinson) and incubated at 37˚C for 7days,	Not stated

1987;**32**:1239-43. Ref ID: 930					procedures and at 30sec, 5 and 10min in n = 43 procedures		subcultures were made onto sheep blood agar at 24hr and 7days	
Effect size: **Blood cultures** n = 7 (2.5% preprocedural blood cultures were positive but were negative post-colonoscopy or post-polypectomy In the colonoscopy-only group n = 7/169 (4.1%) blood cultures were positive at either 10 or 15min (microorganisms isolated: Corynebacterium spp., Escherichia coli, Bacteroides spp., Bacillus spp., S. epidermidis, Clostridium spp.) In the polypectomy group n = 8/223 (3.6%) blood cultures were positive at either 30sec, 5 or 10min (microrganisms isolated: Veionella spp., Pseudomonas spp., Bacillus spp., Peptostreptococcus spp., Escherichia coli, Bacillus spp., S. epidermidis, Streptomyces spp.) There was NS difference between pre and postprocedural positive blood culture rates in the 2 groups No patient developed clinical evidence of sepsis during the 24hr following the procedure								

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
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	RCT	n = 142 (n = 81 undergoing GA, n = 61 receiving treatment in the O/P department London	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	n = 39 upper alginate impression n = 42 separator n = 25 fit/placement of band n = 36 archwire adjustment	Blood samples: baseline sample and 30 second sample taken after the orthodontic procedure		Prevalence and intensity of bacteraemia following 4 orthodontic procedures. 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	Not stated

Effect size:

Prevalence of bacteraemia
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
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

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Lucas V, Roberts GJ, Lucas V, Roberts GJ. Odontogenic bacteremia following tooth cleaning procedures in children 891. *Pediatric dentistry*	RCT Not blinded	n = 155 cleaning procedures Guy's Dental Hospital or Great Ormond Street Hospital	Inclusion: children referred for dental treatment under general anaesthetic (GA), n = 79 male, n = 76 female, aged 21mths to 16yrs 11mths Exclusion: antibiotics within the previous month, haemorrhagic disorders, known viral carriage Bacterial dental plaque and gingivitis were assessed	n = 52 toothbrushing group n = 53 professional cleaning group n = 50 scaling group Blood samples: baseline	n = 50 control group (data taken from a previous study)	1991 to 1994	Blood cultures, intensity of bacteraemia, bacteria isolated Microbiology: 3ml volume of blood was inoculated into each of the aerobic and anaerobic bottles, two commercial broth culture	Not stated

2000;**22**:96-100. Ref ID: 891		London		sample and 30 seconds after the procedure			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	
Effect size: **Positive blood cultures** There was NS difference in the number of positive blood samples in the groups studies There was NS difference in the intensity of bacteraemia (colony forming units per millilitre of blood) in any of the 3 cleaning groups **Intensity of bacteraemia** There was NS difference in the intensity of bacteraemia (cfu/ml blood) in any of the three cleaning groups **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)

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
MacFarlane TW, Ferguson MM, Mulgrew CJ. Post-extraction bacteremia : role of antiseptics and antibiotics. *Br Dent J* 1984;**156**:179-81.	Case control	n = 60 Glasgow	Inclusion: patients attending the department of oral surgery for tooth extraction, 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 The groups were matched for age and sex, and the ratios of premolar to molar teeth in each group were similar	n = 20, 10mls 1% chlorhexidine n = 20, 10mls 1% povidine-iodine 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	n = 20, 10mls normal saline Blood samples: before and 30sec after tooth extraction		Bacteraemia, antibiotic sensitivity The blood cultures were incubated at 37C and subcultured on 1,4 and 8days after initial collection	Not stated
Effect size: **Bacteraemia** Pre-extraction all cultures were negative Post-extraction; saline (n = 4) vs. chlorhexidine (n = 15) p<0.001, povidone-iodine (n = 12) p<0.01								

NS difference between chlorhexidine vs. povidone-iodine

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

Antibiotic sensitivity
Sensitive; penicillin (n = 43/46), ampicillin (n = 46/46), cephaloridine (n = 46/46), erythromycin (n = 45/46), spiromycin (n = 46/46), clindamycin (n = 45/46), vancomycin (n = 46/46), streptomycin (n = 27/46)

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Mansur AJ, Dal Bo CM, Fukushima JT, Issa VS, Grinberg M, Pomerantzeff PM. Relapses, recurrences, valve replacements, and mortality during the long-term follow-up after infective endocarditis. *American Heart*	Cohort study	n = 420 Brazil	Included: adult and paediatric patients discharged after first treatment of endocarditis from a tertiary care hospital; aged 34.2±17.2 (mean ±SD), 2mths to 83yrs; n = 270 (64.3%) men, n = 150 (35.7%) women Infecting micro-organism Streptococci n = 237 56.4% Staphylococcus aureus n = 70 16.7% Coag negative staphylococci n = 21 5% Gram-negative bacteria n = 20 4.58% Other gram-positive bacteria n = 9 2.2% fungi n = 5 1.2% Negative blood cultures n = 58 13.8% Underlying cardiac conditions			Mean follow-up 6.1±4.3yrs for survivors, 3.7±3.7yrs for those who died during follow-up n = 28 (6.7%) were lost to follow-up	Relapses[48] Recurrence[49] Valve replacements, death	Not stated

Journal 2001;**141** :78-86. Ref ID: 551			Valvular heart disease: n = 177, 42.1% Congenital heart disease: n = 49, 11.7% Hypertrophic cardiomyopathy: n = 3, 0.7% Chagas cardiomyopathy: n = 1, 0.2% Endocardial fibroelastosis: n = 1, 0.2% Prosthetic heart valve: n = 91, 21.7% - bioprostheses: n = 82 Endocarditis timeframe First 2 mths post-op: n = 9, 9.9% 2mths – 1yr after valve replacement: n = 18, 19.8% >1yr after valve replacement: n = 64, 70.3%					
Effect size: **Relapses** First episode of endocarditis n = 14 (3.3%); second n = 1 (0.2%) Cardiac defect: Prosthetic valve n = 7 (50% of relapses) Valvular heart disease n = 2 Congenital heart disease n = 1 Cardiac pacemaker n = 1 No known heart disease n = 3									

[48] Resumption of clinical picture of endocarditis in the first 6mths after treatment, an infecting micro-organism of the same genus and species, no change in underlying cardiac condition

[49] Clinical picture and isolation of a micro-organism different from previous episode of endocarditis, change in underling cardiac condition, clinical picture and micro-organism consistent with previous episode of endocarditis greater than 6mths since the previous episode

Outcomes:
Surgical treatment n = 5, 35.7% (n = 3 native value endocarditis, n = 2 prosthetic valve infection)
Death n = 5 (n = 4 due to endocarditis)

Recurrence
One episode (n = 48, 11.4%); two (n = 2, 0.5%); three (n = 1, 0.2%); five (n = 1, 0.2%)

One recurrence was observed from 1-15mths (4.5±3.9yrs)
There was a significant male predominance in those who had 2 episodes of recurrence compared with those who had one (n = 39, 81.2% vs. n = 228, 62.0%), p=0.009.

Cardiac defect:
Unchanged underlying condition n = 24 (50%)
First on a native valve, second on a prosthetic valve n = 18 (37.5%)
Second on a native valve regurgitant resulting from damage by previous endocarditis n = 6 (12.5%)

Outcomes:
Mortality was also higher for those with 2 episodes (n = 26, 54.2% vs. n = 71, 20.8%), p=0.001.
Complications were significantly more frequent in those with 1 compared to 2 recurrences (n = 267, 72.6% vs. n=24, 50.0%), p=0.001

Survival free recurrence
The probability of survival free recurrence decreased progressively, there was a significant difference for curves of increasing ages (in classes), p=0.0026.
The probability of survival free recurrence was NS for the duration of the symptoms of endocarditis; antimicrobial administration before hospital admission; the observation of vegetation on echo; infecting micro-organism; native value compared with prosthetic valve endocarditis; medical or surgical treatment; cardiac, neurological or septic complications; valve replacement

For those with prosthetic valve endocarditis, endocarditis in the first post-op year was a risk factor for recurrent endocarditis (p=0.0264, risk ratio 2.05)

Valve replacements
The probability of survival free valve replacement decreased progressively and was lower for those with recurrent endocarditis (p=0.0157), with prosthetic valve endocarditis (p=0.0091) and with prosthetic valve endocarditis in the first post-op year (p=0.0234).
The probability of survival free valve replacement was NS affected by increasing age; sex; duration of endocarditis symptoms; antimicrobial administration before hospital admission; detection of vegetation on echo; infecting micro-organism; comparison of aortic to mitral valve replacement; frequency of surgical treatment of the endocarditis; frequency of cardiac, neurologic or septic complications; finding of annular abscess at operation

Risk factors for valve replacement were recurrent endocarditis (p=0.0169, risk ratio 1.62) and prosthetic valve endocarditis (p=0.0099, risk ration 1.61)

Deaths
n = 20 died as a result of a new episode of endocarditis

The probability of survival decreased over time, curves showed significant decreases in the age strata (p=0.003).
There was a lower probability of survival in those with recurrent endocarditis (p=0.0007).
The probability of long-term survival was not influenced by sex; duration of symptoms; antimicrobial administration before hospital admission; micro-organism; native or prosthetic valve endocarditis; prosthetic valve endocarditis in the first opst-op year; the detection of vegetations on echo; occurrence of cardiac or septic complications; frequency of surgical treatment of the endocarditis; annular abscess at operation; valve replacement during follow-up.

Risk factors for death were increasing age (p=0.001, risk ratio 1.03) and recurrent endocarditis (p=0.0015, risk ratio 2.06)

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Martin JM, Neches WH, Wald ER (1997) Infective endocarditis: 35 years of experience at a children's hospital. Clin Infect Dis. 24: 669-75	Case series, retrospective analysis	n = 73 (n = 76 cases of endocarditis) New Zealand	Inclusion: medical records from a children's hospital, database created by the department of cardiology and the records of the department of pathology; criteria cited by Saiman et al were modified to be more specific and used to substantiate the diagnosis of endocarditis; median age 9yrs (1mth to 18yrs) Exclusion: >18yrs, endocarditis did not fulfil the criteria			January 1958 to December 1992	Risk factors, antibiotic use, outcome	Not stated
Effect size: n = 62 had congenital heart disease, n = 8 more-complex congenital heart disease								

Risk factors
n = 8 had a dental procedure or cleaning in the mouth; dental work was the only risk factor for bacteraemia in n = 6 of these cases
n = 11 had multiple caries at the time of their admission
n = 7 underwent cardiac catheterisation in the 2mths before endocarditis was diagnosed
n = 3 had a central venous catheter in place before endocarditis developed
n = 7 who had a structurally normal heart developed endocarditis

Antibiotic use
n = 44/76 (58%) episodes the patient had received an antibiotic in the week before the diagnosis of IE was made, the most frequently used were penicillins
There was NS difference in positive cultures between those who had had antibiotics n = 40/44 (91%) and those who had not n = 30/31 (97%)

Outcome
n = 30/73 (41%) recovered without any complications; n = 30/73 (41%) had complicated endocarditis and did not die; n = 13/73 (18%) died
Children with blood cultures positive for S. aureus were more likely to have complications than were those whose cultures were positive for viridans streptococci (p=0.001)
n = 15/73 required surgery during initial hospitalisation for endocarditis for complications of their infection; valve replacement (n = 7), vegetation removal (n = 3), drainage of a brain abscess (n = 3), removal of an infected ventricular patch (n = 1), pacemaker insertion (n = 1)
n = 13/73 (18%) died of immediate complications; n = 7 were early (<4days after admission), n = 6 were due to late complications (>21dyas after hospital admission)
46% of those who died had blood cultures that were positive for S. aureus compared with 28% of those who did not die

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
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	Consecutive case series	n = 140 2 tertiary hospitals, Canada	Inclusion: consecutive ambulatory patients scheduled for transoesophageal echocardiography (TOE) at 2 tertiary hospitals 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	Blood samples: immediately before the procedure, within 5mins after termination of the procedure, 1hr after the procedure		12 weeks	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	Not stated
Effect size: **Positive blood cultures**								

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

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Mellow MH,.Lewis RJ. Endoscopy - related bacteremia. Incidence of positive blood cultures after endoscopy of upper gastrointestinal tract. *Archives of Internal Medicine* 1976;**136**:667-9.	Consecutive case series	n = 100 Harlem Hospital Center, New York	Inclusion: patients undergoing endoscopy of the upper GI tract Exclusion: patients who had received antibiotics within 96hrs prior to the time of endoscopy	Additional manipulations performed during endoscopy included biopsy in n = 58 patients and exfoliative cytology in n = 55	Blood samples: blood cultures were taken prior to endoscopy and 10mins after endoscopy in all patients, for the final n = 28 blood cultures were also taken 5mins after endoscopy		Blood cultures, no organisms were excluded as being possible contaminants Microbiology: Thiogylcollate and trypticase soy were the blood culture media used, bottles were incubated for 7days at 37C and checked visually for growth each day, if there was any sign of growth the broth was subcultured	Not stated

Ref ID: 1065							to blood agar, MacConkey agar and chocolate agar plates	
Effect size: **Blood cultures** n = 3/100 patients had positive blood cultures after endoscopy (type of bacteria; Enterococcus, Diphtheroids, Staphylococcus epidermidis) There was no correlation between associated medical conditions, GI lesions, or endoscopic manipulation and the occurrence of postendoscopy bacteraemia None of the patients with bacteraemia had any detectable clinical sign or symptom of bacteraemia or subsequent sepsis (Cultures of samples from equipment and environment identified in the bacteriologic surveys for items in the room and the equipment were considered unacceptable in an operating room environment, the endoscopy room being essentially a dirty area)								

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Mollison LC, Desmond P, V, Stockman KA, Andrew JH, Watson K, Shaw G *et al*. A prospective-study of septic complications of endoscopic retrograde	Consecutive case series	n = 150 (n = 179 procedures)	Inclusion: ERCP, mean age 58yrs (range 18 to 96yrs), 61% were female Therapeutic procedures were performed in 54%(n = 96), comprising stenting in 21%(n = 37), stone removal in 16%(n = 28) and sphincterotomy alone 17%(n = 31) Exclusion: patients undergoing combined ERCP and concomitant percutaneous transhepatic cholangiography	ERCP[50]	Blood samples: pre-ERCP and within 10mins of the completion of the procedure Bacteraemia was deemed to be significant if the organisms isolated were consistent with a biliary origin	June to November 1991	Blood cultures Microbiology: 10ml samples, 5ml was inoculated into anaerobic (NR-7A) and 5ml into aerobic (NR-6A) Bactec NR-660 system blood culture bottles and then routinely	Not stated

[50] If prophylactic antibiotics were deemed necessary they were not administered until after the collection of the second set of cultures

cholangiopancreatography. *Journal of Gastroenterology and Hepatology* 1994;**9**:55-9. Ref ID: 8945					or if anaerobes were found		processed in the microbiology laboratory	

Effect size:

Blood cultures
Positive blood cultures were detected in association with n = 20 (11%) of procedures
n = 9 (5,2%) of cases were considered to be significant, that the organisms were likely to have come from the biliary tree
n = 7 were after the procedure, n = 1 was prior to the procedure and in n = 1 pre- and post-procedure were positive (post procedure organisms were; Enterobacter aerogens, Enterobacter cloacae, Escgerichia coli, Bacteriodes fragillis, Klebsiella oxytoca, Enterobacter faecalis)

During follow-up clinical septic events occurred in n = 22 (12.6%) of cases

n = 5 of the patients with positive cultures at the time of ERCP subsequently developed clinical sepsis (n = 4 of these had been given prophylactic antibiotics appropriate for the organism)

There was an association between therapeutic procedures and sepsis (p=0.0001) and therapeutic procedures and bacteraemia (p=0.015)

(n = 110 (61%) of ERCP patients had antibiotics peri-ERCP, most commonly gentamicin and ampicillin
n = 70 others received antibiotics at the time of the procedure n = 51 gentamicin alone, n = 29 gentamicin and ampicillin, n = 11 gentamicin plus ampicillin and metronidazole and n = 19 other complications
Antibiotic complications occurred in n = 7/109 (6.4%), n = 4 developed rashes and n = 2 had GI disturbance

<table>
<tr><th>Reference</th><th>Study type/ Evidence level</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>Morris CD, Reller MD, Menashe VD, Morris CD, Reller MD, Menashe VD. Thirty-year incidence of infective endocarditis after surgery for congenital heart defect. JAMA 1998;279:599-603.
Ref ID: 6086</td>
<td>Cohort</td>
<td>From 1958 to present (from population based register started in 1982)[51] [52]

n = 3860, follow-up data available for 88%

USA</td>
<td>Inclusion: Oregan residents who had surgical repair of major congenital heart defects at less than 19yrs of age
Expanded to include 12 major heart defects:

<table>
<tr><th>Defect</th><th>Sample size</th><th>Total pt-yrs follow-up</th></tr>
<tr><td>Tetralogy of Fallot</td><td>497</td><td>7025</td></tr>
<tr><td>VSD</td><td>557</td><td>6310</td></tr>
<tr><td>ASD secundum</td><td>624</td><td>7890</td></tr>
<tr><td>ASD primum</td><td>114</td><td>1117</td></tr>
<tr><td>Coarctation of the aorta</td><td>563</td><td>6675</td></tr>
<tr><td>Aortic valve stenosis</td><td>178</td><td>1814</td></tr>
<tr><td>Pulmonary valve stenosis</td><td>252</td><td>3567</td></tr>
<tr><td>Dexotransposition of the great arteries</td><td>208</td><td>1390</td></tr>
<tr><td>Patent ductus arteriosis</td><td>620</td><td>8751</td></tr>
<tr><td>Complete atrioventricular SD</td><td>165</td><td>996</td></tr>
<tr><td>Pulmonary atresia</td><td>32</td><td>157</td></tr>
<tr><td>Pulmonary atresia with VSD</td><td>50</td><td>262</td></tr>
</table>

Endocarditis was determined using 3 criteria applied to medical records
The median age at operation ranged from</td>
<td>Follow-up status of all individuals in the registry was obtained by a medical questionnaire every 2yrs</td>
<td></td>
<td>Data from the follow-up cycle that began in late 1993 are included in this analysis</td>
<td>Risk of endocarditis, after surgery, overall</td>
<td>National Institutes of Health</td>
</tr>
</table>

[51] To inform the registry, medical records departments in all Oregon hospitals that performed cardiac or thoracic surgery were asked to identify cases
[52] To obtain long term follow-up information, subjects were traced through next of kin, physicians, employment records, motor vehicle registrations, city and telephone directories, and the National Death Index

			0.005yr (2days) for pulmonary atresia to 7.0yrs for aortic valve stenosis, the age of surgery has decreased over time Exclusion: children who had palliative surgery only					

Effect size:

Secundum ASD was the most common defect, pulmonary atresia the least common.

Risk of endocarditis

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

* after definitive surgical repair

After surgery:
Aortic valve stenosis
The highest incidence following surgery was in the cohort with aortic valve stenosis (this includes those with isolated supraventricular or subvalvular aortic stenosis, in whom there were no cases of IE before or after surgery)
Incidence of IE appears to increase more rapidly after 5yrs and by 25yrs the cumulative incidence was 13.3% (3.8%), (SE)

Valve replacement
For those with aortic stenosis the risk for those with valve replacement was compared with those with native valves, 16% (n = 28) had aortic valve replacement
For prosthetic valve n = 3 cases of endocarditis, 10-year incidence of 26% (13%)
For native valve n = 10 cases of endocarditis, 10-year incidence of 5% (2%), 20-year 11% (4%), 25-year 15% (6%)

Coarctation of the aorta
n = 8 cases after surgery, the risk appears to increase with age or time after surgery, at 30yrs cumulative incidence was 3.5% (1.6%)

Tetralogy of Fallot
n = 5 cases after surgery, all occurred within the 10yrs after surgery, cumulative incidence 1.3%(0.6%), this remains constant to 30yrs
n = 3/5 had a residual VSD

Pulmonary atresia with VSD
n = 3 episodes of IE after reparative surgery, (n = 2/3 had a pulmonary homograft)
At 10yrs the cumulative incidence was 6.4% (4.4%)

VSD
Following surgery, n = 4 cases of IE, cumulative incidence at 30yrs, 4.1% (2.1%)
The risk appears to increase 20yrs after surgery, cumulative incidence at 20yrs 0.5%, 25yrs 2.7%

Primum ASD
n = 2 cases of IE, cumulative incidence from 10yrs on 2.8% (2.0%)

Overall
n = 38 cases after surgical repair, n = 7 (18%) deaths distributed among different heart defects
At 25years after surgery the cumulative incidence of IE was 1.3% for tetralogy of Fallot, 2.7% for isolated VSD, 3.5% for coarctation of the aorta, 13.3% for valvular aortic stenosis and 2.8% for primum ASD
Endocarditis occurred in the immediate post-op period in 22% of the cases occurring in children with tetralogy of Fallot, primum ASD, coarctation, pulmonary atresia, and pulmonary atresia with intact septum

(The infection was presumed by the treating physician to be of dental origin in 14%, based on recent dental procedure or poor oral hygiene)

(the authors consider the important outcome of this study to be the recognition of the high risk of endocarditis with aortic stenosis)

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
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	RCT	n = 100	Inclusion: consecutive patients likely to undergo a therapeutic or complicated diagnostic ERCP Exclusion: history of endocarditis or valvular heart disease, history of allergy to antibiotics, antibiotic therapy less than 48hrs before ERCP	n = 50 Group I 2g cefotaxime IV 15mins before endoscopy Blood samples: before endoscopy, 5, 15, 30 and 120mins after beginning the procedure	n = 50 Group II control group	Patients were followed up 3days after ERCP	Bacteraemia Rectal temperature Culture vials were incubated for 7days	Not stated

Effect size:

Bacteraemia
Bacteraemia detected (15 and 30mins) n = 4 of the control group, n = 0 cefotaxime group (E. coli, Peptostreptococcus, S. aureus)
None of the episodes of bacteraemia was followed by clinically evident cholangitis or sepsis

n = 4 of the control group developed cholangitis or sepsis during the 3day follow-up, all had a temperature of 38.5C or more

Bacteraemia or clinical sepsis developed in n = 8/50 control group vs. n = 0 cefotaxime, p<0.01

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Peterson LJ,.Peacock R. The incidence of bacteremia in pediatric patients following tooth extraction. *Circulation* 1976;**53**:676-9. Ref ID: 1066	Controlled trial	n = 107 children	Inclusion: healthy paediatric patients, between the ages of 5 and 13yrs, all teeth were removed using local anaesthesia and forceps extraction technique, the ages of the patients show little variation among the 4 groups	Group I n = 28 required extraction of healthy primary teeth for space management and interceptive orthodontic purposes; removed for reasons other disease Group II n = 34 required removal of primary or	Blood samples: Groups I, II and III had blood drawn within 2mins following the removal of the tooth, while Group IV had blood for cultures taken prior to their dental treatment		Extractions, blood cultures Microbiology: 2ml samples were drawn into Becton-Dickinson Vactainer, the first tube was grown aerobically, the second anaerobically, the culture medium was a peptone broth supplemented with yeast	Not stated

				permanent teeth which had diseased or necrotic pulps and associated abscesses Group III n = 18 removal of permanent teeth for orthodontic reasons Group IV n = 27 restorative dental treatment, this group served as a negative control			extract, vitamins, and amino acids to increase microorganism growth, cultures were incubated at 35˚C, tubes with growth were subcultures at 24 and 48hrs, the original culture tubes were incubated and observed for 16days before being reported as negative	
Effect size: **Extractions** Average number of teeth extracted: Group I (1.4); Group II (1.2); Group III (3.4); Group IV (0) **Blood cultures** Group I, nondiseased primary teeth, positive cultures n = 10/28 (35.7%) Group II, nondiseased primary teeth, positive cultures n = 18/34 (52.9%) Group III, diseased teeth, positive cultures n = 11/18 (61.1%) Group IV, negative controls, no positive cultures NS correlation between number of teeth extracted and resultant condition of the culture Of the n = 39 positive cultures, n = 23 grew two or more organisms								

Organisms found; Streptococcus (n = 20, 29%), Peptostreptococcus (n = 7, 10%), Diptheroids (n = 16, 23%), Staphylococcus (coagulase negative, n = 8, 12%), Bacteroids (n = 8, 12%), Veillonella (n = 3, 4%), Neisseria (n = 6, 9%), Vibrio (n = 1, 1%)

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
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	Systematic review	n = 4694 n = 28 trials (n = 10 placebo controlled, n = 18 no treatment control)						Not stated

Effect size:

Criteria
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. Search strategy made with MeSH headings including prostatectomy, prostatic hyperplasia, transurethral resection of the prostate, antibiotic prophylaxis, antibiotics and postoperative complications. Bibliographies of included studies were hand searched. The Journal of Urology and European Urology 1998 to 2004 for study abstracts.

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

Studies
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

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Rahn R, Schneider S, Diehl O, Schafer V, Shah PM. Preventing post-treatment	RCT Single-blind	n = 120	Inclusion: those who were scheduled for dental treatment involving either intraligamental injection (n = 60), or elective extraction of a molar (n = 60); n = 28 female, mean age 33.6yrs (range 22 to 77yrs) Exclusion: those receiving antibiotics or	n = 40 0.2%chlorhexidine n = 40 10% povidone-iodine	n = 40 control sterile water		Bacteraemia Blood samples processed as recommended by the American Society for Microbiology, all	Mundipharma/Limburg

bacteremia: comparing topical povidone-iodine and chlorhexidine.[see comment]. *Journal of the American Dental Association* 1995;**126**:1145-9			immunosuppressive therapy or who had a history of bacterial endocarditis, rheumatic fever or congenital heart disease 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	Into the sulcus of the affected tooth with an endodontic syringe	Blood samples: before antiseptic, 2, 4, and 6mins after the dental procedure was finished		micro-organisms were identified by standard identification procedures	
Effect size: **Bacteraemia** The blood samples obtained before the dental procedure were completely negative for bacteraemia Post-procedure bacteraemia; control (n = 21, 52.5%), povidone-iodine (n = 11, 27.5%), chlorhexidine (n = 18, 45.0%) Bacteraemia povidone-iodine vs. control, $p<0.05$ Viridans streptococci povidone-iodine and chlorhexidine vs. control, $p<0.01$; NS chlorhexidine vs. control								

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Roberts GJ, Radford P, Holt R. Prophylaxis of dental bacteraemia with oral amoxycillin in children. *British Dental Journal* 1987;**162**:179-82.	Controlled study	n = 108 [53] UK	Inclusion: under 16yrs and required admission for extensive conservative dental work as well as the extraction of at least one tooth Exclusion: allergy to one of the penicillin group or a significant medical disorder The randomised groups were comparable in age and sex	n = 47 oral amoxicillin 50mgs/kg 2hrs before the scheduled time for surgery (mean dose 50.4mg/kg) 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	n = 8 with cardiac abnormalities given oral amoxicillin[54] n = 6 refusers		Bacteraemia, sampling time 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)	Not stated

[53] allocation decided at random
[54] N=2 vomited the oral amoxicillin and were given IV 250mg upon attainment of anaesthesia

				extraction, another 5mins post extraction).				
Effect size: **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 The post extraction samples; 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) **Sampling time** Samples taken 45secs after extraction showed n = 1/9 positive, none of the corresponding samples taken at 5mins was positive. At 5mins n = 5/20 were positive, for the corresponding samples at 2mins n = 10/20 were positive *(the authors note that these results suggest that the optimal sampling time is 2mins or less)*								

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Roberts G,.Holzel H. Intravenous antibiotic regimens and prophylaxis of odontogenic bacteraemia. *British*	Retrospective study	n = 92	Inclusion: children and adolescents with severe congenital heart disease, mean age 8yrs2mths (range1yr5mths to 19yrs8mths) undergoing dental treatment under GA; dental treatment consisted of a mixture of dental extractions and restorations Exclusion: anticoagulant treatment, antibiotic therapy within the last month and known viral carriage	All children received intravenous antibiotic drugs immediately upon attainment of anaesthesia but before the start of dental treatment, the			Bacteraemia Bacteria was speciated using standard microbiological methods with oral streptococci speciated using the API Strep 20 system	Not stated

Dental Journal 2002;**193**:525-7.				antibiotics used were those advised by the child's cardiac physician [55] Where appropriate the dose was adjusted to match the weight of the child			The extent of dental disease was graded using simplified indices for dental plaque, gingivitis and spontaneous gingival bleeding	
Effect size: The two major antibiotic groups used were ampicillin (n = 42) and teicoplanin & amikacin (n = 35)(clindamycin n = 6, teicoplanin n = 2, amikacin n = 1 vancomycin n = 2, ampicillin & clindamycin n = 1, ampicillin & vancomycin n = 1, ampicillin & amikacin n = 4) There was no identifiable pattern of antibiotic usage in relation to underlying cardiac condition **Bacteraemia** There was NS difference in the positive blood cultures with ampicillin (16.7%) and teicoplanin & amikacin (22.2%) Data were compared with a contemporaneous examining the percentage positive cultures following multiple extractions The ampicillin group was significantly less than the multiple extractions, 16.7% vs. 54.2%, p=0.0001. this was also seen with the teicoplanin & amikacin group vs. multiple extractions, 22.2% vs. 54.2%, p<0.003 There was NS relationship between the presence or absence of bacterial dental plaque and/or gingivitis All isolated organisms exhibited full antibiotic sensitivity during routine testing **Follow-up** All patients had an uneventful recovery without any signs and symptoms of endocarditis								

[55] ampicillin was used as first choice, the use of teicoplanain and amikacin combined was required as part of the hospital infection control policy where there were concerns about antibiotic resistant Staphylococcus aureus

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Roberts GJ, Holzel HS, Sury MR, Simmons NA, Gardner P, Longhurst P. Dental bacteremia in children. *SO: Pediatric cardiology* 1997;**18**:24-7. Ref ID: 4116	RCT [56]	n = 735	Inclusion: children referred to Guy's Dental Hospital or GOSH for dental treatment under general anaesthetic, n = 383 male, n = 352 female, mean age 9yrs 3mths	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	Blood samples: one sample taken 30sec after each procedure	1991 to 1993	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	Not stated

[56] 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 of the patient, the third was the cardiac group all of whom had antibiotic prophylaxis and therefore formed a separate group of patients

				placement Group E – oral surgery group; single extractions, multiple extractions, and mucoperisoteal flaps Group F – groups having antibiotic prophylaxis; cardiac patients				
Effect size: **Blood cultures** All procedures were associated with a bacteraemia, highest association intraligamental injection, lowest fast drill Positive blood cultures; - 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):
- 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%
- rubber dam placement 4.8 to 35.1%
- 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,

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Roberts GJ, Simmons NB, Longhurst P, Hewitt PB. Bacteraemia following local anaesthetic injections in children. *British Dental*	RCT	n = 143 children Guy's Dental Hospital, London	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	n = 50 baseline, blood taken before any dento-gingival manipulation n = 32 buccal infiltration n = 32 modified intraligamental	Blood samples: taken 30sec after injection[58]		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	Not stated

[57] for the study groups, one of the three injection techniques was selected using random number tables
[58] only one sample of blood was taken from each child

Journal 1998;**185**:295-8. Ref ID: 2440				n = 29 conventional intraligamental [57]			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	

Effect size:

Blood cultures
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

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

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
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	RCT[59]	n = 257 children GOSH and Guy's and St Thomas' Hospital Trust, London	Inclusion: healthy children receiving dental treatment under general anaesthetic, n = 141 male, n = 116 female, mean age 9yrs 1mth (range 2yrs to 19yrs 6mths) Exclusion: those who had taken antibiotics within the previous month, known viral carriage and haemorrhagic disorders	n = 54 baseline (no procedure) n = 51 rubber bam placement n = 49 slow drill (60seconds) n = 47 fast drill (60seconds) n = 56 matrix band and wedge	Blood samples: baseline before any dento-gingival manipulation was carried out and 30sec after each of the procedures		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	Not stated

[59] randomisation by random number table

Effect size:

Blood cultures
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

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Roberts GJ, Jaffray EC, Spratt DA, Petrie A, Greville C, Wilson M *et*	RCT Not blinded	n = 500	Inclusion: children attending Eastman Dental Hospital for treatment under general anaesthetic, the mean age of the children was 7.6yrs (range 3.4 to 18.9) Exclusion: antibiotic usage within the	Children were allocated to one of the time groups in random permuted	Other comparison time groups		Percentage prevalence of positive cultures, intensity of bacteraemia, speciation of the	British heart foundatio n grant

al. Duration, prevalence and intensity of bacteraemia after dental extractions in children. *Heart (British Cardiac Society)* 2006;**92**:1274-7. Ref ID: 2375			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	blocks; 10sec, 30sec, 1min, 2min, 4min, 7.5min, 15min, 30min, 45min, 1hr			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	
Effect size: **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
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[60]

(it is appropriate to estimate that dental bacteraemia is quenched within about 12min of completing dental extractions)

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Rolando N, Gimson A, Philpott-Howard J et al. (1993) Infectious sequelae after endoscopic sclerotherapy of	RCT [61]	n = 97 (n = 115 procedures) London	Inclusion: patients admitted for sclerotherapy for bleeding oesophageal varicies Exclusion: <18yrs, antimicrobials within the preceding 72hrs, history of allergy to imipenem/cilastatin Groups were comparable for age, sex, encephalopathy grade, ascites and biochemical parameters	n = 47 IV imipenem/cilastatin over 20min Blood samples: before and immediately after each endoscopic procedure	n = 50 control IV dextrose-saline		Bacteraemia Blood culture bottles examined twice a day for the first 2days and daily for a further 5days	Merck, Sharpe & Dohme Ltd

[60] 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
[61] Patients were sequentially assigned using computer-generated randomisation tables

oesophageal varices: role of antibiotic prophylaxis. Journal of Hepatology 18: 290-4								
Effect size: **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) There were NS differences in outcome between the two groups								

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Roudaut R, Lartigue CM, Texier-Maugein J, Dallocchio M. Incidence	Consecutive case series	n = 82 France	Inclusion: patients referred fro transoesophageal echocardiography Exclusion: had received antibiotics before the procedure, was febrile, had any suspicion of infective endocarditis	n = 44 (group I) n = 38 (group II)	Blood samples: - group I blood cultures taken before procedure, immediately	Rectal temperature of the n = 62 hospitalised patients	Bacteraemia, fever, follow-up Microbiology: Aerobic and anaerobic blood	Not stated

of bacteraemia or fever during transoesophageal echocardiography: A prospective study of 82 patients. *European Heart Journal* 1993;**14**:936-40. Ref ID: 3797			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		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[62]	was measured twice a day for a mean of 6 days after the procedure. A third (34%) were examined a few months later to evaluate any occurrence of endocarditis	culture bottles (BCB system roche) were inoculated and incubated for 10days at 37˚C	

[62] in addition in group II cotton swabs were used to take smear samples from the surface of the endoscope after the procedure

Effect size:

Incidence of bacteraemia
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)[63]

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[64]

[63] 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
[64] 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

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Salman L, Prince AS, Gersony W. Pediatric infective endocarditis in the modern era. *The Journal of Pediatrics* 1993;**122**:847-52. Ref ID: 11630	Case review	n = 62 cases of paediatric IE USA	Children treated at a hospital in Columbia, to be included patients had to meet blood culture and/or clinical criteria; n = 39(63%) male, ages ranged from 1mth to 19yrs (median age 8.2yrs)			15years January 1977 to February 1992		Not stated

Effect size:

Prior medical conditions

n = 62 cases of paediatric IE, 70% had structural heart disease

Complex cyanotic heart disease	22
VSD	9
Other acyanotic lesions	5
Mitral valve prolapse	4
Rheumatic heart disease	3

Outcome

Mortality rate n = 13 (21%)

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
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	RCT [65]	n = 96 (n = 100 procedures)	Inclusion: ERCP Exclusion: history or signs of endocarditis or valvular heart disease, history of allergy to antibiotics, antibiotic therapy less than one week prior to ERCP Two groups were matched for age, underlying disease of the pancreaticobiliary tract, duration of ERCP, interventions during ERCP (such as sphincterotomy or stone extraction)	n = 50 cefotaxime 2g IV 15min before starting ERCP Blood samples; during and 5mins after ERCP	n = 50 control group, no antibiotic therapy		Bacteraemia Two pairs of bottles of enriched trypticase soy broth for aerobic and anaerobic culture, one of the pairs containing a resin for the absorption of antibiotics (Bactec NR6A, NR7A, NR16A, NR17A), culture vials were incubated for 7days	Not stated
Effect size: **Bacteraemia** No blood cultures were positive prior to ERCP Significant difference between cefotaxime (n = 1/50, 2%) vs. control group (n = 8/50, 16%), p<0.02 Duration of the procedure NS difference between those who had a bacteraemia and those who did not Manipulations such as papilotomy, stone extraction, or balloon dilatation of the bile duct NS difference the frequency of bacteraemia when compared with simple								

[65] Randomised using a closed envelope method

diagnostic ERCP n = 2 patients with a bacteraemia developed fever >38C (not accompanied by leukocytosis or sings of cholangitis) Most of the micro-organisms found in the blood cultures were bacteria of the normal oropharyngeal flora (streptococcus milleri, streptococcus salivarius, streptococcus mitis, streptococcus pneumoniae, enterococus faecalis, enterococcus faecium, aerococcus viridans, corynebacterium pseudotuberculosis, klebsiella pneumoniae)

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
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. Gastrointesti	RCT [66]	n = 31 (n = 39 episodes of bleeding) Australia	Inclusion: those undergoing 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 Patients could enrol in the study on more than one occasion Post allocation patients were stratified into those with and those without ascites There was no difference between the groups in cause of liver disease, use of ET tubes, need for vasopressin or balloon tamponade	n = 19 1g cefotaxime IV immediately before procedure Blood samples: before endoscopy, 5mins, 4hrs and 24hrs after sclerotherapy	n = 20 No antibiotic	Study between August 1989 to December 1991	Bacteraemia Cultures were performed using standard aerobic and anerobic techniques at 37C, organisms were identified using conventional means	Not stated

[66] Allocation by selection of a sealed envelope containing a random number

nal Endoscopy 40: 680-4								
Effect size: **Blood cultures** n = 1/19 positive at 5mins with cefotaxime (alpha-haemolytic streptococcus) n = 6/19[67] control groups positive cultures (p=0.04 vs. cefotaxime); n = 5 positive at 5mins, n = 2 positive at 4hrs (alpha-haemolytic streptococci, veillonella sp, streptococcus milleri, streptococcus salivarius, neisseria sp – were identified) At 24hrs no positive cultures with either group Oral flora including alpha-haemolytic streptococci were found on the endoscope **Follow-up** The presence of bacteraemia was not correlated with fever after sclerotherapy Clinical sepsis did not develop in any of the patients during the 24hrs after sclerotherapy n = 7 (18%) died during hospital admission, this was NS difference between those who received antibiotics and the control group								
Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Sett SS, Hudon MP, Jamieson WR et al. (1993) Prosthetic valve endocarditis. Experience with porcine bioprostheses 6739.	Retrospective review	n = 56 Canada	Inclusion: patients who had endocarditis related to a porcine bioprosthesis between 1975 and 1988, those who had undergone concomitant procedures, such as coronary artery bypass, were included; diagnosis was based on two positive blood cultures and histopathologic evidence; mean age at initial surgical intervention 57yrs (range 27 to 81yrs)				Outcomes, death, survival	Not stated

[67] N=1 with staphylococcus epidermis not considered in further analysis

Journal of Thoracic & Cardiovascular Surgery 105: 428-34								

Effect size:

PVE diagnosed in n = 56/3200

Outcomes
Overall mortality n = 18/56, 32%; mortality rate n = 6/8, 75% with early PVE and n = 12/48, 25% with late PVE [68]

The most common organism was Staphylococcus epidermis (n = 12, n = 4 died), Streptococcus viridans (n = 8, n = 2 died), Staphylococcus aureus (n = 7, n = 3 died), Candida albicans (n = 4, n = 2 died)

Causes of death with early PVE were septicaemia, congestive heart failure, thrombotic occlusion of a mitral prosthesis
Causes of death with late PVE were congestive heart failure, hepatic and renal failure, septicaemia, ruptured mycotic aneurysm, adult respiratory distress syndrome

n = 6 had previous NVE, in only n = 1 was the organism the same as with the original NVE, Streptococcus viridans

91% of those with late PVE survived after combined medical and surgical treatment vs. 62% with medical therapy alone, $p<0.01$

n = 26 reoperated cases, findings showed perforation (n = 8, 31%), vegetations (n = 9, 35%), dehiscence (n = 11, 42%), annular abscess (n = 7, 27%)

Both early and late groups, univariate analysis showed renal status, presence of ongoing sepsis, mode of treatment, presence of fever, previous dental procedure, lack of dental prophylaxis, time to diagnosis, and age >65yrs, were predictors of death ($p<0.05$)
Multivariate analysis, renal status ($p<0.05$), mode of treatment ($p<0.05$), time to diagnosis ($p<0.04$) and age ($p<0.05$) were predictors of early death

Follow-up; n = 1 subsequent death related to recurrent PVE

[68] Endocarditis diagnosed within 60days of operation was classed as early endocarditis, cases that occurred after 60days were classed as late endocarditis

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
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	RCT [69] Double-blind	n = 109 side effects study n = 82 dental bacteraemia study London	Inclusion: adult patients undergoing dental extractions in the out-patient department, age range 18 to 78yrs, male:female ratio 3:1, Inclusion: healthy adults aged between 18 and 71yrs attending the out-patient department were also studied	n = 56 1.5g erythromycin stearate orally 1hr before dental extraction n = 40 erythromycin	n = 53 matched placebo n = 42 placebo	7days	Bacteraemia, side-effects	Abbott Laboratories

[69] Random code and coded envelopes containing either erythromycin or placebo of identical appearance, the number of the envelope issues to each patient was recorded and numbers decoded only after the trial on side-effects was completed

Effect size:

Streptococcal bacteraemia
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
The total numbers of 1litre blood culture bottles yielding growth of viridans streptococci were n = 20/240 (8%) inoculated with blood from those receiving erythromycin and n = 87/252 (35%) inoculated from the placebo group

Side-effects
n = 29/56 (52%) receiving erythromycin reported GI side-effects compared with n = 10/53 placebo group

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Shull HJ, Jr., Greene BM, Allen SD, Dunn GD, Schenker S. Bacteremia with upper gastrointestinal endoscopy. *Annals of Internal Medicine* 1975;**83**:212-4. Ref ID: 1069	Case series	n = 50 USA	Inclusion: male patients referred for upper GI endoscopy Exclusion: intravenous or urinary catheter or other obvious mechanical breaches of the skin, febrile, leukocytosis (total leukocyte count greater than 10000/mm3), had received antibiotics for 2wks before the procedure, other evidence of infection from clinical records		Blood samples: before, during, at 5min after and 30min after the procedure		Bacteraemia Microbiology: Cultures were incubated at 37˚C, bottles were examined visually for growth after 18hrs incubation and daily or every other day thereafter, each bottle was subcultured at 48hrs and after 10days	Veterans Administration, National Institute of Mental Health

Effect size:

Bacteraemia [70]
Bacteraemia was detected in n = 4/50 (8%) of the participants, none of the blood specimens taken during endoscopy were positive, bacteraemia was detected at 5min or 30min or both (organisms identified; Neisseria perflava, Streptococcus salivarius, Propionobacterium acnes, S. mitis, Acinetobacter calcoaceticus, Staphylococcus epidermidis)
n = 11 participants had biopsies taken, none had any positive blood cultures

Follow-up of those with positive cultures showed no clinical manifestations of bacteraemia

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
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*	Case series	n = 132 (n = 135 procedures) National Taiwan University Hospital Taiwan	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		Blood samples: 30 to 60mins before the procedure, immediately after, 180 to 240mins after the procedure[71]	October 1990 to August 1991	Blood cultures, throat swab 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.	Not stated

[70] the following organisms were excluded as contaminants unless they were found in both flasks, or in one flask and in significant numbers on the corresponding pour plate; Staphylococcus epidermis, Bacillus species and aerobic diptheroids
[71] A cotton swab took smear samples from the throat 30 to 60mins before the procedure

1992;**124**:1541-4. Ref ID: 3820							Positive vials were subcultured on appropriate media and gram staining was performed	

Effect size:

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

Blood cultures [72]
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)

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Silk KL, Ali	Case	n = 50	Inclusion: patients having nasal		Blood samples:		Blood cultures,	Not

[72] 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

MB, Cohen BJ, Summersgill JT, Raff MJ. Absence of bacteremia during nasal septoplasty. *Archives of Otolaryngology Head Neck Surgery* 1991;**117**:-55. Ref ID: 4847	series	USA	septoplasty, age range 15 to 87yrs (mean age 33.3yrs), n = 21 female, n = 29 male, all patients had septal deviation		immediately prior to surgical incision, 5 and 15min following the onset of surgery		nasal swabs Microbiology: 10ml sample, 5ml were injected into each of two blood culture bottles containing trypticase soy broth incubated at 37˚C, subcultured onto blood and mannitol salt agar plates at 24hrs and examined for turbidity daily for 2wks	stated
Effect size: **Blood cultures** None of the blood cultures taken from the n = 50 patients either prior to surgery or during the procedure showed bacterial growth **Nasal swabs** n = 23/50 (46%) of patients showed S aureus in nasal swabs (n = 19 (82.6%) of these yielded S aureus in all four cultures), n = 6/50 yielded coagulase negative staphylococci and n = 1/50 Pseudomonas aeruginosa								

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Sontheimer J, Salm R, Friedrich G, Vonwahlert J, Pelz K. Bacteremia following operative endoscopy of the upper gastrointestinal-tract. *Endoscopy* 1991;**23**:-72. Ref ID: 4843	Controlled study	n = 160	Inclusion: patients undergoing interventional endoscopy, patients were included irrespective of age, sex, general condition or endoscopic measures taken Exclusion: antibiotic treatment within the previous 48hrs, indwelling venous or arterial catheters, signs of localised or general infection or sepsis	n = 120 endoscopic operative measures Blood samples: prior to the examination, 3 to 5min after the potentially dispersing event, 30min after the end of the examination	n = 40 control group (n = 15 diagnostic endoscopies without therapeutic measures; n = 25 who in addition had sample biopsies taken)		Bacteraemia (certain, questionable, contamination) Microbiology: Aerobes were cultivated by incubation for 4 to 6days at 36˚C under 5 to 10% CO2, the colonies were then inoculated to CO agar in order to obtain pure cultures. Anaerobes were streaked on HCB agar and cultivated in an anerobian receptacle for a minimum of 6days at 36˚C.	Not stated
Effect size: **Endoscopic measures** n = 15 diagnostic control group n = 25 gastroscopy with biopsy excision n = 25 dilative oesophageal interventions n = 25 sclerotherapy n = 25 ERCP and interventional measures n = 25 endoscopic percutaneous n = 20 laser treatment of tumours								

Bacteraemia
Certain bacteraemia[73] was identified in n = 18/160 (11.25%), the germ spectrum comprised aerobic and anaerobic, which were found as flora of the upper GI tract, mixed cultures of two different germs were found in n = 7/18

Positive culture findings were classified as questionable bacteraemia[74] in n = 29 (18.12%), in the other n = 10 (6.25%) the culture findings were identified as contamination, in n = 3 cases the entire culture medium batch had been contaminated

Bacteraemia appears to occur significantly more frequently ($p<0.05$) following operative endoscopies (gastroscopy including sample excision n = 5 positive bacteraemia, 12.5%) than after diagnostic endoscopies (surgical endoscopy n = 42 positive bacteraemia, 35.0%)

Within the group of patients in whom bacteraemia was not identified, n = 113, leukocytes (5700 to 6700) and rectal temperature (37.3 to 37.4) showed slight increases, whereas there was a greater increase in those where bacteraemia was identified, n = 47, leukocytes (4700 to 9700) and in rectal temperature (37.2 to 38.8)

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Strom BL, Abrutyn E, Berlin JA, Kinman JL, Feldman RS, Stolley PD *et al*. Risk factors for infective endocarditis:	Case-control	n = 416 enrolled potential case-patients n = 287 community acquired	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		Controls and case-patients were matched for age, sex, race, education, occupation and dental insurance		Prior infection, medical procedures and therapies, oral hygiene	NIH grant

[73] minimum of 3 colonies of the same germ species in ≥2/6 media, provided the germ is known to be local flora at the site of intervention; strictly anaerobic germs were isolated, irrespective of the number of their colonies on the media
[74] germ count below 3/10ml of blood, germs were not identified in the patient's secretion and not known to be at the site of intervention, 3 or more colonies of the same germ species grew on one culture medium only, one and the same germ species was found at time 0, 3to5, and 15min

oral hygiene and nondental exposures. *Circulation* 2000;**102**:2842-8. Ref ID: 31		IE not associated with IV drug use n = 273 interviewed case-patients From August 1988 – November 1990 surveillance for IE in 54 hospitals Philadelphia	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		Cases were more likely to have self-reported prior kidney disease, to report physician diagnosed diabetes			
Effect size: **Prior infection as a risk factor** An association between endocarditis and skin infection was NS with multivariate analysis[75] 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. 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 **Medical procedures and therapies** 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								

[75] The elevated OR for skin infection disappeared after the analysis was restricted to subjects with cardiac valvular abnormalities

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[76] 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

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

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Strom BL AEBJeal. Dental and cardiac risk factors for infective endocarditis: a population-	Case-control	n = 416 enrolled potential case-patients n = 287 communi ty	Surveillance completed for IE in 54 hospitals Philadelphia 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.	Cases; information was obtained from case-patients by a structured telephone interview, medical and dental records	One control from the community selected for each case-patient (using a modification of the Waksberg random-digit	From August 1988 – November 1990	Primary risk factor variables were host characteristics [78], (reflecting the information that would be available to a practitioner	National Heart, Lung and Blood Institute

[76] Adjusted for cardiac valvular abnormality and diabetes
[77] Interviewers and medical records abstractors were not blinded but were extensively trained in good interviewing and abstracting techniques
[78] Due to the study focusing on indications for an antibiotic prophylaxis

based case-control study. *Ann Int Med* 1998;**129**:761-9. Ref ID: 492		acquired IE not associated with IV drug use n = 273 interviewed case-patients	Excluded: <18yrs, IV drug users, those who developed endocarditis in the hospital Case records were examined and classified by experts in IE, agreement in 2 out of 3 was required to determine a case or not a case [77]	were subsequently requested	dialling method) Controls and case-patients were matched for age, sex and neighbourhood of residence		about to perform a procedure for which prophylaxis might be indicated) (Any valvular heart abnormality - defined from self-reporting structured telephone interviews, dental visit information was obtained from dental records)	

Effect size: (all CI 95%)

Infecting organisms
n = 272/287 had multiple positive blood cultures[79]

Cardiac risk factors
Patient-reported history of any cardiac valvular abnormality was highly associated with IE (adjusted[80] odds ratio 16.7, CI 7.4 to 37.4)

Risk factor	Cases (n = 273)	Controls (n = 273)	Adjusted OR[81] (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)

*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

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

[79] Of the 15 case-participants with negative cultures, 12 received antibiotics before admission, 4 had histopathologic evidence of endocarditis, 10 had echocardiographic evidence of valve vegetation
[80] Adjusted for socioeconomic status variables (ethnic group, education, occupation, health insurance status, and dental insurance status)
[81] Adjusted for socioeconomic status variables (ethnic group, education, occupation, health insurance status, and dental insurance status), diabetes mellitus and severe kidney disease

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Takeda S, Nakanishi T, Nakazawa M, Takeda S, Nakanishi T, Nakazawa M. A 28-year trend of infective endocarditis associated with congenital heart diseases: a single institute experience 4882. *Pediatrics International* 2005;**47**:392-6. Ref ID: 4882	Case series	n = 183	Inclusion: patients with congenital heart diseases, patients who were diagnosed as definite endocarditis according to Duke criteria Exclusion: any patients with IE who were within 1yr post cardiac surgery			1971 to 1998	Preceding events, microorganisms	Not stated

Effect size:

Preceding events
Preceding events were documented in n = 61/183 patients with n = 122 (69%) where preceding events were unclear
n = 38 (21%) included dental treatment[82], of these n = 15 (9%) were prevention, n = 3 (2%) periapical infection and n = 7 (4%) dental caries
n = 3 (2%) had atopic dermatitis as a preceding events and n = 10 (5%) were others

Microorganisms
The most frequently isolated organism was Streptococcus sp. n = 106/185 (57%), with Staphylococcus sp. n = 26 (14%), Enterococcus sp. n = 4 (2%), negative blood culture n = 29 (16%)
The microbiological profile did not change during the 28yrs of the study

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Tleyjeh IM, Steckelberg JM, Murad HS, Anavekar NS, Ghomrawi HM, Mirzoyev Z *et al*. Temporal trends in infective endocarditis: a population-based study in Olmsted County, Minnesota. *JAMA* 2005;**293**:3022-8.	Population based survey	n = 102 patients n = 107 episodes USA	Data from a centralised system which links diagnostic and procedure information from virtually all sources of healthcare in the county; adults ≥18yrs; cases defined by Beth Israel and Duke criteria; mean age 54.1yrs in 1980-84 to 67.4yrs in 1995-2000; male predominance which was consistent (67 to 83%)			30years 1970 to 2000	Incidence, underlying heart disease	Public Health Service National Institutes of Health

[82] N=7 were given prophylactic antibiotics, their regimen did not follow the recommendations of the AHA

Ref ID: 534								

Effect size:

Incidence
The overall adjusted incidence of IE ranged from 5.0 to 7.0 cases per 100,000 person-years, NS change during the study period

Underlying heart disease
n = 107 episodes of IE, underlying cardiac disease

Prosthetic valve	23(21%)
Rheumatic heart disease	14(13%)
Mitral valve prolapse	18(17%)
Congenital heart disease	8(7%)
Bicuspid aortic valve	7(7%)
Acquired valvular disease	12(11%)
(Previous IE)	8(7%)

The proportions of cases with MVP and congenital heart disease NS changed over time
In the subgroup of IE cases with identified underlying heart disease there was a significant increasing trend in MVP over time (p=0.04), and a decreasing trend in rheumatic heart disease NS, however numbers were small

Reference	Study	Number	Patient characteristics	Intervention	Comparison	Length of	Outcome	Source

	type/ Evidence level	of patients				follow-up	measures	of funding
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	RCT [83]	n = 106 Spain	Inclusion: patients with mental and behavioural disabilities who underwent dental extractions under GA, n = 52 male, mean age 25.8±11.4yrs (range 8 to 57yrs) Exclusion: use of antibiotics in the previous 3mths, use of oral antiseptics, any type of congenital or acquired immunodeficiency , disease that predisposes the patient to infections or bleeding There were NS differences between the groups with regard to age, sex, oral health status, or number of teeth extracted	n = 53 underwent endotracheal intubation and oesophageal packing and then had their mouths filled with 0.2% chlorhexidine digluconate solution for 30sec	n = 53 control group Blood samples: baseline, 30sec after final dental extraction , 15mins and 1hr[84] after finishing surgical procedure		Bacteraemia Blood cultures were processed in the bactec 9240, gram staining was performed	Xunta de Galicia, Spain

[83] Randomisation was based on a single sequence of random assignments created by applying a computer-generated randomisation list
[84] The final blood sample could only be obtained from N=50 patients

Effect size:

Bacteraemia
Positive blood cultures at baseline; 9% chlorhexidine, 8% control
Bacteraemia 30sec; chlorhexidine 79% vs. control 96%, p=0.008
Bacteraemia 15min; chlorhexidine 30% vs. control 64%, p<0.001
Bacteraemia 1hr; chlorhexidine 2% vs. control 20%, p=0.005

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
Polymicrobial culture results 29% vs. 11%, p=0.005

The most frequently identified were Streptococcus species (64% control, 68% chlorhexidine), then Staphylococcus species (11% control, 8% chlorhexidine), Neisseria species (8% control, 5% chlorhexidine)

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
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	Case series	n = 53 Santiago de Compostela University Hospital, Spain	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 immunodeficiency		Blood samples: baseline (after nasotracheal intubation and before local anaesthetic injection), 30sec after final dental extraction, 15min and 1hr after finishing the surgical procedure[85] Oral health status was graded in each patient using a specifically designed and previously validated scale		Bacteraemia, factors related to the development of bacteraemia Microbiology: Bottles with aerobic and anaerobic culture media were processed in Bactec 9240, each positive culture was gram stained, Bacteria isolated were identified using biochemical tests provided by the Vitek system	Grant from Xunta de Galicia

[85] the final blood sample could only be obtained from 50 patients because of technical reasons

Effect size:

Oral health scale
n = 10 (19%) were grades 0-1, n = 21(40%) were grade 2 and n = 22(41%) were grade 3

Bacteraemia
At baseline, 9.4% had positive blood cultures, at 30sec 96.2%, at 15min 64.2% and at 1hr 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

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Van der Meer JT TJVHMMF. Epidemiology of bacterial endocarditis in The Netherlands. I. Patient characteristics. *Arch Intern Med.* 1992;**152**:1863-8. Ref ID: 518	Prospective consecutive case series	n = 559 reported episodes of suspected endocarditis following, n = 438 episodes in n = 432 patients Netherlands	All cases of patients in the Netherlands who were suspected of having BE on the basis of blood cultures, reported by microbiologists Exclusion: due to the application of Von Reyn criteria and being denied access Median age was 52yrs (range 2-89yrs) A recurrence was considered to be when there was at least 6-mths between episodes or when a different micro-organism was isolated	Patients were visited for an in-person interview while in hospital and medical records were reviewed	1st November 1986 to 1st November 1988		Patient characteristics, native valve endocarditis, prosthetic valve endocarditis	Netherlands Heart Foundation

Effect size: [86]

n = 349/438 (79.7%) involved a native valve and n = 89 (20.3%) involved a prosthetic valve
The crude incidence of BE was 15 per million person-years, adjusted for age and sex was 19 per million person-years

Native valve
NVE – total n = 349, crude incidence of NVE was 12 per million person-years, adjusted for age and sex was 15 per million person-years
n = 197 (56.4%) had a previously known cardiac lesion predisposing to BE
n = 145 (41.6%) had heart disease at admission that had not been recognised previously
n = 7 (2%) had no heart disease

[86] Population figures of January 1988 adjusted for births, deaths, and migration were used to estimate incidence rates

Mitral valvular disease (n = 125, 35.8%) and aortic valvular disease (n = 110, 31.5%)
Mitral valve prolapse was present in n = 29 (8.3%), of these 86% (n = 25) were known to have the condition

Underlying heart disease in n = 349 NVE

Aorta	**110(31.5%)**	**Mitral**	**125(35.8%)**
Bicuspid valve	2	Prolapse	1
Bicuspid valve & AOI/AOS	3	Prolapse & regurgitation	27
Sclerotic valve	7	Prolapse & stenosis	1
Regurgitation	64	Regurgitation	89
Regurgitation & stenosis	17	Regurgitation & 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 & stenosis	36	Pulmonary regurgitation	1
Congenital heart disease	**38(10.9%)**	Pulmonary & tricuspid regurgitation	1
ASD	1	**Other**	**19(5.4%)**
VSD	13		
VSD & right sided valvular disease	6		
Patent arterial duct	5		
Fallot's tetralogy	5		
Other	8		

Prosthetic valve
PVE – total n = 89, crude incidence of PVE was 3 per million person-years, adjusted for age and sex was 6 per million person-years
n = 11 (12.4%) had early PVE (≤60 days after implantation) and n = 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

Previous endocarditis
n = 50 one or more recurrences, n = 6 had 2 episodes during the time of the survey, n = 44 previous endocarditis and one episode during the study time
n = 51 recurrences (n = 30 NVE and n = 21 PVE)

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of fundin g
van der Meer JT, Thompson J, Valkenburg HA, Michel MF. Epidemiology of bacterial endocarditis in The Netherlands. II. Antecedent procedures and use of prophylaxis. *Arch Intern.Med* 1992;**152**:1869-73. Ref ID: 32	Prospective case series	n = 427	Included: late prosthetic or native valve endocarditis	Structured questionnaire to interview patients (pr proxy respondents) about procedures undergone within 180 days of the onset of symptoms, all information was checked with dental and/or medical practitioners If antibiotic prophylaxis had been used the dose and route of administration were checked with the presciber and/or pharmacist			Antecedent procedures Use of prophylaxis	Netherla nds Heart Foundati on

Effect size:

Antecedent procedures
n = 149/427 (34.9%) had undergone a procedure within 180days of the onset of symptoms, n = 31 were excluded as it was unlikely that the agent isolated from the blood was related to the procedure, n = 29 excluded as the procedure did not have indications for prophylaxis [87].
Therefore n = 89 (20.8%) had undergone a procedure for which prophylaxis was indicated within the previous 180days of the onset of symptoms; n = 48 (24.4%) of those with NVE (n = 197) who were known to have heart disease, n = 25 (16.4%) of those who were not and n = 16 (20.5%) of the n = 78 with late PVE

Prophylaxis indications
Prophylaxis was definitely indicated in n = 55 of the 89, for n=34 of the procedures the indication for prophylaxis was not certain (33 had had dental cleaning and 1 had had a cystoscopy)

Actual prophylaxis
NVE
n = 8/48 (16.7%) with NVE who had known heart disease had antibiotics in accordance with guidelines, n = 2 received antibiotics not in accordance with guidelines (should have provided adequate protection)
In those cases where endocarditis developed despite prophylaxis, the bacteria never were resistant to the administered antibiotics

For n = 25 procedures in patients with native valves without known heart disease, prophylaxis would have been indicated had the cardiac lesion been known

Those known to have heart disease and those not did NS differ in the proportion of dental procedures; 92% (n = 44/48) and 76% (n = 19/25) respectively

PVE
n = 9/16 (56.3%) of those with prosthetic valves had antibiotics, n = 8 received antibiotics not in accordance with guidelines (could be considered to offer equivalent protection)
n = 5/16 had cardiac surgery, n = 8/16 had a dental procedure

Dental status, recent dental procedure
Endocarditis due to α-haemolytic streptococci in those with NVE appeared to be associated with; the presence of known heart disease, natural dentition, the performance of recent dental procedures, with endocarditis occurring x4.9 more often among those with all 3 factors than among those without any (RR 4.9, CI 2.8 to 8.7). For those with 1 or 2 factors the risk was in between (RR 1.9, CI 1.0 to 3.5 and RR 2.9, CI 1.6 to 5.3 respectively).

In those with late PVE; natural dentition, and a recent dental procedure, endocarditis was caused by α-haemolytic streptococci x2 as often as in other patients with

[87] Recommendations for the use of antibiotic prophylaxis to prevent endocarditis were established by a working group from the Netherlands Heart foundation and

late PVE (RR 2.6, CI 1.4 to 4.6)

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
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.	Case control	n = 48 Netherlands	Cases included: those with known cardiac disease 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	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 Cases from Nov 1986 to Nov 1988 who	Controls selected from outpatients of the cardiology department of the university hospital and 4 regional hospitals, of n = 200 controls included in the analysis, none got endocarditis within 180 days of the procedure		Procedures, interval from procedures to onset, antibiotic prophylaxis	Netherlands Heart foundation

corresponded with the recommended prophylaxis in the US and GB

			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)	were consecutively admitted to hospital				

Effect size:

Cases
Total number of procedures was n = 48, n = 44 dental and n = 4 other, prophylaxis was definitely indicated in n = 28 of the 48 procedures. For the other n = 20 the indication for prophylaxis was not certain, all involved the removal of tartar
Median interval between the procedure and onset of symptoms was 72.5 days (range 3-170) for those with a possible indication for prophylaxis and 10 days (range 0-175) for other procedures, p<0.001
Antibiotics were given in n = 8/48 (17%) cases[88]
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, 1/104 (1%) of those with a possible indication[89]

Cases and controls
The interval between procedure and onset of symptoms or interview was significantly shorter for cases (median interval 30, range (0-175) than was the interval between procedure and interview for controls (median interval 75, range (0-179). This difference disappeared for procedures with a possible indication and increased for those with a definite indication when analysed separately
(the authors consider that this difference suggests a causal relationship between endocarditis and procedures with a high risk for bacteraemia, such as dental root work or dental extractions, but not between endocarditis and the scaling of teeth)

The use of prophylaxis was similar between cases (17%) and controls (13%).

[88] in accordance with Netherlands Heart Foundation in N=6/8 cases, in the other N=2 the antibiotics could be considered equivalent
[89] in accordance with Netherlands Heart Foundation in N=15 controls, in the other N=11 the antibiotics could be considered equivalent

For procedures within 180days of onset of symptoms[90], the OR was 1.04 (90%CI, 0.36 to 2.99) for first time episodes and 3.63 (0.98 to 13.4) for recurrent episodes For procedures within 30days of onset of symptoms[91], the OR was 0.51 (0.11 to 2.29) for first time episodes and 2.13 (0.48 to 9.44) for recurrent episodes *(the authors consider that the stratified OR of 0.51 for cases with first-time endocarditis and a procedure within 30days of onset seems to provide the best estimate of the risk reduction obtained with prophylaxis, since 30days is a more likely incubation period than 180days. On the assumption that the incubation period is 30days, the protective effect of prophylaxis is 49%, this is NS)* Endocarditis developed within 30days of a procedure in n = 25/197 (12.7%) of those with a previously diagnosed heart lesion

[90] stratified for age and certainty of indication
[91] stratified for age and certainty of indication

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Verheul HA, van den Brink RB, van Vreeland T et al. (1993) Effects of changes in managemen t of active infective endocarditis on outcome in a 25-year period. American Journal of Cardiology 72: 682-7	Case series	n = 130 (n = 141 episodes) Study between 1966 and 1991 The Netherla nds	Inclusion: consecutive patients with a diagnosis of active endocarditis at the cardiology department, von Reyn criteria used to define probable and possible episodes of IE Exclusion: endocarditis of a valve prosthesis 59% of patients had a murmur or cardiac lesion was known before admission			The end of the follow-up period was 1st January 1991 (only 1 patient was lost to follow-up), total follow-up 790patient-years, mean follow-up was 8.7yrs (range 0.3 to 23.5)	Early mortality, late mortality and survival, late morbidity	Not stated

Effect size:

Early mortality
Overall 26%, medically treated was 27% at 1mth and 29% at 3mths [92]
Causes of death (medically treated); severe heart failure and cardiogenic shock (n = 13), acute intractable rhythm disturbances (n = 6), major cerebral emboli (n = 5), ruptured cerebral mycotic aneurysms (n = 2), DIC (n = 1), bleeding oesophageal varices (n = 1)

Logistic regression analysis marked heart failure as an independent determinant of mortality within 3mths after admission
Early mortality with severe heart failure was 68% (RR 21.1; 7.4 to 60.3, 95%CI) compared with those without severe heart failure
High risk for urgent surgery or death, or both; patient with heart failure (RR 47.6; 9.1 to 249.0, 95%CI); those with aortic valve endocarditis (RR 3.0; 1.7 to 14.3, 95%CI)

Late mortality and survival
n = 91/101 survived the hospital phase, during follow-up n = 19 (29%) died (cardiac cause of death n = 13)

Late morbidity
n = 60 medically treated patients; valve replacement n = 17 (28%), relapsing endocarditis n = 1, recurrent endocarditis n = 10
n = 31 surgically treated patients; recurrent endocarditis n = 1
At the end of follow-up n = 64 patients were alive, of these n = 45 were without recurrent endocarditis or valve replacement, only n = 33/45 were without any cardiac complaints

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Wahlmann U, Al Nawas B, Jutte M, Wagner W. Clinical and	RCT [93]	n = 59 Germany	Inclusion: patients with multiple tooth extraction in preparation for radiotherapy of oral cancer, n = 54 male, mean age 46yrs (range 31 to 81yrs)	n = 30 1.5g IV cefuroxime 10mins before multiple tooth extractions	n = 29 placebo (0.9% NaCl)		Bacteraemia Cefuroxime levels were determined by	Not stated

[92] Death within 30days after admission or operation was defined as early mortality; late mortality was defined as death after 3months; relapsing endocarditis was defined as persistent infection after termination of antibiotic treatment after a complete course
[93] details of randomisation not given

microbiological efficacy of single dose cefuroxime prophylaxis for dental surgical procedures. *International Journal of Antimicrobial Agents* 1999;**12**:253-6			Exclusion: those with allergy to cephalosporins, had received antibiotics in the past 3wks, those with an absolute indication for perioperative chemoprophylaxis	Blood samples: 10mins and 40mins after the start of the administration of the drug (for cefuroxime levels), at the start of the surgical procedure, 30min later in the control group			HPLC Blood was inoculated into a Signal System and processed according to the manufacturer's recommendations	
Effect size: A mean of 8.8 teeth were extracted in each patient **Bacteraemia** n = 54/118 cultures were positive A significantly lower rate of bacteraemia was identified after cefuroxime administration at 10min (cefuroxime n = 7/30, 23% vs. 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%) There was NS difference in the occurrence of bacteraemia and oral hygiene or periodontal status The duration of the surgical procedure had NS effect on bacteraemia rates There was NS difference for <6 or 6-10; for >10 teeth extracted there was a statistically significant difference n = 7 (70%) cefuroxime vs. n = 8 (89%) control group n = 46/53 (87%) strains studies were susceptible to cefuroxime								

Reference	Study type/	Number of	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of

	Evidence level	patients						funding
Wang A, Pappas P, Anstrom KJ et al. (2005) The use and effect of surgical therapy for prosthetic valve infective endocarditis: a propensity analysis of a multicenter, international cohort 728. American Heart Journal 150: 1086-91	Cohort	n = 355	Inclusion: PVE from the International Collaboration on Endocarditis Merged Database (ICE-MD), (7sites in 5countries contribute), Duke criteria used to determine PVE Exclusion: recent history of IV drug use				In-hospital complications	Not stated
Effect size: n = 2212 in the merged database, definite PVE in n = 355 **In-hospital complications** Total; CHF 38.6%, systemic embolisation 27.3%, brain embolisation 18.9%, intracardiac abscess 19.4%, inhospital death 24.1% CHF significantly more likely following surgery vs. no surgery (28.0% vs. 53.4%, p<0.001) they were also significantly more likely to have intracardiac abscess (8.2% vs. 35.1%, p<0.001) Logistic regression analysis of variables independently associated with inhospital mortality in patients with PVE and matched propensity for surgical treatment; S aureus infection (OR 3.67, 1.39 to 9.74, P=0.009) and brain embolisation (OR 11.12, 4.16 to 29.73, p<0.001) were independently associated with inhospital mortality								

Multivariate analysis of n = 137 patients who had a high propensity score for surgery similar results were found to be predictive of inhospital death; S aureus (OR 4.28; 1.23 to 14.91), brain embolisation (OR 2.52; 1.02 to 6.21)

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
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	Observational cohort	n = 556	Inclusion: patients with PVE defined by Duke criteria enrolled in the International Collaboration on Endocarditis-Prospective Cohort Study (61 medical centres in 28 countries)			Study from June 2000 to August 2005	In-hospital mortality, complications and outcomes	American Heart Association Grant-in-Aid
Effect size: n = 2670 with definite IE, n = 556 (20.1%) PVE Those with PVE; aortic valve n = 384 (69.1%), mitral valve or ring n = 280 (50.4%), prosthetic pulmonic valve n = 31 (5.6%) 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								

Complications and outcomes
Significant difference PVE vs. NVE;
- other systemic embolisation higher with NVE; 83 (14.9%) vs. 468 (24.7%), p<0.001
- in-hospital death higher with NVE; 127 (22.8%) vs. 310 (16.4%), p<0.001

NS difference between PVE and NVE;
- heart failure, stroke, surgery during admission, persistent bacteria

Regional comparison – mortality
In-hospital mortality rates were NS different between the regions

PVE in-hospital death n = 127 (22.8%) was predicted by age,
- healthcare associated infection n = 62 (30.5%), adjusted OR 1.62 (1.08 to 2.44), p=0.02
- S aureus infection n = 44 (34.4%), adjusted OR 1.73 (1.01 to 2.95), p=0.05
- heart failure n = 60 (32.8%), adjusted OR 2.33 (1.62 to 3.34), p<0.001
- stroke n = 34 (33.7%), adjusted OR 2.25 (1.25 to 4.03), p=0.007
- intracardiac abscess n = 47 (32.6%), adjusted OR 1.86 (1.10 to 3.15), p=0.02
- persistent bacteraemia n = 27 (55.1%), adjusted OR 4.29 (1.99 to 9.22), p<0.001

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
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	Consecutive case series	n = 100	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	n = 50 group I convention laparoscopy	n = 50 minilaproscopy Blood samples: immediately before laproscopy and within 5mins after the procedure		Blood cultures 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	Not stated

Effect size:

Blood cultures
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

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Yigla M, Oren I, Bentur L, Solomonov A, Elias N, Altshuler R *et al*. Incidence of bacteraemia following fibreoptic bronchoscopy. *European Respiratory Journal* 1999;**14**:789-91. Ref ID: 5944	Consecutive case series	n = 200 Rambam Medical Centre, Israel	Inclusion: underwent fibreoptic bronchoscopy during the study period. Mean age 54±24yrs (range 6mths to 94yrs), n = 29 (14.5%) were <18yrs and N-171 (85.5%) adults, n = 152 (76%) males, n = 48 (24%) females. n = 119 (59.5%) bronchoscopy for suspected malignant tumours, n = 20 for recurrent pneumonia, n = 14 for haemoptysis, n = 13 for stridor, n = 8 diffuse lung infiltrates, n = 6 bronchiectasis, n = 8 other Exclusion: patients with current respiratory tract infection or febrile illnesses and those receiving antibiotic therapy within a week prior to the bronchoscopy	Procedures were performed transnasally using flexible, fibreoptic bronchoscopes (size 3.6-6mm) n = 90 (45%) bronchial biopsy, brushing and lavage n = 57 (28.5%) brushing and lavage n = 39 (19.5%) lavage n = 11 (5.5%) transbronchial biopsy, brushing and lavage n = 3 bronchoscopy solely for observation, no specimens obtained	Blood samples: immediately following the bronchoscopy, 10 to 20mins later (prebronchoscopy blood cultures from the first 100 patients were negative, excluding transient incidental bacteraemia)		Bronchoscopy findings, bacteriological findings Microbiology: aerobic and anaerobic blood culture bottles, incubated in a Bac-T-Alert incubator for a period of ≤5days at 37˚C	Not stated

Effect size:

Fibreoptic bronchoscopy findings
n = 70 had a normal study and n = 130 showed abnormalities (n = 50 inflamed bronchial mucosa, n = 49 endobronchial lesions, n = 31 signs of external pressure on major bronchi)

Bacteriological findings
Blood cultures
n = 26 (13%) had positive blood cultures following fibreoptic bronchoscopy, these were n = 13 at 0 and 20min; n = 13 at 20min+ (organisms identified were Staphylococcus coagulase negative (n = 18), Staphylococcus coagulase positive (n = 3), Nonhaemolytic streptococci (n = 2), Beta haemolytic streptococci (n = 1), Kledsiella rhinoscleromatis (n = 1), Klebsiella species (n = 1)
Defining true bacteraemia as episodes in which two postbronchoscopy positive blood cultures yielded the same organism decreased the bacteraemia rate to 6.5% (n = 13/200)

Lavage fluid
Cultures from lavage fluid yielded normal flora in n = 120 patients and potentially pathogenic bacteria in n = 80

Procedures
For the n = 13 with true bacteraemia showed that bronchial biopsy, brushing and lavage were performed in n = 5; brushing and lavage in n = 4; lavage only in n = 2 (the remaining n = 2 had no specimens obtained with bronchoscopy solely for observation)

Indications for fibreoptic bronchoscopy, macroscopic findings, size of bronchoscope used, and rate of invasive procedures performed during bronschocopy did not differ significantly between the n = 13 patients with true bacteraemia and the n = 187 without bacteraemia

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Yildirim I, Okur E, Ciragil P, Aral M, Kilic MA, Gul M. Bacteraemia	Consecutive case series	n = 64	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	n = 33, group I Blood samples: pre-operative (after intubation),	n = 31, group II Blood samples: pre-operative (after intubation),		Blood cultures Microbiology: 6ml (those under 10yrs), 16-18ml)those >10yrs),	Kahramanmaras Sutcu University Research

during tonsillectomy. *Journal of Laryngology & Otology* 2003;**117**:619-23. Ref ID: 238			female Exclusion: any cardiovascular risk factors, had received antibiotic therapy for at least 20days before the operation	early post-operative (within 2mins after tonsillectomy) and post-operative (60mins after tonsillectomy) Tonsillar surface and deep tissue cultures were taken	post-operative (15 and 60mins after tonsillectomy) Tonsillar surface and deep tissue cultures were taken		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	Fund

Effect size:

Blood cultures
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[94], 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 without hospitals

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Zuccaro G, Jr., Richter JE, Rice TW, Achkar E, Easley K, Lewis J *et al*. Viridans streptococcal bacteremia after esophageal stricture dilation.[see comment].	Controlled trial	n = 153 USA	Inclusion: consecutive patients with dysphagia presenting for upper endoscopy and stricture dilation, without valvular disease[95]. 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	n = 103 with dysphagia having upper endoscopy and stricture dilation Blood samples: pre-procedure, 5, 20 and 30mins after the procedure	n = 50 control, without dysphagia or oesophageal disease undergoing upper endoscopy for reasons unrelated to swallowing disorders	9mth study period	Blood cultures Microbiology: 20ml sample, 10ml inoculated into commercially prepared blood culture bottles, the bottles were then incubated for 5days ion the BacT/Alert instrument, when a blood culture	Not stated

 Group A β-haemolytic streptococci
[95] those with valvular disease had antibiotics according to AHA guidelines

Gastrointestinal Endoscopy 1998;**48**:568-73. Ref ID: 5981							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	

Effect size:

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)

Blood cultures
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

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

6.5 Appendix 5 – References

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6.6 Appendix 6 – De novo economic analysis

Aims

A simple economic evaluation was undertaken to estimate the cost-effectiveness of antibiotic prophylaxis for infective bacterial endocarditis in adults with predisposing cardiac conditions undergoing dental procedures.

In the model, nine antibiotic prophylaxis options were compared with each other and against a strategy of no antibiotic prophylaxis. The prophylactic options explored were those set out in BNF 54 (see table 11).

Table 1 Antibacterial prophylaxis options (based on section 5.1, table 2 of adult BNF [54])

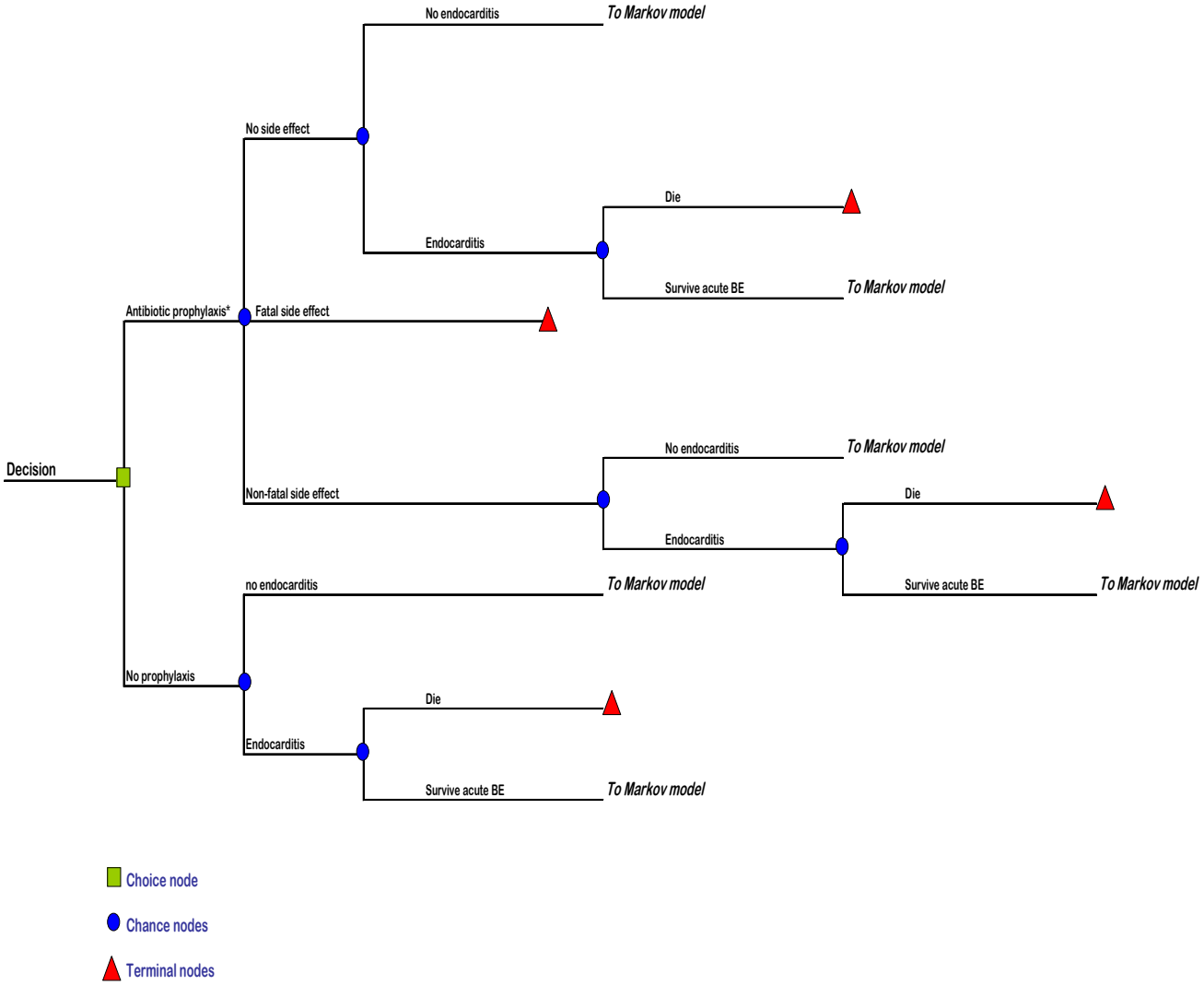
Dental procedures under local or no anaesthesia		
Patients who have not received more than a single dose of a penicillin in the previous month, including those with a prosthetic valve (but not those who have had IE)	oral amoxicillin 3g 1 hour before procedure	Strategy 1
Patients who are penicillin-allergic or have received more than a single dose of a penicillin in the previous month.	oral clindamycin 600 mg 1hour before the procedure	Strategy 2
Previous endocarditis	amoxicillin plus gentamicin as under general anaesthesia	Strategy 5a
Dental procedures under general anaesthesia		
No special risk (including patients who have not received more than a single dose of a penicillin in the previous month)	EITHER IV amoxicillin 1 g at induction, then oral amoxicillin 500 mg 6 hours later; OR oral amoxicillin 3 g four hours before induction then amoxicillin 3 g orally as soon as possible after procedure.	Strategies 3 and 4 respectively
Special risk (patients with a prosthetic valve or who have had endocarditis)	IV amoxicillin 1g + IV gentamicin at induction 120 mg, then oral amoxicillin 500 mg 6 hours later	Strategy 5b
Patients who are penicillin-allergic or who have received more than a single dose of a penicillin in the previous month.	EITHER IV vancomycin 1g over at least 100 minutes then IV gentamicin 120mg at induction or 15 min before procedure OR IV teicoplanin 400 mg + gentamicin 120 mg at induction or 15 min before procedure OR IV clindamycin 300 mg over at least 10 min at induction or 15 min before procedure then oral or IV clindamycin 150 mg 6 hours later.	Strategies 6, 7 and 8 respectively

As is apparent from the strategies listed above, different subgroups of patients would be selected for different strategies. For example, those patients with a known allergy to penicillin undergoing a dental procedure requiring only local anaesthesia would receive oral clindamycin, according to the recommendations in BNF 54. Dental procedures may need to be undertaken under general anaesthesia, for example due to severe disability: under these circumstances, strategies 3 to 8 become relevant. For these reasons therefore, all strategies will be compared to a no prophylaxis option.

Method

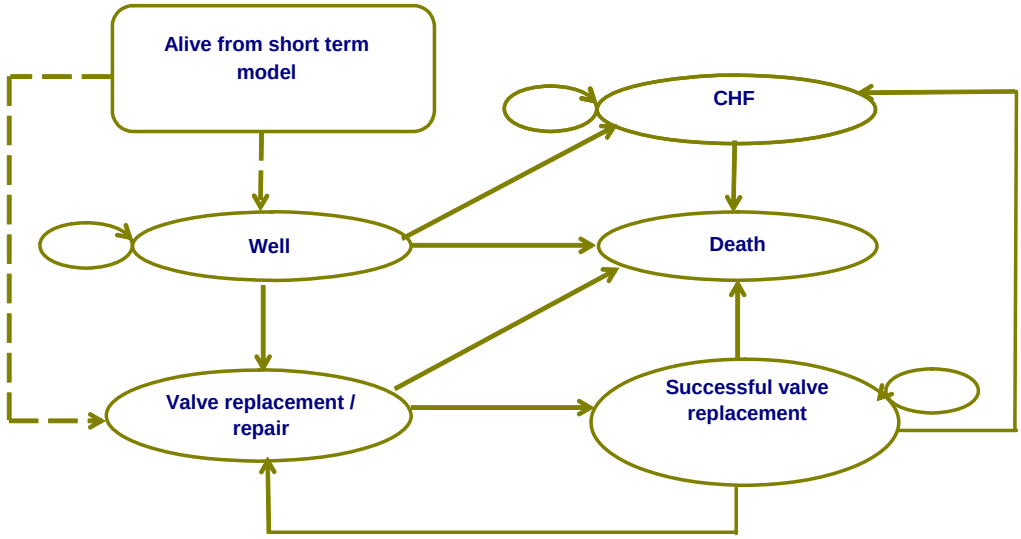
The economic evaluation was based on the one developed by Agha et al. It consists of a decision tree representing the short term (3-month) consequences for at risk patients undergoing a dental procedure requiring a course of antibiotic prophylaxis (as per current recommendations). In addition, a 5-state Markov process was used to estimate long term costs and health outcomes (see figures 1 and 2). This deterministic cohort model was developed using the Microsoft software package Excel.

Figure 1 Diagrammatic representation of the short-term (3 month) decision tree



* Eight antibiotic prophylaxis strategies are being evaluated

Figure 2 Diagrammatic presentation of the Markov process. States in the model are represented by the ovals, transitions between states by the arrows.



The short term model generates an estimate of the number of endocarditis cases prevented following a single course of antibiotics. In addition it also provides an estimate of the cost per endocarditis case prevented. The costs and outcomes generated in the short term model cover a period of approximately 3 months and assume that IE will develop within 60 days of a dental procedure and that treatment will last up to 6 weeks.

The Markov process provides an estimate of health outcomes in terms of quality-adjusted life years (QALYs). The analysis adopts a lifetime horizon (50 years), and follows a hypothetical cohort of 10 million individuals from a given starting age until death. (An analysis based on a 10-year time horizon was also undertaken.) Cycle length was set at 1 year. Simple deterministic sensitivity analyses were used to explore the contribution of individual parameters to overall uncertainty in the cost effectiveness estimates. 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. Consequently probabilistic sensitivity analysis was not undertaken.

Transition probabilities and treatment effects

Table 12 sets out the transition probabilities and epidemiological parameter estimates used in the short term model and for the Markov process. A half

cycle correction was applied to costs and QALYs when modelling long term outcomes.

Risk of IE following a dental procedure

The estimate of risk used by Agha et al in their base case analysis was considered by the GDG to over inflate the actual risk by a wide margin. Consequently for the present analysis an estimate of 4.1 cases per million procedures was used as the base case value. This lower estimate was taken from the study by Clemens and Ransohoff (1984). In that study it was assumed that patients would on average undergo 1.5 dental procedures per year.

Clemens and Ransohoff (1984), Agha et al (2005) and Duval et al (2006) used a similar approach when estimating the risk of developing IE following a dental procedure. The approach taken in all these studies is based on the following equation:

Risk of IE following an unprotected dental procedure = (Incidence of IE multiplied by the proportion of incident cases that would have occurred in adults with a predisposing cardiac condition (PCC) multiplied by the proportion of PCC IE cases attributed to dental procedures) **divided by** (number of dental procedures per patient per year multiplied by the prevalence of PCC).

Using Duval's French survey data, the risk of developing IE in the absence of antibiotic prophylaxis can be calculated for all patients with a PCC, for patients with a prosthetic valve, and for patients with a native valve, as shown below.

Risk of BE (all PCCs) = (35 per million x 52.1% x 5.2%) divided by (1.32 x 3.3%)

22 per million (per dental procedure)

Risk of BE (native valves) = (35 per million x 35.8% x 6.1%) divided by (1.54 x 2.7%)

18 per million (per dental procedure)

Risk of BE (prosthetic) = (35 per million x 16.4% x 3.1%) divided by (0.33 x 0.6%)

93 per million (per dental procedure)

As can be seen, the risk of developing infective endocarditis was calculated to be 22 per million for all individuals with a PCC. This was also the exact estimate used by Agha et al in their base case analysis, although with different input parameters into the equation. In the present study, sensitivity analysis was undertaken on the base case risk estimate using the alternative values of 22 per million and 93 per million, taking into account differences in the estimated number of dental procedures received by individuals per year as indicated in the French study.

Table 2 Summary of model epidemiological parameters, values and sources

Parameter	Base case	Lower	Upper	Source/comment
Estimated risk of IE following a dental procedure	4.1 per million	NA	22 - 93 per million	Clemens & Ransohoff (1984), Duval et al (2006). See text. Base case assumed 1.5 dental procedures per year.
Efficacy of prophylaxis	0.5	0.25	0.75	Assumed (see text)
Probability of mortality from acute endocarditis – native valves	0.164	Varied by +/- 50%		This was used as the base case value. Wang et al (2007); Tornos et al (1992)
Probability of mortality from acute endocarditis – prosthetic valves	0.228	Fixed		Wang et al (2007)
Annual probability of developing congestive heart failure (CHF) following acute endocarditis	0.083	Varied by +/- 50%		Frary et al, 1994. Cumulative incidence of CHF after IE in MVP patients was 50%. Estimate here based on mean follow up of 8 years
Annual probability of developing congestive heart failure (CHF) (non endocarditis cases)	0.006	Varied by +/- 50%		Frary et al, 1994. Cumulative incidence of CHF after IE in MVP patients was 5%. Estimate here based on mean follow up of 8 years
Annual probability of valve replacement during or immediately following acute IE)	0.34	Varied by +/- 50%		Tornos et al (1992)
Annual probability of valve replacement, years 1 to 10 (non endocarditis cases)	0.004	Varied by +/- 50%		Zuppiroli et al (1995)
Probability of valve replacement, years 1 to 10 (endocarditis cases) – applies to redo surgery too	0.013	Varied by +/- 50%		Estimate based on UK valve registry data for PVE patients (Edwards et al, 1998)
Probability of redo valve replacement, years 1 to 10 – all patients	0.013	Varied by +/- 50%		Estimate based on UK valve registry data for PVE patients (Edwards et al, 1998)
Probability of valve replacement, after ten years (all patients) –	0.004	Varied by +/- 50%		Zuppiroli et al (1995)

applies to redo surgery too				
Probability of death from valve surgery.	0.082	Varied by +/- 50%		Lung et al, 2003. Euro Heart Survey on Valvular disease – 'Mitral Valve Repair or replacement + CABG'
Overall mortality risk by age and sex	E and W all-cause mortality data			Government Actuary's Department, 2003-2005 interim life table data. A mortality profile excluding cardiovascular death risk was also applied in sensitivity analysis (source data: Fox et al, 2006)
Probability of death for patients with a 'successful' valve replacement	Weibull function (lambda = 0.144; gamma = 0.368			Long-term survival following surgery for prosthetic endocarditis (UK heart valve registry). Edwards et al, 1998 (see text for further details)
Probability of death for all patients developing CHF	Weibull function as per patients with a 'successful' valve replacement / repair			Edwards et al, 1998
Probability of non fatal hypersensitivity to amoxicillin	0.00	0	0.1	deShazo and Kemp (1997); cited in Agha et al (2005)
Probability of non fatal hypersensitivity to clindamycin	0.00	0	0.1	Assumed
Probability of non fatal hypersensitivity to vancomycin	0.00	0	0.1	Assumed
Probability of non fatal hypersensitivity to gentamicin	0.00	0	0.1	Assumed
Probability of non fatal hypersensitivity to teicoplanin	0.00	0	0.1	Assumed
Probability of fatal anaphylaxis from amoxicillin	0 per million	N/A	40 per million	Idsoe et al (1968), Ahlstedt (1984); cited in Agha et al (2005)
Probability of fatal anaphylaxis from other antibiotics	0 per million	Fixed	5 per million	Mazur et al (1999) clindamycin. Assumed same value for other antibiotics.

According to the data presented by Duval et al (2006), the prevalence of PCC varies by age.

Table 3 Prevalence of PCC by age

Age	%
25–35	1
35–45	< 1
45–55	3.3
55–65	6
65–75	7
75–84	About 7.5

Consequently, the starting age of the hypothetical cohort of patients was set at 50 years of age (all male).

Antibiotic effectiveness

There is no RCT evidence on the efficacy of antibiotic prophylaxis in the population of interest. Of the available case control data, the Cochrane review found no statistically significant effect of penicillin prophylaxis, even when the pooled estimate was based using studies previously excluded. Agha et al (2005) estimated a pooled OR of 0.46 (CI, 0.2 – 1.1) after applying the Mantel Haenzel procedure on the data from four case control studies (Van der Meer et al, 1992; Strom et al, 1998, Lacassin et al, 1995; and Imperiale & Horwitz, 1990). For the present analysis it was assumed that the relevant antibiotic strategies were all potentially equally effective (there is no evidence to suggest otherwise). Given the absence of any robust data to inform the effectiveness estimate, the base analysis assumed that antibiotics reduced the risk of infective endocarditis by half. This estimate was varied by +/- 50% in sensitivity analyses.

Short term outcomes from an acute endocarditis infection

In the base case, it was assumed that there would be a 16.4% risk of death from an acute endocarditis infection. This was based on data from patients who developed native valve infective endocarditis (Wang et al, 2007). For patients with a prosthetic valve, the short term risk of death was assumed to be 22.8% (Wang et al, 2007). It was also assumed that 34% of all cases of

infective endocarditis would require valve replacement during or immediately after an acute IE infection. This estimate was based on a cohort study of Spanish patients with native valve infective endocarditis (Tornos et al, 1992).

Adverse consequences of antibiotic prophylaxis

It has been reported that fatal anaphylactic reactions to penicillin occur in 15 to 25 per million patients receiving a course of penicillin (Idsoe et al, 1968). Based on the assumptions made by Clemens and Ransohoff in their own analysis, Devereux et al drew a distinction between allergic reactions (including fatal ones), associated with penicillin administered orally (risk of fatal anaphylaxis = 0.9 per million for oral amoxicillin) and a penicillin provided parenterally (risk of fatal anaphylaxis = 15 per million for intravenous ampicillin). In the present instance, it was assumed for each of the penicillin strategies considered in the base case analysis, that individuals have a zero risk of fatal anaphylaxis (patients with a known penicillin allergy would receive alternative strategies). However, it is not clear how many individuals may have an unknown allergy to penicillin, and consequently this estimate was varied between 0.9 and 40 per million in sensitivity analyses.

For other antibiotics considered in the present analysis, the base case estimate also assumes a zero risk of fatal anaphylaxis.

In terms of non fatal allergic reactions, the base case assumes a zero rate of allergic reactions. Reported allergic reactions seem to be often accompanied by poor documentation of the specific allergic reaction (Lee et al, 2000). Sensitivity analysis explored the impact of increases in the probability of non fatal allergic reactions (up to 10%) for all of the antibiotics considered.

Long-term survival and outcomes

It was assumed that individuals who did not develop IE in the short term model, and those patients who recovered from IE without valve replacement would be subject to an all-cause mortality risk based on their age and sex. This annual probability of death was taken directly from the UK Government's Actuarial department. For those patients requiring valve surgery and also those developing congestive heart failure, a risk of death was estimated from

published registry data in patients who developed prosthetic valve endocarditis (Edwards et al, 1998). One, five and ten year survival in this cohort of patients was 67.1%, 55% and 37.6% respectively. Standard regression techniques were used to estimate a Weibull function from this survival data (R squared = 0.87) to which was added the annual probability of death for the general population based on age and sex as described above.

The annual probability of developing congestive heart failure in survivors of infective endocarditis was assumed to be 8.3% based on data from an observational cohort of patients with MVP who developed infective endocarditis (Frary et al, 1994). The mean follow-up in this study was 8 years. This source also provided an estimate of the annual probability of developing CHF in patients with uncomplicated MVP: 0.6%. This estimate was used for patients who do not develop infective endocarditis in the short term model.

The probability of valve replacement in the hypothetical cohort who do not develop IE was estimated to be 0.4% based on data from a prospective study of 316 patients with echocardiographic MVP (mean age 42 +/– 15 years). The mean period of follow-up was 8.5 years (Zuppiroli et al, 1995). UK registry data (Edwards et al, 1998) was used to estimate an annual probability (1.3%) of valve replacement in years 1 to 10 in survivors of an acute episode of infective endocarditis. Individuals in the 'successful valve replacement' heath state, were assigned a re-replacement probability of 1.3%. After ten years, all probabilities relating to the risk of requiring valve replacement were assigned the value of 0.4%. The risk of death from valve surgery was estimated to be 8.2% based on evidence derive from the Euro Heart Survey on valvular disease (Lung et al, 2003).

The analysis also attempted to explore the ongoing risk of infective endocarditis in the hypothetical cohort, and the recurring costs and potential benefits of antibiotic prophylaxis. Quality adjusted life years in the model were adjusted to take into account the future risk of infective endocarditis after antibiotic prophylaxis, taking also into account the risk of fatal anaphylaxis. The model assumes that the risk of developing IE is fixed over the time

horizon of the model (no adjustment is made to the risk of IE according to prior history), and that individuals do not switch to different antibiotic options.

Health related quality of life weights

The New York Heart Association (NYHA) functional classification scheme was the basis for assigning utility weights to the health states in the model (see table 14). Utility estimates were assigned as fixed values within the model.

Table 4 Utility weights used in the model

Health states	Estimate	Lower	Upper	Source / comment
Well	0.930	0.923	0.945	Kirsch and McGuire, 2001. It was assumed that all patients will be in NYHA class I
Valve replacement / repair needed	0.525	0.506	0.546	Calvert et al, 2005. It is assumed that preoperatively, patients will be predominantly in NYHA classes III and IV. (Alexiou et al, 2000). This is probably lower than might be expected, especially since the cycle length is one year.
Successful valve replacement	0.855	0.838	0.879	Kirsch and McGuire, 2001. It is assumed that surviving patients will predominantly be in NYHA classes I and II post valve replacement (Pomerantzeff et al, 2005, Jamieson et al, 1990)
Congestive heart failure	0.610	0.591	0.631	Calvert et al, 2005. The assumption here is that all patients developing CHF will be in NYHA class III. Agha et al (2005) assigned a quality of life weight of 0.57 for the health state "Valve replacement and CHF". Caviness et al (2004) assigned a quality of life weight of 0.40 for CHF.
Hospitalisation with heart failure	0.570	0.480	0.800	McAllister et al, 2005

All patients who do not develop IE, and those who survive an acute episode of IE without valve replacement in the short term model enter the 'Well' state in the long term model. The health-related quality of life for this state was assigned a value of 0.930.

A health related quality of life adjustment for an acute episode of IE was not applied in the model.

Costs

Costs were considered only from the perspective of the NHS. The unit costs of health services were obtained whenever possible from standard national sources. Table 15 summarises the unit cost and resource use estimates considered in the model.

In terms of hospitalisation costs, data was primarily sourced from the National Schedule of Reference Costs 2005-6 for NHS trusts. The average cost cited

within the Schedule for endocarditis (HRG E17) appears less than would be expected, given that IV antibiotic treatment duration could be up to 6 weeks. Therefore, the average cost was uplifted to take into account IV antibiotic treatment using excess bed data for HRG E17 for the increased length of stay. Antibiotic treatment strategies were based on recent recommendations (BSAC, 2007). For simplicity, the base case assumes that all patients are methicillin resistant. Treatment in that instance consists of vancomycin (1g iv 12 hourly) plus rifampicin (300 - 600 mg 12 hourly by mouth). For patients with endocarditis in presence of intracardiac prosthesis, the following regimen is recommended: flucloxacillin (2g 4-6 hourly IV) plus rifampicin (300-600 mg 12 hourly by mouth)

In terms of the long term costs of congestive heart failure and valve replacement/repair, it was assumed that two outpatient cardiology visits are made per year. Patients with CHF are hospitalised on average 0.53 times a year (NICE Chronic Heart Failure guideline, 2003. Available from http://guidance.nice.org.uk/CG5).

For individuals who do develop a non fatal hypersensitivity reaction to an antibiotic, it was assumed that the only cost incurred would be a primary care visit. This is likely to be an underestimate of the true cost, especially since some hypersensitivity reactions may lead to hospitalisation.

When recurring costs were estimated, it was assumed that only one procedure would be undertaken per dental visit, and this may have overestimated the costs of antibiotic prophylaxis. Using the data from Duval et al (2006), for all patients with a PCC, it was assumed that individuals would undergo 1.3 procedures per year. For patients with prosthetic valves, this estimate falls to 0.3 procedures per year.

In the base case, costs and health outcomes were discounted at 3.5% per year in accordance with current NICE recommendations (see the NICE ‘Guide to the methods of technology appraisal’, available from www.nice.org.uk/201973).

Table 5 Unit cost estimates used in the model

Cost	Estimate	Range	Source / comment
Antibiotic prophylaxis (per course)			
Oral amoxicillin 3g 1 hour before procedure	£0.63	Fixed	Adult BNF, September 2007 (Number 54)
oral clindamycin 600 mg 1hour before the procedure	£3.84	Fixed	Adult BNF, September 2007 (Number 54)
IV amoxicillin 1 g at induction, then oral amoxicillin 500 mg 6 hours later;	£1.27	Fixed	Adult BNF, September 2007 (Number 54)
Oral amoxicillin 3 g four hours before induction then oral amoxicillin (3 g)	£1.27	Fixed	Adult BNF, September 2007 (Number 54)
IV amoxicillin 1g plus IV gentamicin at induction 120 mg, then oral amoxicillin 500 mg 6 hours later	£4.21	Fixed	Adult BNF, September 2007 (Number 54); For strategy 5a, add administration costs (see below)
IV vanco 1g over at least 100 minutes then IV gentamicin 120mg at induction or 15 min before procedure.	£19.05	Fixed	Adult BNF, September 2007 (Number 54)
IV teicoplanin 400 mg plus gentamicin 120 mg at induction or 15 min before procedure	£38.56	Fixed	Adult BNF, September 2007 (Number 54)
IV clindamycin 300 mg over at least 10 min at induction or 15 min before procedure then oral or IV clindamycin 150 mg 6 hours later	£9.30	Fixed	Adult BNF, September 2007 (Number 54) Cost estimate based on IV clindamycin being used post procedure.
Secondary care and outpatient costs			
Hospitalisation cost for endocarditis	£3,323	Lower: £1359 Upper: £4528	Non elective cost from National Schedule of Reference Costs 2005-6 for NHS trusts (E17, “Endocarditis”).
Overall hospitalisation cost for endocarditis	£7,013	Up to £10,125 for patients prosthetic valve	Non elective cost from National Schedule of Reference Costs 2005-6 for NHS trusts (E17, “Endocarditis”). To this has been added IV antibiotic treatment costs based on current BSAC guidelines. Reference costs suggest an average length of stay of only 11 days. Therefore cost

		endocarditis	supplemented in line with expected overall treatment duration (4 to 6 weeks) using excess bed day cost data for HRG E17.
Hospitalisation costs for valve surgery	£11,689	Lower: £5,205 Upper: £12,347	Non-elective cost. National Schedule of Reference Costs 2005-6 for NHS trusts. (Based on HRG E03 description – "Cardiac Valve Procedures")
Fatal anaphylaxis	£475	Lower: £331 Upper:£716	Non-elective cost. National Schedule of Reference Costs 2005-6 for NHS trusts. (Based on HRG S26 description – "Shock and anaphylaxis")
Hospitalisation cost for heart failure (< 70 years)	£1390	Lower: £854 Upper: £1963	Non-elective cost. National Schedule of Reference Costs 2005-6 for NHS trusts. (Based on HRG E19 description – "Heart failure or Shock <70 w/o cc")
Hospitalisation cost for heart failure (> 69 years)	£1694	Lower: £1208 Upper: £2560	Non-elective cost. National Schedule of Reference Costs 2005-6 for NHS trusts. (Based on HRG E19 description – "Heart failure or Shock >69 or w cc")
Cardiology OP visit	£104	Lower: £75 Upper: £123	National Schedule of Reference Costs 2005-6 for NHS trusts; Adult outpatient follow-up attendance data (TOPS FUA)
Anticoagulation services	£134	Lower: £102 Upper: £187	National Schedule of Reference Costs 2005-6 for NHS trusts. Based on speciality code HACCF, "Anti-Coagulant Clinic: Face to Face Total Attendances". (TOPS FU)
Administration costs for IV antibiotic prophylaxis (strategy 5a only)	£120	Lower: £90 Upper: £151	National Schedule of Reference Costs 2005-6 for NHS trusts. Based on outpatient speciality code 140F – "Oral surgery: face to face total attendances" (TOPS FAA)
Other costs			
Annual drug cost for patients who have undergone valve surgery	£92.68	Lower: £46.34	Assumed a maintenance dose of warfarin of 6 mg per day. (Lower cost = 3 mg; upper value = 9 mg). Unit costs of

		Upper: £139.03	warfarin from BNF 54
		Lower £200.75	Based on resource use estimates for patients in NYHA class III (Fox et al 2006; Technology Appraisal assessment report)
Annual drug cost for patients with heart failure	£247.61	Upper: £341.07	
Cost for non fatal allergic reaction	£25	Fixed	PSSRU 2005/6. GP consultation lasting 10 minutes

Results

Short term model

In the base case if ten million patients underwent prophylaxis, an estimated 21 cases of IE are prevented and deaths due to BE are reduced from 7 to 3. Table 6 presents the data on the estimated short term costs associated with each strategy.

Table 6 Short term costs (base case analysis)

Antibiotic strategy	AB drug and administration costs	Other costs	Total	Cost per BE death averted (versus no AB)
No antibiotic	£0	£450,298	£450,298	NA
Oral amoxicillin (strategy 1)	£6,342,857	£225,149	£6,568,006	£1,819,663
Oral clindamycin (strategy 2)	£38,383,333	£225,149	£38,608,482	£11,349,847
IV amoxicillin then oral amoxicillin (strategy 3)	£12,657,143	£225,149	£12,882,292	£3,697,797
Oral amoxicillin before and after (strategy 4)	£12,685,714	£225,149	£12,910,863	£3,706,295
IV amoxicillin, IV gent then oral amoxicillin (strategy 5a)	£1,242,057,143	£225,149	£1,242,282,292	£369,372,990
IV amoxicillin, IV gent then oral amoxicillin (strategy 5b)	£42,057,143	£225,149	£42,282,292	£12,442,592
IV vanco and IV gent (strategy 6)	£190,500,000	£225,149	£190,725,149	£56,595,732
IV teicoplanin and IV gent (strategy 7)	£385,600,000	£225,149	£385,825,149	£114,626,666
IV clindamycin (strategy 8)	£93,000,000	£225,149	£93,225,149	£27,595,137

Tables 7 (10 years) and 8 (50 years) provide estimates derived from the long term model of the incremental cost per QALY for the various antibiotic prophylactic options. These estimates exclude the costs and potential benefits

of ongoing antibiotic use. Tables 9 and 10 present the same results including these long term costs and benefits.

The difference between each antibiotic prophylaxis option in terms of average QALYs per person is very small. For the base case (50 year time horizon), the no antibiotic prophylaxis option generated a mean 15.255 QALYs per person. For all of the antibiotic options, the QALY gain was of the order of only 0.00001. This is equivalent to an extra 5 minutes of quality adjusted time. If the potential benefits of ongoing prophylaxis are included, this QALY gain increases to 0.00009, equivalent to approximately 50 minutes of quality adjusted time.

Table 7 Ten year incremental cost effectiveness ratios (antibiotics versus no antibiotics). Excluding estimated costs and potential benefits of future antibiotic prophylaxis. (Base case)

Antibiotic strategy	Costs per person	QALYs per person	Incremental cost effectiveness ratio (versus no antibiotics)
No antibiotic	£673	7.53409	NA
Oral amoxicillin (strategy 1)	£674	7.53410	£204,167
Oral clindamycin (strategy 2)	£679	7.53410	£1,276,523
IV amoxicillin then oral amoxicillin (strategy 3)	£675	7.53410	£415,498
Oral amoxicillin before and after (strategy 4)	£675	7.53410	£416,454
IV amoxicillin, IV gent then oral amoxicillin (strategy 5a)	£859	7.53410	£41,562,056
IV amoxicillin, IV gent then oral amoxicillin (strategy 5b)	£679	7.53410	£1,399,481
IV vanco and IV gent (strategy 6)	£701	7.53410	£6,367,687
IV teicoplanin and IV gent (strategy 7)	£731	7.53410	£12,897,453
IV clindamycin (strategy 8)	£687	7.53410	£3,104,478

Table 8 Lifetime (50 year time horizon) incremental cost effectiveness ratios (antibiotics versus no antibiotics). Excluding estimated costs and potential benefits of future antibiotic prophylaxis. (Base case)

Antibiotic strategy	Costs per person	QALYs per person	Incremental cost effectiveness ratio (versus no antibiotics)
No antibiotic	£2,507	15.25255	NA
Oral amoxicillin (strategy 1)	£2,508	15.25256	£88,069
Oral clindamycin (strategy 2)	£2,513	15.25256	£551,284
IV amoxicillin then oral amoxicillin (strategy 3)	£2,509	15.25256	£179,356
Oral amoxicillin before and after (strategy 4)	£2,509	15.25256	£179,769
IV amoxicillin, IV gent then oral amoxicillin (strategy 5a)	£2,693	15.25256	£17,953,043
IV amoxicillin, IV gent then oral amoxicillin (strategy 5b)	£2,513	15.25256	£604,397
IV vanco and IV gent (strategy 6)	£2,536	15.25256	£2,750,466
IV teicoplanin and IV gent (strategy 7)	£2,565	15.25256	£5,571,067
IV clindamycin (strategy 8)	£2,521	15.25256	£1,340,889

Table 9 Ten year incremental cost effectiveness ratios (antibiotics versus no antibiotics). Analysis includes estimated costs and potential benefits of future antibiotic prophylaxis. All other parameters are as per base case analysis.

Antibiotic strategy	Costs per person	QALYs per person	Incremental cost effectiveness ratio (versus no antibiotics)
No antibiotic	£673	7.53406	NA
Oral amoxicillin (strategy 1)	£683	7.53408	£427,682
Oral clindamycin (strategy 2)	£732	7.53408	£2,626,526
IV amoxicillin then oral amoxicillin (strategy 3)	£692	7.53408	£861,013
Oral amoxicillin before and after (strategy 4)	£692	7.53408	£862,973
IV amoxicillin, IV gent then oral amoxicillin (strategy 5a)	£2,567	7.53408	£85,231,144
IV amoxicillin, IV gent then oral amoxicillin (strategy 5b)	£737	7.53408	£2,878,649
IV vanco and IV gent (strategy 6)	£964	7.53408	£13,065,848
IV teicoplanin and IV gent (strategy 7)	£1,261	7.53408	£26,454,992
IV clindamycin (strategy 8)	£815	7.53408	£6,374,708

Table 10 Lifetime (50 year time horizon) incremental cost effectiveness ratios (antibiotics versus no antibiotics). Analysis includes estimated costs and potential benefits of future antibiotic prophylaxis. All other parameters are as per base case analysis.

Antibiotic strategy	Costs per person	QALYs per person	Incremental cost effectiveness ratio (versus no antibiotics)
No antibiotic	£2,508	15.2524	NA
Oral amoxicillin (strategy 1)	£2,534	15.2525	£248,912
Oral clindamycin (strategy 2)	£2,668	15.2525	£1,513,095
IV amoxicillin then oral amoxicillin (strategy 3)	£2,561	15.2525	£498,047
Oral amoxicillin before and after (strategy 4)	£2,561	15.2525	£499,175
IV amoxicillin, IV gent then oral amoxicillin (strategy 5a)	£7,701	15.2525	£49,005,022
IV amoxicillin, IV gent then oral amoxicillin (strategy 5b)	£2,684	15.2525	£1,658,048
IV vanco and IV gent (strategy 6)	£3,304	15.2525	£7,514,982
IV teicoplanin and IV gent (strategy 7)	£4,120	15.2525	£15,212,810
IV clindamycin (strategy 8)	£2,897	15.2525	£3,668,040

Sensitivity analysis

A number of sensitivity analyses were undertaken. All the analyses described below are based on analyses that include the recurring costs and potential benefits associated with ongoing prophylaxis unless otherwise stated.

Risk of infective endocarditis

A sensitivity analysis was performed on the estimate of the risk of developing IE following a dental procedure. Keeping all other parameters as per the base case and excluding the estimated costs and potential benefits of future prophylaxis, it was found that the risk of developing IE had to be at least 16 cases per million procedures for the incremental cost per QALY of strategy 1 to reduce to around £20,000 (50 year time horizon). When the estimated costs and potential benefits of future prophylaxis are included in the analysis, this threshold risk rises to 48 per million.

Costs

A sensitivity analysis was performed whereby all costs were varied as a set between their upper and lower estimates. All other parameters are kept at their base case estimates. The results are presented in table 11.

Table 11 Sensitivity analysis on cost. All other parameters are at their base case values (50 year time horizon).

	Lower cost estimate	Upper cost estimate
Antibiotic strategy	**Incremental cost effectiveness ratio (antibiotic vs. "No antibiotic")**	
No antibiotic	NA	NA
Oral amoxicillin (strategy 1)	£249,313	£248,723
Oral clindamycin (strategy 2)	£1,513,496	£1,512,906
IV amoxicillin then oral amoxicillin (strategy 3)	£498,448	£497,858
Oral amoxicillin before and after (strategy 4)	£499,575	£498,985
IV amoxicillin, IV gent then oral amoxicillin (strategy 5a)	£49,005,422	£49,004,833
IV amoxicillin, IV gent then oral amoxicillin (strategy 5b)	£1,658,449	£1,657,859
IV vanco and IV gent (strategy 6)	£7,515,382	£7,514,792
IV teicoplanin and IV gent (strategy 7)	£15,213,211	£15,212,621
IV clindamycin (strategy 8)	£3,668,440	£3,667,851

Utilities

An analysis was undertaken varying all utility estimates as a set between their upper and lower estimates. The results are presented in table 12.

Table 12. Sensitivity analysis on utility estimates – all other parameters kept at their base case values (50 year time horizon).

	Lower estimate (all utilities)	Upper estimate (all utilities)
Antibiotic strategy	**Incremental cost effectiveness ratio (antibiotic vs. "No antibiotic")**	
No antibiotic	NA	NA
Oral amoxicillin (strategy 1)	£251,185.82	£244,636.69
Oral clindamycin (strategy 2)	£1,526,917.02	£1,487,105.97
IV amoxicillin then oral amoxicillin (strategy 3)	£502,596.91	£489,492.79
Oral amoxicillin before and after (strategy 4)	£503,734.52	£490,600.74
IV amoxicillin, IV gent then oral amoxicillin (strategy 5a)	£49,452,678.99	£48,163,307.84
IV amoxicillin, IV gent then oral amoxicillin (strategy 5b)	£1,673,194.29	£1,629,569.38
IV vanco and IV gent (strategy 6)	£7,583,630.31	£7,385,903.63
IV teicoplanin and IV gent (strategy 7)	£15,351,778.19	£14,951,513.94
IV clindamycin (strategy 8)	£3,701,547.17	£3,605,037.38

Age

Starting age influences the estimate of cost effectiveness, with antibiotic prophylaxis appearing to be more cost effective for younger age groups. However, in an analysis that only varies starting age and includes the recurring costs and potential benefits of antibiotic prophylaxis (all other parameters are kept at their base case values), the estimated 50-year incremental cost effectiveness ratio for strategy 1 at a starting age of 20 years (male) is around £234,000 per QALY.

Overall mortality risk

When the overall mortality risk in the model was changed from an estimate of all-cause mortality to one that excluded deaths from cardiac causes (Fox et al, 2006; Technology Appraisal report - http://guidance.nice.org.uk/page.aspx?o=217495), the base case (including the recurring costs and potential benefits of ongoing antibiotic prophylaxis) incremental cost effectiveness ratio for strategy 1 fell from £249,000 per QALY to £244,000 (50 years).

Other sensitivity analyses

Table 13 presents the results from a number of univariate sensitivity analyses. Only the results from strategies 1 and 2 are presented.

Table 13 Results from a series of univariate sensitivity analysis on certain epidemiological parameters used in the model. Results presented for strategies 1 and 2 only.

Parameter	Value	Strategy 1	Strategy 2
Efficacy of prophylaxis	Lower – 25% effective	£503,448	£3,031,864
	Upper – 75% effective	£164,069	£1,006,853
Probability of mortality from acute endocarditis – native valves	Lower – 0.082	£466,344	£2,835,846
	Upper – 0.246	£169,728	£1,031,374
Annual probability of developing CHF following acute endocarditis	Lower – 0.042	£248,888	£1,512,956
	Upper – 0.125	£248,928	£1,513,186
Annual probability of developing CHF (non endocarditis cases)	Lower – 0.003	£244,677	£1,487,562
	Upper – 0.009	£253,049	£1,538,035
Annual probability of valve replacement during or immediately following acute IE)	Lower – 0.17	£254,452	£1,546,412
	Upper – 0.51	£243,605	£1,481,181
Annual probability of valve replacement, years 1 to 10 (endocarditis cases)	Lower – 0.007	£249,693	£1,517,792
	Upper – 0.020	£248,173	£1,508,647
Probability of valve replacement, years 1 to 10 (non endocarditis cases)	Lower – 0.002	£246,474	£1,498,147
	Upper – 0.006	£251,380	£1,528,220
Probability of valve replacement, after ten years (all patients)	Lower – 0.002	£249,383	£1,516,255
	Upper – 0.006	£248,457	£1,510,036
Probability of death from valve surgery.	Lower – 0.041	£249,031	£1,513,796
	Upper – 0.123	£248,793	£1,512,395
Probability of further valve replacement surgery after prior surgery – all patients (years 1 to 10 only)	Lower – 0.007	£248,931	£1,513,201
	Upper – 0.020	£248,894	£1,512,991
Probability of non-fatal allergic side effects	0.5%	£279,684	£1,543,867
Probability of non-fatal allergic side effects	1%	£310,455	£1,574,638
Probability of non-fatal allergic side effects	5%	£556,627	£1,820,810
Probability of non-fatal allergic side effects	10%	£867,343	£2,128,526

Using the Duval et al estimates for all PCC and prosthetic valves

Tables 14 and 15 apply the following risk estimates based on the Duval et al study: 22 per million cases of IE following a single dental procedure (all PCC and 93 per million cases of IE following a single dental procedure (prosthetic valves) respectively. All other parameters are kept at their base case values except for the mortality risk from IE as it applies to patients with prosthetic

valves and the overall cost of treating acute endocarditis in patients with prosthetic valves.

Table 14 Applying the Duval et al risk of developing IE for all patients with a PCC (22 per million cases per dental procedure). All other parameters are kept at their base case values (50 year time horizon).

Antibiotic strategy	Costs per person	QALYs per person	Incremental cost effectiveness ratio (versus no antibiotics)
No antibiotic	£2,511	15.2516	NA
Oral amoxicillin (strategy 1)	£2,533	15.2521	£44,880
Oral clindamycin (strategy 2)	£2,652	15.2521	£278,559
IV amoxicillin then oral amoxicillin (strategy 3)	£2,557	15.2521	£90,932
Oral amoxicillin before and after (strategy 4)	£2,557	15.2521	£91,140
IV amoxicillin, IV gent then oral amoxicillin (strategy 5b)	£7,115	15.2521	£9,057,252
IV amoxicillin, IV gent then oral amoxicillin (strategy 5b)	£2,666	15.2521	£305,353
IV vanco and IV gent (strategy 6)	£3,216	15.2521	£1,387,984
IV teicoplanin and IV gent (strategy 7)	£3,940	15.2521	£2,810,897
IV clindamycin (strategy 8)	£2,855	15.2521	£676,892

Table 15 Applying the Duval et al risk of developing IE for all patients with a prosthetic valve (93 per million cases per dental procedure). Except for the costs of treating acute endocarditis and the mortality risk associated with acute prosthetic endocarditis, all other parameters in the model are kept at their base case estimates (50 year time horizon).

Antibiotic strategy	Costs per person	QALYs per person	Incremental cost effectiveness ratio (versus no antibiotics)
No antibiotic	£2,514	15.2507	NA
Oral amoxicillin (strategy 1)	£2,519	15.2516	£5,124
Oral clindamycin (strategy 2)	£2,552	15.2516	£40,962
IV amoxicillin then oral amoxicillin (strategy 3)	£2,525	15.2516	£12,187
Oral amoxicillin before and after (strategy 4)	£2,525	15.2516	£12,219
IV amoxicillin, IV gent then oral amoxicillin (strategy 5a)	£3,800	15.2516	£1,387,296
IV amoxicillin, IV gent then oral amoxicillin (strategy 5b)	£2,556	15.2516	£45,072
IV vanco and IV gent (strategy 6)	£2,710	15.2516	£211,108
IV teicoplanin and IV gent (strategy 7)	£2,912	15.2516	£429,331
IV clindamycin (strategy 8)	£2,609	15.2516	£102,052

Multiway sensitivity analysis on the risk of infective endocarditis (using the Duval et al data), fatal anaphylaxis risk and antibiotic efficacy

Table 16 presents the results of a multiway deterministic analysis involving the following parameters: fatal anaphylaxis risk from amoxicillin, antibiotic efficacy, and risk of developing IE following a dental procedure. Only strategies 1 and 2 are presented. Fatal anaphylaxis risk was varied between 0.9 and 40 per million, but the results for 40 per million were the same as

those for a setting of 20 per million and consequently are not presented. It appears that even for a risk of 22 per million (the baseline value used by Agha et al, the cheapest strategy is not cost effective at a threshold of £20-30,000 per QALY when the fatal anaphylaxis risk is 0.9 per million and antibiotic efficacy is assumed to be 75%. For the other strategies (results not presented, except for strategy 2), ICERs ranged from £85,600 to £1.9 million. If however mortality from acute endocarditis is increased by 50% from 16.4% to 24.6%, the ICER for strategy 1 falls to £24,467 per QALY. The ICERs for the other strategies ranged from £51,000 to £1.3 million per QALY.

Table 16 50-year ICERs for strategies 1 and 2 only, including long-term costs and benefits of ongoing prophylaxis.

Where there is an entry of 'dominated', this means that the strategy is more costly and less effective than no antibiotics. Future costs and potential benefits of ongoing prophylaxis are included in the analysis.

		Duval et al: all PCC – 22 per million risk			Duval et al: prosthetic valve – 93 per million risk		
		Antibiotic efficacy			Antibiotic efficacy		
Fatal anaphylaxis risk for amoxicillin (deaths per million)	**Prophylactic strategy**	**75%**	**50%**	**25%**	**75%**	**50%**	**25%**
0.9	AB strategy 1	£40,837	£84,737	£1,655,766	£1,667	£5,531	£18,497
	AB strategy 2	£183,845	£278,559	£562,705	£25,483	£40,962	£87,401
10	AB strategy 1	dominated	dominated	dominated	£3,416	£31,091	dominated
	AB strategy 2	£183,845	£278,559	£562,705	£25,483	£40,962	£87,401
20	AB strategy 1	dominated	dominated	dominated	dominated	dominated	dominated
	AB strategy 2	£183,845	£278,559	£562,705	£25,483	£40,962	£87,401

Discussion

The present analysis makes two key assumptions. Firstly that individual dental procedures can lead directly to the development of infective endocarditis, and secondly that antibiotic prophylaxis can reduce that risk. The modelling that has been undertaken previously, and the present analysis also, highlights two key competing risks – the risk of fatal anaphylaxis as it principally relates to amoxicillin, and the risk of developing IE following a particular dental procedure. Additionally based on the sensitivity analyses undertaken in the present study, mortality from acute endocarditis and non-fatal antibiotic side effects are also potentially important factors influencing the cost effectiveness of antibiotic prophylaxis.

The base case analysis appeared to indicate that antibiotic prophylaxis is highly cost ineffective. Even ignoring the long term costs and potential benefits of antibiotic prophylaxis, the lowest ICER obtained was approximately £88,000 (50 year time horizon). In contrast, using the values of risk estimated by Duval et al, the model demonstrates that antibiotic prophylaxis strategies can be highly cost effective. Indeed 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 strategy 1 to reduce to around £20,000 (50 year time horizon). When the estimated costs and potential benefits of future prophylaxis are included in the analysis, this threshold risk rises to 48 per million. However, Duval et al based estimates may be highly optimistic, even in individuals considered at 'high risk'.

The Duval analysis appears to indicate that for all individuals with a PCC, approximately 5% of all IE cases are attributable to a dental procedure. As simple daily dental brushing is known to be a source of bacteraemia, the actual risk ascribed to an individual dental procedure is likely to be a lot less than the estimate of 22 per million: if it is assumed that individuals brush their teeth twice a day and undergo on average two dental procedures per year, then the proportion of PCC IE cases attributable to a dental procedure could be of the order of 0.3% (2 / [2 x 365 days]), approximately 17 fold lower than the figure estimated by Duval et al. Using these data, the estimated risk of

developing IE from a dental procedure is about 0.8 cases per million. This is even lower than the base case estimate (4.1 cases per million) used in the present analysis.

A key limitation of the analysis is the fact that it is assumed that all antibiotic strategies are equally effective (or 'ineffective') in the prophylaxis of IE. However no clear evidence exists to distinguish between any of the agents considered in the analysis. Furthermore, as mentioned earlier, there is no clear evidence – at least for penicillin – that antibiotic prophylaxis actually reduces the risk of developing infective endocarditis following a dental procedure (Oliver et al, 2004).

When attempting to estimate the recurring costs and benefits of antibiotic prophylaxis against IE, no attempt was made to adjust the risk of developing IE based on prior history. This is a limitation of the design of this study. In addition, the analysis did not take into account of the fact that patients could plausibly switch between different antibiotic prophylaxis regimens depending on, for example, the incidence of non fatal side effects. This could be particularly relevant in the case of amoxicillin containing regimens, and would likely therefore, reduce the cost effectiveness of such a strategy. The present study assumes that the allergy status of the patient is known beforehand, and that the rate of antibiotic side effects in all instances is zero (in the base case). This is a conservative assumption and if a proportion of patients have an unknown allergy status and the rate of antibiotic side effects is not zero then this would most likely reduce the cost effectiveness of antibiotic prophylaxis.

Another important limitation of the analysis is that it does not take into account the impact of potentially increasing the risk of antibiotic resistant pathogens secondary to widespread and ongoing dental prophylaxis. Such an outcome would again most likely reduce the cost effectiveness of antibiotic prophylaxis.

The application of the available mortality risk data in the present analysis can be questioned, in particular the use of all-cause mortality data from the general population of England and Wales. Ideally, a background mortality risk profile that excludes non cardiac causes should be used in this instance.

However, it can be argued that the model does not fully capture cardiac mortality in this population, although this is unlikely to impact on significantly on the incremental results. Furthermore, the model predicts a ten year survival for the entire hypothetical cohort of patients of 92%: this is broadly in line with observational follow up data in patients with initially uncomplicated MVP (Frary et al, 1994). Mean age at start of follow-up was 51 +/- 18 years in this US study, with an estimated survival at ten years of 90%.

In summary, the model suggests that prophylactic antibiotic strategies not cost effective under all scenarios explored in the present analysis unless optimistic assumptions are made principally with regard to the risk developing IE following a dental procedure.

6.7 Appendix 7 – Health economics evidence tables

This section provides evidence tables that summarise the data provided in the published economic evaluations identified for the purpose of this guideline. Two modelling studies (Bor and Himmelstein, 1984 and Tzukert et al, 1986) were also reviewed but since they did not consider costs, no further details are presented here.

Note: Economic evaluations that examined antibiotic prophylaxis for individuals with joint disease/ prosthetic joints undergoing dental procedures were excluded from detailed consideration since they do not consider the relevant patient population covered by this guideline.

Published economic evaluations were quality assessed using methods as described in the current Guidelines methods manual.

Data extraction tables for included studies – Dental procedures

Primary Source	Clemens JD, Ransohoff DF. A quantitative assessment of pre-dental antibiotic prophylaxis for patients with mitral-valve prolapse. J Chronic Dis. 1984;37(7):531-44
Author	Clemens
Date	1984
Type of economic evaluation	Cost effectiveness analysis
Currency used	US dollars
Year to which costs apply	1981
Perspective used	Third party payer
Timeframe	<1 year / Lifetime
Comparators	No antibiotic prophylaxis Two prophylaxis regimens ("oral" versus "parenteral" penicillin) and no prophylaxis. Authors argued that streptomycin not relevant for MVP population, although it might be used for patients with prosthetic valves.
Source(s) of effectiveness data	Efficacy estimated on the basis of expert opinion. In base case it was assumed that antibiotics were 70% effective. A range of 10 - 100% was tested
Source(s) of resource use data	Published sources and authors assumptions
Source(s) of unit cost data	Bacterial endocarditis costs: Maryland Health Services Cost Review Commission (MHSCRC) [1979] Antibiotic costs: fee schedule of the Yale-New Haven Hospital. Costs of providing antibiotic prophylaxis included not only the direct costs of the drugs but also the costs for 'drug handling' and administration where relevant. Penicillin reaction costs: fee schedule of the Yale-New Haven Hospital and MHSCRC
Modelling approach used	Simple decision tree
Summary of effectiveness results	Cases of IE / spared years of life. Not clearly reported Cases of IE No prophylaxis: 4.1 per million Parenteral penicillin 1.8 per million Oral penicillin 1.8 per million

	Spared years of life (discounted at 5%): Oral penicillin – varied from -9.2 (age at dental procedure = 10) to +2.3 (age at dental procedure = 70)	
Summary of cost results	Per million procedures (discounted at 5% for 'cost per spared year of life model') No prophylaxis Parenteral penicillin Oral penicillin	 $54,703 $35,903,191 $3,748,886
Summary of cost-effectiveness results	Cost per prevented case and cost per spared year of life In base case the parenteral prophylaxis strategy caused a net loss of life at higher cost when estimating cost per prevented case and cost per life year saved. Cost per prevented case: Oral penicillin In cost per spared year of life model, life is only spared after the age of 50 at a cost of $1.3 million per spared year of life.	 $2,638,702
Sensitivity analysis	Discount rate varied between 0 and 10% in sensitivity analysis; varied antibiotic efficacy and relative risk of endocarditis in MVP (according to ranges cited in text). Results sensitive to absolute risk of post dental endocarditis in MVP and to the annual discount rate. At an endocarditis risk of 18.7 cases per million procedures (an "extremely high value"), the cost per spared year of life would range from $72,000 to $190,000, varying inversely with age. At a discount rate of 0%, the cost per spared year of life would extend from $269,000 to $718,000, varying directly with age.	
Main Conclusions	Authors concluded that their results are only applicable to 'ordinary' dental procedures in persons with 'reasonably good' oral hygiene. Authors also stated that the suffering caused by adverse events plus the wider societal impacts (e.g. loss of productivity) must be factored into clinical decision making. The authors note that at the individual level, the choice is whether to spend a small sum of money to reduce the risk of IE from one improbable level to another while at the same time incurring a risk of a fatal penicillin reaction which appears to be of the same order of improbability as the risk of endocarditis.	

Primary Source	Gould, IM and Buckingham, JK. Cost-effectiveness of prophylaxis in dental practice to prevent infective endocarditis. Br Heart J 1993; 70: 79-83
Author	Gould
Date	1993
Type of economic evaluation	Cost cosequence analysis
Currency used	UK pounds
Year to which costs apply	1991/92
Perspective used	Third party payer (NHS)
Timeframe	Unclear – Lifetime?
Comparators	No prophylaxis versus penicillin
Source(s) of effectiveness data	It was assumed that penicillin was 100% effective. Explored impact of halving effectiveness by 50% in sensitivity analyses. No clear basis for this base case estimate, although it was commented that a "lack of case reports of failed prophylaxis where currently recommended regimes are used does suggest that [penicillin] is very effective."
Source(s) of resource use data	Resource use was based on an inspection of the notes of 63 patients who had had IE in Grampian over the decade 1980-90. Few details given, although data is presented on relation between cost of care and survival after infective endocarditis (Cost = £1923 + £620/yr).
Source(s) of unit cost data	Costs of a stay in hospital, valve replacement operations and outpatient visits were supplied by the health authority.
Modelling approach used	Not clear, but appears to be a simple decision analysis

Summary of effectiveness results	Not clearly reported. (1) High risk patients after all at risk dental procedures It was noted that the risk of death for at risk individuals undergoing high risk dental procedures is about 0.65 / 10,000 procedures. As the mortality is about 20%, the risk of non-fatal IE is 2.6 cases / 10,000 procedures (2) Restricting prophylaxis for high risk patients to dental extractions It was assumed that 95% of cases of IE associated with dental procedures are attributable to dental extractions. The risk of death in this group is 5.7 deaths for 10,000 procedures (3) Providing prophylaxis to high risk patients after high risk procedures other than extractions. Providing prophylaxis will save only three lives in a million procedures.
Summary of cost results	Not clearly reported. Discounted at 6% (1) High risk patients after all at risk dental procedures Cost saving of approximately £7750 (2) Restricting prophylaxis for high risk patients to dental extractions Cost saving of approximately £264,000 (3) Providing prophylaxis to high risk patients after high risk procedures other than extractions. Costs of providing antibiotics exceed savings. Costs of providing antibiotics = £23,727 per 10,000 procedures
Summary of cost-effectiveness results	Saving / cost per life saved Restricting prophylaxis for high risk patients to dental extractions Cost saving of approximately £264,000 Providing prophylaxis to high risk patients after high risk procedures other than extractions. £1 million per life saved
Sensitivity analysis	Limited analyses. Undertook sensitivity analysis on antibiotic efficacy and mortality after IE. Sensitivity analyses did not alter conclusion that prophylaxis is cost effective for at risk patients undergoing extraction.
Main Conclusions	Study concluded that prophylaxis should be limited to patients undergoing extractions. The authors noted that prophylaxis was (at that time) currently provided to only about 50% of patients thought to be at high risk - "savings might be achieved by extending antibiotic cover for dental extractions and reducing such cover for other high risk procedures".

Primary Source	Devereux, Frary, Kramer-Fox et al. Cost-effectiveness of infective endocarditis prophylaxis for mitral valve prolapse with or without a mitral regurgitant murmur. Am J Cardiol, 1994;74:1024-1029.
Author	Devereux
Date	1994
Type of economic evaluation	Cost effectiveness analysis
Currency used	US dollars
Year to which costs apply	1990
Perspective used	Third party payer Costs included direct costs of antibiotic prophylaxis, costs of anaphylaxis, and costs relating to IE.
Timeframe	Lifetime
Comparators	No antibiotic prophylaxis Three antibiotic regimens considered: (A) oral amoxicillin; (B) oral erythromycin; (C) IV ampicillin.
Source(s) of effectiveness data	Estimates of antibiotic efficacy were based on ones used in analyses by previous authors (Clemens and Ransohoff, 1984 and Bor and Himmelstein, 1984). The efficacy of antibiotic prophylaxis was assumed to be 80% for amoxicillin and ampicillin and 60% for erythromycin.
Source(s) of resource use data	Published estimates and authors assumptions.
Source(s) of unit cost data	Antibiotics - patient charges sourced from several pharmacies in the vicinity of The New York Hospital Medicare fee schedules.
Modelling approach used	Simple decision tree
Summary of effectiveness results	Cases of IE prevented / Net years of life saved All patients with mitral valve prolapse (per 1 million dental procedures) — Cases prevented / net years of life saved

	No prophylaxis	0 / 0
	Amoxicillin	32. / 176.0
	Erythromycin	24.0 / 136.0
	Ampicillin	17.0 (-243.0)
	Patients with Mitral prolapse with a systolic murmur	
	No prophylaxis	0 / 0
	Amoxicillin	80.0 / 450.0
	Erythromycin	60.0 / 341.0
	Ampicillin	65.0 / 29.0
	(discounting does not appear to have been applied)	
Summary of cost results	All patients with mitral valve prolapse (per 1 million dental procedures)	US $
	No prophylaxis	1,831,000
	Amoxicillin	5,502,000
	Erythromycin	4,234,000
	Ampicillin	27,161,000
	Patients with Mitral prolapse with a systolic murmur	
	No prophylaxis	4,595,000
	Amoxicillin	6,056,000
	Erythromycin	5,336,000
	Ampicillin	27,701,000
	(discounting does not appear to have been applied)	
Summary of cost-effectiveness results	Cost per IE case prevented / cost per year of life saved All patients with mitral valve prolapse (per 1 million dental procedures)	Cost per IE case prevented / cost per year of life saved
	Amoxicillin	118,803 / 20,846
	Erythromycin	100,926 / 17,708
	Ampicillin	1,507,738 / Life lost
	Patients with Mitral prolapse with a systolic murmur	
	Amoxicillin	18,540 / 3,254
	Erythromycin	12,396 / 2,714
	Ampicillin	357,125 / 791,301
Sensitivity analysis	Limited sensitivity analyses Explored impact on costs by using a higher risk subgroup (MVP patients with a mitral systolic murmur - result: lower costs). Also explored impact of changing population prevalence of MVP, % of IE post dental, efficacy of prophylaxis, costs of IE, costs of antibiotics, years of life lost (increased from 5.7 years to 7.5 years). Sensitivity analysis suggested that erythromycin prophylaxis might be cost saving under some scenarios.	
Main Conclusions	The authors concluded that prevention with oral antibiotics of the cumulative morbidity and incremental health care costs due to IE in MVP patients is reasonably cost-effective for MVP patients with mitral murmurs. It was noted that the present results suggest better cost effectiveness for MVP patients than previous analyses published in 1984. This difference, according to the authors, is largely due to the subsequent recognition that the risk of IE is strongly concentrated in MVP patients with a mitral regurgitant murmur.	

Primary Source	Agha Z, Lofgren RP, VanRuiswyk JV. Is antibiotic prophylaxis for bacterial endocarditis cost-effective? Med Decis Making. 2005 May-Jun;25(3):308-20.
Author	Agha
Date	2005
Type of economic evaluation	Cost-effectiveness analysis and cost-utility analysis.
Currency used	US dollars
Year to which costs apply	The price year was 2003. All cost data were adjusted to 2003 based on the medical care component of the Consumer Price Index.
Perspective used	Societal
Timeframe	Lifetime (55 years)
Comparators	Eight management strategies (including no prophylaxis) for IE in patients undergoing dental procedures who have underlying cardiac conditions. The strategies were: no antibiotics; oral amoxicillin 2 g, administered 1 hour before the procedure; oral clarithromycin 500 mg, administered 1 hour before the procedure; oral clindamycin 600 mg, administered 1 hour before the procedure; oral cephalexin 2 g, administered 1 hour before the procedure; intravenous or intramuscular ampicillin 2 g, administered 30 minutes before the procedure; intravenous or intramuscular cefazolin 1 g, administered 30 minutes before the procedure; and intravenous clindamycin 600 mg, administered 30 minutes before the procedure.
Source(s) of effectiveness data	Pooled analysis of four case control studies examining the effectiveness of antibiotic prophylaxis. Pooled odds ratios with 95% confidence intervals were calculated, after testing for heterogeneity, using the Mantel-Haenszel procedure.
Source(s) of resource use data	Resource use based on published estimates referenced by the authors.
Source(s) of unit cost data	Medicare fee schedules (1997) for hospitalisation costs Drug Topics Red Book (antibiotic acquisition costs). Comprised the average wholesale price of the drug, plus an average dispensing cost based on published data. The indirect costs of patient or caregiver time lost were estimated. The value assigned to a lost workday was the amount for a fulltime wage earner, and the value assigned to a lost "no work" day was the amount as reported by the Bureau of Labor Statistics. Patients requiring intravenous antibiotic administration were estimated to have lost the productivity equivalent of a 0.5 workday
Modelling approach used	Simple decision tree for short term outcomes and Markov process for long term costs and effects
Summary of effectiveness results	Cases of IE prevented /QALYs Under the base-case assumptions, if 10 million patients underwent prophylaxis compared with the no-prophylaxis strategy, the outcomes would be: Amoxicillin / ampicillin: 119 cases of BE prevented but a net loss of 181 lives (-30,311 QALYs) secondary to anaphylaxis Clarithromycin: 119 prevented cases of BE, 19 prevented deaths from BE, and 1,125 QALYs saved Oral cephalexin / IV cefazolin: 119 prevented cases of BE, 9 prevented deaths from BE, and 827 QALYs saved Oral clindamycin / IV clindamycin: 119 prevented cases of BE, 19 prevented deaths from BE, and 1,118 QALYs saved Secondary analyses were reported for patients with high-risk cardiac conditions only and with prior beta-lactam antibiotic use. In the high-risk group, if 10 million patients underwent prophylaxis with any of the seven prophylaxis strategies, there would be 237 endocarditis cases prevented for patients with prior BE and 475 cases prevented for patients with prosthetic heart valves. (QALYs discounted at 3%)
Summary of cost results	The total intervention costs for the 55-year horizon time strategies were not reported. Costs discounted at 3%

Summary of Cost-effectiveness results	Annual cost per QALY (US$) Cost effective ratios presented for each prophylaxis option. Base case: Oral clarithromycin Oral cephalexin Oral clindamycin IV cefazolin IV clindamycin For the base-case analysis, clarithromycin prophylaxis was the most cost-effective strategy and cephalexin was second best. All other antibiotic regimens were eliminated based on simple dominance (i.e. they were more costly and less effective than clarithromycin). Amoxicillin and ampicillin were eliminated from consideration as they resulted in a net loss of lives For high-risk patients, in patients with prior endocarditis: Oral clarithromycin Oral cephalexin Oral clindamycin IV cefazolin IV clindamycin The strategy was not effective for oral amoxicillin or for ampicillin (intravenous). In patients with prosthetic valve: Oral clarithromycin Oral cephalexin Oral clindamycin IV cefazolin IV clindamycin Oral amoxicillin IV ampicillin	 $88,007 per QALY gained $99,373 per QALY gained $101,142 per QALY (eliminated) $199,430 per QALY gained (eliminated) $411,093 per QALY gained (eliminated) $40,334 $37,916 $46,678 $79,886 $199,783 (as reported in the text) $16,818 $14,060 $19,936 $33,480 $96,029 $160,871 $498,488
Sensitivity analysis	To test the influence of all variables on the model results, one-way sensitivity analyses were conducted. The values of each model estimate for epidemiological parameters and health outcomes, health state utility values and costs were varied across the ranges in the paper. The base-case findings were sensitive to changes in the risk of antibiotic fatal side effects, the incidence of bacterial endocarditis, potentially preventable cases, the cost of antibiotics, the incidence of dental visits requiring prophylaxis, age of the target population, and the discount rate. One-way sensitivity analyses of all other variables did not result in any of the antibiotic prophylaxis strategies achieving the predefined threshold of $50,000 or $100,000 per QALY gained.	
Main Conclusions	Authors concluded that: Routine use of amoxicillin and ampicillin for endocarditis prophylaxis is not safe. Predental antibiotic prophylaxis is cost-effective only for persons with moderate or high risk of developing endocarditis Clarithromycin should be considered the drug of choice and cephalexin (a cephalosporin) as an alternative drug of choice	

Data extraction tables for included studies - non dental procedures (urinary catheterisation in the Emergency department)

Primary Source	Caviness AC, Cantor SB, Allen CH, Ward MA. A cost-effectiveness analysis of bacterial endocarditis prophylaxis for febrile children who have cardiac lesions and undergo urinary catheterization in the emergency department. Pediatrics. 2004 May;113(5):1291-6.
Author	Caviness
Date	2004
Type of economic evaluation	Cost effectiveness analysis
Currency used	US dollars
Year to which costs apply	2000
Perspective used	Third party payer Costs included direct costs of antibiotic prophylaxis, costs of anaphylaxis, and costs relating to IE.
Timeframe	Lifetime
Comparators	The strategies were: no antibiotics; oral amoxicillin 50 mg/kg 1 hour before; vancomycin 20 mg/kg IV over 1-2 hours completed within 30 mins of starting the procedure
Source(s) of effectiveness data	Prophylactic efficacy of antibiotics in preventing BE after genitourinary procedures was determined from "1 clinical trial and 2 decision analyses". The RCT examined efficacy of mezlocillin for transurethral prostatectomy. Decision analyses were: Bor & Himmelstein, Clemens and Ransohoff. Antibiotic efficacy was estimated to be 89%, with a range of 0% - 100%.
Source(s) of resource use data	Antibiotic regimens based on AHA guidelines (1997). Also author assumptions and published sources.
Source(s) of unit cost data	Healthcare Cost and Utilization Project data for 2000 (for hospital costs for endocarditis and mitral valve replacement) Medicaid charges for 2000 (outpatient visit costs) Drug Topics Red Book 2001 (antibiotic acquisition costs). Opportunity cost to the parent was taken as the number of hours of work missed while waiting for antibiotic delivery. An average hourly earning of $15.80 was taken from the US Department of Labor Bureau of Labor Statistics for 2000
Modelling approach used	Simple decision tree
Summary of effectiveness results	Excluding antibiotic deaths: The antibiotic strategy would prevent 7 cases of BE per 1 million children treated, with an incremental effectiveness of only 0.00005 QALYs. QALYs discounted at 3% Including antibiotic deaths: Not adjusted for BE incidence Amoxicillin & vancomycin 24.91079 QALYs No prophylaxis 24.91124 QALYs Excluding antibiotic deaths: Amoxicillin & vancomycin 24.91129 QALYs No prophylaxis 24.91124 QALYs In terms of BE incidence, incremental effectiveness = 0.000007
Summary of cost results	No prophylaxis $1.47 Amoxicillin $495.30 Vancomycin $667.63 (Costs discounted at 3%)
Summary of cost-effectiveness results	Cost per QALY / cost per case prevented Excluding antibiotic deaths: Amoxicillin: $10 million per QALY gained / $70 million per BE case prevented Vancomycin: $13 million per QALY gained / $95 million per BE case averted Including antibiotic related deaths – antibiotic strategy less effective (net loss of life) and more costly.
Sensitivity analysis	The authors state that sensitivity analysis was conducted by varying study costs and probabilities. Uncertain probabilities that were varied in the sensitivity analysis include the prevalence of bacteria causing UTI and BE, the prophylactic efficacy of antibiotics in preventing bacteremia, the incidence of bacteremia after UC, and the incidence of BE after bacteremia. All costs were varied from $0 to twice the point estimate for sensitivity analysis. Uncertain costs that were varied included the ED opportunity costs; the parental opportunity costs; and the cost of endocarditis hospitalization, endocarditis surgery, and caring for CHF. QALE was varied for BE, no BE, and CHF. The discount

	rate was also varied between 0% and 5% for both costs and clinical outcomes. (The results of these analyses were not fully reported). Below a threshold value of 0.0000023 for anaphylactic death, the use of antibiotics would be more effective than no antibiotics.
Main Conclusions	In the emergency department, BE prophylaxis before UC in febrile children who are aged 0 to 24 months and have moderate-risk cardiac lesions is not a cost-effective use of health care resources.