Prophylaxis against infective endocarditis: antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures

Full guideline

Draft for consultation, November 2007

This guideline was developed following the NICE short clinical guideline process. This document includes all the recommendations, details of how they were developed and summaries of the evidence they were based on.

Contents

1 Summary

1.1 Foreword

(To be added in the final version)

1.2 Patient-centred care

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

Treatment and care should take into account patients' needs and preferences. People considered to be at increased risk of infective endocarditis who may require antimicrobial prophylaxis before an interventional procedure should, where appropriate, 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.dca.gov.uk/menincap/bill-summary.htm).

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, carers and relatives should have the opportunity to be involved in decisions about the patient's care and treatment.

Carers and relatives should also be given the information and support they need.

1.3 List of recommendations and care pathway

1.3.1 Key priorities for implementation (key recommendations)

- Antibiotic prophylaxis against infective endocarditis (IE) is not recommended for patients at risk of IE undergoing dental procedures.
- Patients at risk of IE should achieve and maintain high standards of oral health, this requires both:
  - patient's responsibility and
  - professional facilitation (with an emphasis on preventative dentistry).
- Antibiotic prophylaxis is recommended for patients at risk of IE undergoing Endoscopic retrograde cholangiopancreatography (ERCP), manipulation of the biliary tract, and invasive oesophageal procedures and lower gastrointestinal (GI) tract procedures.

Antibiotic prophylaxis is recommended for patients at risk of IE for transurethral resection of the prostate (TURP), transrectal prostatic biopsy, lithotripsy and all urological procedures involving urethral manipulation except urethral catheterisation.

- Antibiotic prophylaxis to prevent IE is not recommended for patients at risk of IE (see exceptions in 1.3.2.5) undergoing:
  - ear, nose and throat (ENT), upper respiratory tract and upper GI tract procedures
  - bronchoscopy.
- Antibiotic prophylaxis to prevent IE is not recommended for patients at risk of IE undergoing obstetric and gynaecological procedures.
- Antimicrobial regimens should be modified to cover endocarditis-causing organisms when procedures are undertaken at a site of infection or potential infection in patients at risk of IE.

1.3.2 List of recommendations

People with cardiac conditions and their risk of developing IE

1.3.2.1 The following patients should be regarded as being at increased risk of developing infective endocarditis (IE) and should receive antibiotic prophylaxis as outlined in the recommendations below, those with:

- acquired valvular heart disease with stenosis or regurgitation
- valve replacement
- structural congenital heart disease (including surgically corrected or palliated structural conditions; excluding isolated atrial septal defect, repaired ventricular septal defect or repaired patent ductus arteriosus)
- hypertrophic cardiomyopathy.

Interventional procedures for which antibiotic prophylaxis is and is not recommended

1.3.2.2 Antibiotic prophylaxis against IE is not recommended for patients at risk of IE undergoing dental procedures.

1.3.2.3 Chlorhexidine mouthwash for prophylaxis against IE is not recommended for patients at risk of IE undergoing dental procedures.

1.3.2.4 Patients at risk of IE should achieve and maintain high standards of oral health, this requires both:

- patient's responsibility and
- professional facilitation (with an emphasis on preventative dentistry).

1.3.2.5 Antibiotic prophylaxis is recommended for patients at risk of IE undergoing endoscopic retrograde cholangiopancreatography (ERCP), manipulation of the biliary tract, and invasive oesophageal procedures and lower gastrointestinal (GI) tract procedures.

1.3.2.6 Antibiotic prophylaxis is recommended for patients at risk of IE for transurethral resection of the prostate (TURP), transrectal prostatic biopsy, lithotripsy and all urological procedures involving urethral manipulation except urethral catheterisation.

1.3.2.7 Antibiotic prophylaxis to prevent IE is not recommended for patients at risk of IE (see exceptions in 1.3.2.5) undergoing:

- ear, nose and throat (ENT), upper respiratory tract and upper GI tract procedures
- bronchoscopy.

1.3.2.8 Antibiotic prophylaxis to prevent IE is not recommended for patients at risk of IE undergoing obstetric and gynaecological procedures.

1.3.2.9 Antimicrobial regimens should be modified to cover endocarditis-causing organisms when procedures are undertaken at a site of infection or potential infection in patients at risk of IE.

1.3.2.10 The following antibiotic regime should be used as prophylaxis against IE: amoxicillin plus gentamicin or for penicillin allergic patients teicoplanin plus gentamicin.

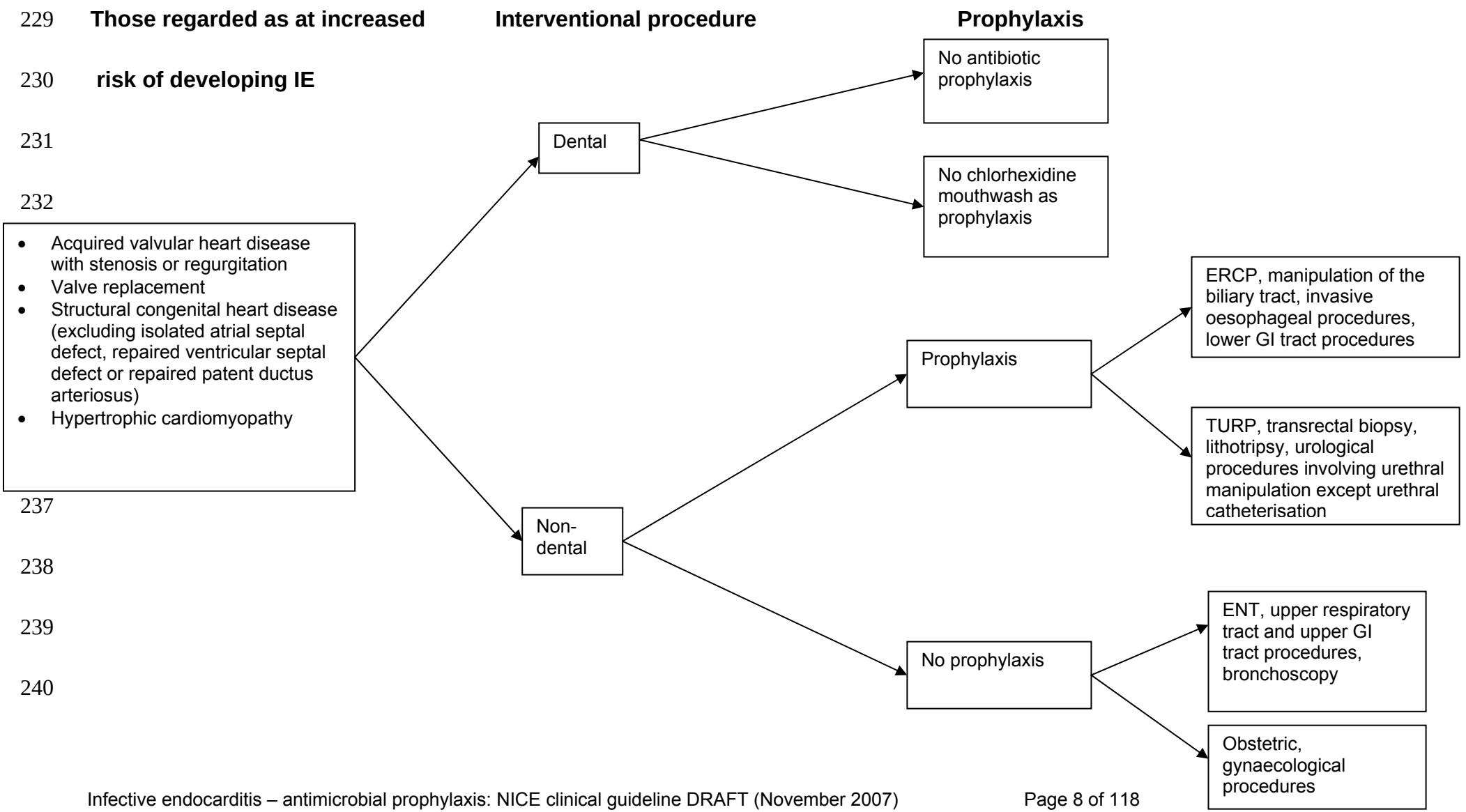
Patient information and support

1.3.2.11 Patients at risk of IE should receive clear and consistent information about IE including (a) the likely benefits and risks of antibiotic prophylaxis and (b) the specific symptoms that may indicate that a healthcare professional should consider a diagnosis of IE.

1.3.2.12 Patients at risk of IE should receive information about the importance of maintaining good oral health.

1.3.2.13 Patients at risk of IE should be informed of potential risks of undergoing medical and non medical invasive procedures (such as body piercing or tattooing).

1.3.3 Care pathway



1.4 Overview

1.4.1 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 less than 10 per 100,000 normal population. Despite advances in diagnosis and treatment, infective endocarditis (IE) remains a life-threatening disease with significant mortality (approximately 20%) and morbidity.

The predisposing factors for the development of IE have changed over the past 50 years, mainly with the decreasing influence of rheumatic heart disease and the increasing impact of prosthetic heart valves, nosocomial infection and intravenous drug misuse; nevertheless the potential seriousness of the impact of IE on the individual has not changed (Prendergast, 2006 54 /id).

There is a long history in the published medical literature of case reports in which IE is reported as having been preceded by an interventional procedure, most frequently with specific reference to dentistry. IE can be caused by a range of different organisms, many of which could potentially be transferred into the blood during an interventional procedure. *Streptococci*, *staphylococcus aureus* and *enterococci* are important causative organisms.

Although it is accepted that the majority of cases of IE are not caused by interventional procedures (Brincat, 2006 93 /id), nonetheless, 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 144 /id) and the applicability of these models to humans has been questioned. With a rare but serious condition such as IE it is difficult to plan

and execute research using experimental study designs; furthermore there would be strong ethical issues in the withholding of antibiotic prophylaxis from a group of participants. Consequently, the evidence available in this area is limited, being chiefly drawn from observational (case control) studies.

The rationale that forms the logic for prophylaxis against IE is: endocarditis usually follows bacteraemia, certain healthcare 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 14 /id).

For prophylaxis to be effective, certain requirements must be fulfilled: the identification of patients at risk, identification of the procedures that are liable to provoke bacteraemia, deliberation on an effective prophylactic regimen, and finally there must be a favourable balance between the risks of side-effects from prophylaxis and from developing the disease (Moreillon, 2004 141 /id). Underlying these principles is the assumption that antibiotic prophylaxis is effective in humans for the prevention of IE in dental and non-dental procedures. However, this assumption is now considered by many researchers in the field to be not proven (Prendergast, 2006 54 /id) and this has led to calls to significantly reduce the use of antibiotic prophylaxis in this setting.

Throughout the history of prophylaxis being offered against IE, professional organisations have sought to clarify the groups of patients who are considered to be at an increased risk of IE and the procedures (dental and non-dental) for which prophylaxis may be considered. This guideline has considered the decision-making and conclusions of existing relevant national and international guidelines in order to help inform its own decision making. This has been important because for many of the key clinical questions covered in this guideline a satisfactory evidence base does not exist. Four clinical guidelines on the prevention of IE are discussed in subsequent sections: American Heart Association (AHA), 2007 (Wilson, 2007 521 /id), British Society for Antimicrobial Chemotherapy (BSAC), 2006 (Gould, 2006 6 /id),,

European Society of Cardiology (ESC), 2004 (Horstkotte, 2004 15 /id) and British Cardiac Society (BCS)/Royal College of Physicians (RCP), 2004 (Advisory Group of the British Cardiac Society Clinical Practice Committee, 2004 22 /id).

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

1.4.2 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) is a NICE short clinical guideline.

The Institute has established a 'short' clinical guideline programme that addresses only part of a care pathway. They are intended to allow the rapid (9–11 month timescale) development of guidance for which the NHS requires urgent advice.

Short clinical guidelines are developed by an independent Guideline Development Group (GDG) supported by a technical team based within the Institute (the short clinical guidelines technical team). This technical team is constituted and undertakes the same functions as the established National Collaborating Centre (NCC) technical teams. The technical team does not have voting rights on recommendations made by the Guideline Development Group. The development and quality assurance of the short clinical guidelines will be overseen by a Guidelines Commissioning Manager, Director of the Centre for Clinical Practice and Executive Lead.

The short clinical guideline programme consists of four phases which follow those of the standard guideline programme:

1. Referral of topic to NICE by the Department of Health.

2. Scoping the short clinical guideline topic.

3. The development phase, which begins with the first meeting of the GDG and ends when a draft document is submitted by the GDG for stakeholder consultation.

4. The validation phase, which consists of consultation with stakeholders and the public on the draft guidance, receiving advice from the guideline review panel and expert reviewers, preparation of the final draft, and sign off by Guidance Executive and publication.

To meet the time requirements and minimise the complexity of development key stages of the current standard guidelines process have, however, been adapted. The key changes that are required to the current standard guidelines process relate to the scoping and development stages. A process guide to the short guidelines programme setting out in detail the short guideline development methods has been published (insert weblink) and should be read in conjunction with the current NICE Guidelines Manual.

1.4.3 1.3.3 Using this guideline

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

The full version of the guideline is available from www.nice.org.uk/CGXX. 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/CGXX ***[Applies to the final version of the guideline after publication]***

1.4.4 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. However, healthcare professionals need to apply their general medical knowledge and clinical judgement when applying recommendations that may not be appropriate in all circumstances. Decisions to adopt any particular recommendation should be made in the light of individual patients' views and circumstances as well as available resources. 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 which provide summary information to help clinicians and patients discuss options.

1.4.5 Using flowcharts

Flowcharts are inevitably a simplification and cannot capture all the complexities and permutations affecting the clinical care of individuals. Flowcharts presented in this guideline are designed to help communicate the key elements of treatment, but are not intended for rigid use or as protocol.

2 Evidence review and recommendations

2.1 People with cardiac conditions and their risk of developing IE

2.1.1 Introduction

Patients with certain cardiac conditions are known to be at an increased risk of developing IE[a]. Existing 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 an increased risk and those whose risk is considered to be little or no greater than the general population. However, the stratification of patients into high or low risk groups has proved to be difficult. This difficulty was acknowledged by Steckelberg and Wilson (Steckelberg, 1993 371 /id) who highlighted that the degree of risk associated

[a] 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 this paper.

with specific valvular lesions cannot be directly inferred from their frequency among endocarditis patients, as the prevalence of these lesions varies widely. The arbitrary nature of some of the decisions concerning risk identification has also been discussed (Durack, 1995 14 /id). Nonetheless, consideration of which underlying conditions impact on a person's risk of developing IE is important because this 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 54 /id). Therefore when considering prophylaxis against IE, in tandem with detailing which underlying cardiac conditions impact on a person's risk of developing IE, it is logical also to consider whether the underlying cardiac condition also impacts on the outcome of IE.

Existing guidelines in the area

Stratification of those with cardiac conditions into risk groups has proved difficult and has been tackled by existing guidelines in different ways. The American Heart Foundation (AHA) (Wilson, 2007 521 /id) guidelines considered the underlying conditions that over a lifetime have the highest predisposition to IE and which conditions are associated with the highest risk of adverse outcomes when IE develops. The British Society for Antimicrobial Chemotherapy (BSAC) (Gould, 2006 6 /id) guideline defined a category of high-risk cardiac factors requiring antibiotic prophylaxis. The British Cardiac Society (BCS) / Royal College of Physicians (RCP) (Advisory Group of the British Cardiac Society Clinical Practice Committee, 2004 22 /id) defined those with pre-existing 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 (Horstkotte, 2004 15 /id) considered that it was impossible to determine the relative risk of specific cardiac conditions and sought to identify those associated with an IE risk that is higher than 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 which allow this risk to be directly compared between different cardiac conditions. Initially seven were included; three cohort studies (Gersony, 1993 539 /id; Li, 1998 3609 /id; Morris, 1998 6086 /id) and four case–control studies (Clemens, 1982 1272 /id; Danchin, 1989 7167 /id; Hickey, 1985 1242 /id; Strom, 1998 5998 /id). Due to the limited evidence relating to the range of possible predisposing cardiac conditions, case series studies (n = 11) of patients who had had IE that had considered possible pre-disposing cardiac conditions and that included 50 or more participants were also been reviewed and the relevant results presented.[b]

The impact of underlying cardiac conditions on the outcomes of IE was considered. Outcome data were identified from five cohort studies, a national survey paper and twelve case series papers. Three studies used data from the International Collaboration on Endocarditis Database.

2.1.3 Pre-existing cardiac conditions in adults and children and their effect on the risk of developing IE

Recommendation number 1.3.2.1

The following patients should be regarded as being at increased risk of developing IE and should receive antibiotic prophylaxis as outlined in the recommendations below, those with:

- acquired valvular heart disease with stenosis or regurgitation
- valve replacement

[b] 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.

- structural congenital heart disease (including surgically corrected or palliated structural conditions; excluding isolated atrial septal defect, repaired ventricular septal defect or repaired patent ductus arteriosus)
- hypertrophic cardiomyopathy.

2.1.4 Evidence review

Congenital heart disease

a) Aortic stenosis, pulmonary stenosis, ventricular septal defect

The Second Natural History Study (1983-89) (Level 2+) followed-up a cohort (n = 2401) of those 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, 1993 539 /id).

BE incidence rate; aortic stenosis (n = 22/462), an incidence rate of 27.1 per 10,000 person-years (17.0 to 41.0); pulmonary stenosis (n = 1/592), an incidence rate of 0.9 (0.02 to 5.2) and with VSD (n = 32/1,347), an incidence rate of 14.5 (9.9 to 20.5).

The ratio of post-operated aortic stenosis compared with non-operated was 2.6 (1.1 to 6.6), p = 0.0150, with BE more than twice as likely to develop in operated than in those with aortic stenosis that were medically managed. For those with aortic stenosis there was no significant difference in the incidence of BE in those with and without regurgitation.

For VSD the ratio of non-operated to post-operated was 2.6 (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 n = 2,401 NHS 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, 1998 3609 /id). This included n = 185 patients (n = 214 episodes of IE), who were divided into Group I (un-operated or palliative procedures; n = 128) and Group II (who had had definitive repair including aortic, pulmonary, mitral and/or tricuspid valvotomy, repair or valve replacement; n = 57).

Left ventricular outflow tract lesions were the most frequent of those in which IE developed in n = 42 patients (n = 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 (n = 31 patients, n = 37 episodes) with n = 6 patients (n = 6 episodes) in Group II.

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

c) Repair of major congenital heart defects

A cohort study (Level 2+) was completed in the USA, reported on those who had had surgical repair of major congenital heart defects; this was further expanded to include 12 major heart defects (n = 3,860, follow-up data available for 88%) (Morris, 1998 6086 /id).

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

[c] 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*	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.

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[d]. The incidence appeared to increase more rapidly after 5 years, and by 25 years the cumulative incidence was 13.3% (SE 3.8%). For those with aortic stenosis 16% (n = 28) had aortic valve replacement; for prosthetic valves there were n = 3 cases of IE (10-year incidence 26%), for native valves there were n = 10 cases of IE (10-year incidence 5%). IE in other underlying conditions, following surgery: coarctation 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 ASD, coarctation, pulmonary atresia, and pulmonary atresia with intact septum.

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

Case control studies [e]

a) Valvular disease

A population based case-control study (Level 2+) was undertaken in the USA (Strom, 1998 5998 /id). There was one control for each case matched for age, sex, ethnicity, education, occupation and dental insurance status; cases (n = 273) were identified from surveillance of 54 hospitals in eight counties, 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[f] odds ratio 16.7; 7.4 to 37.4)

Table 2 Risk of IE with valvular disease

Risk factor	Cases (n = 273)	Controls (n = 273)	Adjusted OR[g] (CI 95%)
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 *	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)

*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 1 of these factors were only reported once.

b) Mitral valve prolapse

There were three studies (Level 2+) which used a case-control methodology to consider the risk of endocarditis in those with mitral valve prolapse (MVP).

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

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

[g] 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, 1982 1272 /id)	(Danchin, 1989 7167 /id)	(Hickey, 1985 1242 /id)
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 6 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 pre-existing 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, 1982 1272 /id). There were three age and sex matched controls for each case; cases were identified from records that fulfilled the criteria for BE (n = 51), controls were selected from those who had undergone echocardiography during the period covered in the study (n = 153)[h]. 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.

[h] Controls with antecedent heart disease were excluded.

A French case-control study (Level 2+) reported on MVP as a risk factor for IE (Danchin, 1989 7167 /id). This study used two age and sex matched controls for each case; cases (n = 48) were identified from records of those with BE admitted to cardiology and cardiovascular surgery, controls (n = 96) were identified from a random sample 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, also considered MVP and BE (Hickey, 1985 1242 /id). There were three age, sex and date of echocardiography matched controls for each case; cases (n = 56) were selected from those admitted with BE, controls (n = 168) were selected from inpatients who did not have BE and underwent an echocardiography during the study period[i]. 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.

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

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

Reference	Study/Dates/Location	Relevant results
(Benn, 1997 3640 /id)	Retrospective review January 1984 to December 1993 Denmark	Predisposing factors in n = 62 episodes (n = 59 patients) of IE Congenital heart disease – total 7 Aortic stenosis 2 Aortic, mitral and triscuspid regurgitation 1 Floppy mitral valve 1 Fistula in septum 1 Ebstein's anomaly 1 Transposition of great arteries and VSD 1 Acquired heart disease – total 34 Aortic valve prosthesis 6 Mitral valve prosthesis 2 Pacemaker and mitral valve prosthesis 1 Aortic regurgitation 5 Aortic stenosis 6 Mitral stenosis 8 Mitral stenosis, rheumatic 3 Aortic stenosis, rheumatic 3
(Bouza, 2001 3442 /id)	Prospective study March 1994 to October 1996 Spain	n = 109 episodes of IE (n = 39 IVDU), underlying conditions Native valve endocarditis 52 Cardiac diseases 18(34.6%) Rheumatic valves 6(11.4%) Arteriosclerotic valves 4(7.7%) Mitral prolapse 1(2%) Other 7(13.4%) Prosthetic valve endocarditis 18 Cardiac diseases 18(100%) Valvular prosthesis 18(100%) (previous endocarditis) 3(16.6%)
(Cecchi, 2004 5098 /id)	Prospective multicentre survey January 2000 to December 2001 Italy	n = 147 cases IE, n = 104 considered related to predisposing heart disease Prosthetic valves 37(25%) Native valves 67(45%) Mitral valve prolapse 25 Aortic stenosis 5 Aortic stenosis and insufficiency 6 Mitral stenosis 2 Mitral stenosis and insufficiency 3 Aortic insufficiency 6 Mitral insufficiency 3 Mitral and aortic insufficiency 5 Bicuspid aortic valve 8 Interventricular septal defect 1 Previous mitral valvuloplasty 2 Aortic valve sclerosis 2
(Choudhury, 1992 6781 /id)	Retrospective review January 1981 to July	n = 190 episodes (n = 186 patients) of IE, underlying heart disease (rheumatic heart disease n = 79(42%), normal n = 17(9%))

	1991 India	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		
(Chu, 2004 69 /id)	Case review 1997 to 2002 New Zealand	n = 65 episodes (n = 62 patients) of IE, predisposing heart conditions (normal valves 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%)
				Implantable cardioverter defibrillator	1(1.6%)
		*post repair			
(Dyson, 1999 191 /id)	Epidemiological review March 1987 to March 1996 Wales	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%)
		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	1(1.3%)		

		cardiomyopathy
(Griffin, 1985 10723 /id)	Population based study 1950 to 1981 Minnesota, USA	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
(Mansur AJ, 2001 551 /id)	Case series Mean follow-up 6.1years for survivors, 3.7 for those who died Brazil	n = 420 adult and paediatric, underlying cardiac conditions Valvular heart disease 177(42.1%) Congenital heart disease 49(11.7%) Hypertrophic cardiomyopathy 3(0.7%) Chagas cardiomyopathy 1(0.2%) Endocardial fibroelastosis 1(0.2%) Prosthetic heart valve 91(21.7%)
(Salman, 1993 555 /id)	Case review in children January 1977 to February 1992 USA	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
(Tleyjeh IM, 2005 534 /id)	Population-based survey 1970 to 2000 USA	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%)
(van der Meer, 1992 1124 /id)	Consecutive case series November 1986 to November 1988 Netherlands	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 (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 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

Underlying heart disease in n = 349 NVE

Aorta	110(31.5%)	Mitral	125(35.8%)
Bicuspid valve	2	Prolapse	1
Bicuspid valve and AOI/AOS	3	Prolapse and regurgitation	27
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		
Fallot's tetralogy	5		
Other	8		

Prosthetic valve

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

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

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Evidence statement

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

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

- *isolated atrial septal defect*
- *repaired ventricular septal defect*
- *repaired patent ductus arteriosus.*

2.1.5 Pre-existing cardiac conditions associated with relatively poorer outcomes from IE

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, 1998 3609 /id). This included n = 185 patients (n = 214 episodes of IE), who were divided into Group I (un-operated or palliative procedures; n = 128) and Group II (who had had definitive repair including aortic, pulmonary, mitral and/or tricuspid valvotomy, repair or valve replacement; n = 57).

Recurrent attacks of IE occurred in n = 21, 11%(n = 19 Group I); VSD (n = 6), congenital corrected transposition of the great arteries with VSD and pulmonary stenosis (n = 3), pulmonary atresia with VSD (n = 2), single ventricle (n = 2), MVP (n = 2), Fallot with aortic regurgitation (n = 1), transposition of the great arteries with VSD (n = 1), congenital abnormal valves (n = 2).

The cardiac lesions of the n = 8 (n = 3 Group I and n = 5 Group II) 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.

The Second Natural History Study (Level 2+) (1983-89) followed-up a cohort (n = 2,401) of patients with aortic stenosis, pulmonary stenosis and ventricular septal defect (Gersony, 1993 539 /id). Those with aortic stenosis had complications in n = 13/22 and those with VSD had complications in n = 15/32.

A prospective observational cohort study (Level 2+) included patients with PVE enrolled in the International Collaboration on Endocarditis-Prospective Cohort Study from 61 medical centres in 28 countries, from June 2000 to August 2005, n = 2670 with IE (Wang, 2007 2926 /id). Those with PVE compared with those with NVE had significantly higher rates of in-hospital death (22.8% vs. 16.4%, $p < 0.001$) and other systemic embolisation (not stroke) (24.7% vs. 14.9%, $p < 0.001$). Complications which 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[j] identified no significant difference in in-hospital mortality for those with PVE.

A study (Level 2+) in the USA considered data collected by the International Collaboration on Endocarditis-Merged Endocarditis Database, n = 159 (Anderson, 2005 542 /id). n = 45/159 involved a prosthetic valve and n = 114 involved native valves. With enterococcal endocarditis those with PVE were significantly more likely to have intracardiac abscesses vs. NVE, $p = 0.009$, whereas those with enterococcal NVE were significantly more likely to have detectable vegetations vs. PVE, $p<0.001$. Rates of complications were not significantly different between the PVE and NVE for; heart failure, all embolism, CNS complications, stroke, valvular surgery during this episode, and death during hospitalisation (14% vs. 12%).

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

The International Collaboration on Endocarditis Merged Database (Level 2+) was used to consider a cohort who had surgical therapy for PVE, n = 355 (Wang, 2005 728 /id). In-hospital complications were; CHF 38.6%, systemic embolisation 27.3%, brain embolisation 18.9%, 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.

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

Reference	Study/Dates/Location	Relevant results
(Bouza, 2001 3442 /id)	Prospective study March 1994 to October 1996 Spain n = 109 patients	Mortality: IE related mortality was 25.7% (total n = 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; n = 16(30.7%) of those with NVE; n = 2(33%) of those with early PVE; n = 6(50%) of those with late PVE
(Chu, 2004 69 /id)	Case review 1997 to 2002 New Zealand n = 62 patients	Mortality: Overall n = 20; n = 11(55%) with NVE; n = 6(30.0%) with PVE
(Dyson, 1999 191 /id)	Epidemiological review March 1987 to March 1996 Wales n = 125 patients	Mortality: Overall n = 21; n = 9(12.3%) with NVE; n = 12(24.5%) with PVE
(Gentry 1989 1813 /id)	Consecutive case review 1983 to 1989 USA n = 94 patients	Therapeutic failure:[k] Overall failure 24% (14% death; 11% relapse); NVE failure was 28% (17% death; 11% relapse); PVE failure was 20% (10% death; 10% relapse)
(Mansur AJ,	Case series	Relapse[l]:

[k] Defined as relapse caused by the same organism or as in-hospital death.

[l] 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.

2001 551 /id)		Overall n = 14
	Mean follow-up 6.1years for survivors, 3.7 for those who died	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
	Brazil	
	n = 420 adult and paediatric patients	Valve replacement: PVE was a risk factor for having valve replacement (risk ratio 1.61, p = 0.0099)
(Calderwood, 1986 7394 /id)	Case series/review	n = 76/116 (64%) complicated PVE[m]
	1975 to 1982	Mortality: n = 27(23%) during initial hospitalisation
	USA	Significantly lower with coagulase-negative staphylococci (OR<1)
	n = 116 with prosthetic valve endocarditis	Complications: n = 89 discharged; n = 71 had mild or no CHF, n = 13 moderate CHF, n = 5 severe CHF
		Relapse: n = 11 (12%) (not significantly affected by valve site or infecting organism)
(Habib, 2005 2147 /id})	Consecutive case series	Mortality: n = 22(21%) died in-hospital 32mth mean follow-up; n = 61(58%) survival
	January 1991 to March 2003	Significantly associated with in-hospital mortality; severe co-morbidity (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)
	France	
	n = 104 with prosthetic valve endocarditis	Predictors of in-hospital death; severe heart failure (OR 5.5, 1.9 to 16.1, 95%CI), S aureus infection (OR 6.1, 1.9 to 19.2, 95%CI)
		Complications: Similar between early and late endocarditis
(Sett, 1993 6739 /id)	Retrospective review	PVE incidence: n = 56/3200 (1.8%)

[m] 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 days of more days during antibiotic therapy; new or progressive abnormalities of cardiac condition.

	1975 to 1988 Canada n = 3200 with porcine bioprosthesis	Mortality: Overall n = 18(32%); early PVE 75%, late PVE 25% [n] Predictors of death; renal status, presence of ongoing sepsis, mode of treatment, presence of fever, previous dental procedure, lack of dental prophylaxis, time to diagnosis, age>65yrs ($p < 0.05$) 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, 1998 3598 /id)	*National survey* *1992 to 1996* *Slovakia* *n = 180 native valve endocarditis*	*Mortality:* *n = 40(22.2%), n = 140 survival at Day60* *Risk factors for death; age>60yrs (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, 1993 6685 /id)	*Consecutive case series* *1966 to 1991* *The Netherlands* *n = 130*	*Mortality:* *n = 91(90%) survived the hospital phase* *Mean follow-up 8.7yrs, n = 64 (63%) survival, of these n = 45 did not have recurrent endocarditis or valve replacement* *Complications:* *Heart failure (RR 47.6, 9.1 to 249.0, 95%CI) and aortic valve endocarditis (RR 3.0, 1.7 to 14.3, 95%CI) were associated with a high risk for urgent surgery or death or both*
(Ishiwada N, 2005 560 /id)	*Case series/(registered by professional body)* *1997 to 2001* *Japan* *n = 188 paediatric and adults with CHD*	*Mortality:* *n = 20(10.6%), highest mortality <1yr old (n = 5/16, 31.3%)* *Complications:* *Occurred in 67%; no significant difference in complications between causative organisms*
(Martin JM, 1997 556 /id)	*Retrospective review* *1958 to 1992* *USA* *n = 73 paediatric patients*	*Mortality:* *n = 13 (18%) died during initial hospitalisation* *Complications:* *n = 30(41%) recovered with no complications* *n = 30 (41%) had complications*

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

Evidence statement

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 death compared with those with native valve endocarditis.

Evidence to recommendations

The Guideline Development Group 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 Guideline Development Group debated the potential for confusion which can arise from stratification of risk groups. Acknowledgement was given that there are those with certain cardiac conditions who have a higher risk than others, notably those with prosthetic valves. However, given the difficulties in relative risk definition, the Guideline Development Group decided that a simple classification of conditions into either at risk or not at risk groups would assist with clarity.

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

The Guideline Development Group considered that where cardiac conditions were not associated with an increased 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 Guideline Development Group. The focus of the discussion was on the difference in mortality rates identified between prosthetic and native valve endocarditis. While the Guideline Development Group noted that those with prosthetic valves have increased rates of mortality they also noted the overall high levels of morbidity and mortality with IE irrespective of underlying cardiac condition. The Guideline Development Group 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 IE

2.2.1 Introduction

Infective endocarditis 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 pre-existing cardiac conditions (see section 2.1 'Risk/outcomes of developing IE with cardiac conditions'). 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 an increased risk of this bacteraemia leading to the development of IE. Consideration also has to be given that transient bacteraemias arise spontaneously with normal daily activities such as chewing or toothbrushing (Moreillon, 2004 141 /id). . This is likely to contribute to the cases of IE which occur without a history of specific dental or surgical procedures (as many as 60-75% of cases) (Steckelberg, 1993 371 /id).

Experimental animal models have shown that bacteraemia can cause IE; however, the intensity of bacteraemia used has been very high when compared with that which has been detected in both adults and children following interventional dental procedures (Roberts, 1999 34 /id). It is important therefore to determine whether there is any evidence of a level of post-procedure bacteraemia which can be considered to be significant in terms of the aetiology of IE – that is, a threshold level that is considered to result in an increased risk of developing IE.

It is also important to consider the organisms which cause bacteraemia following interventional procedures and which in certain cases lead to the development of IE. A population-based study which collected data in the Netherlands during a 2-year period identified the following groups of

organisms in cases of bacterial endocarditis (BE): viridans streptococci (n = 200/419, 48%), staphylococci (n = 124/419, 30% – staphylococcus 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 commonest 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 X): dental, upper and lower gastro-intestinal (GI) tract, genitourinary tract and upper and lower respiratory tract procedures.

2.2.2 Existing guidelines

Interventional procedures

Dental procedures: the AHA guideline (Wilson, 2007 521 /id) discussed case reports/reviews which 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, 2006 6 /id; Horstkotte, 2004 15 /id; Advisory Group of the British Cardiac Society Clinical Practice Committee, 2004 22 /id). The ESC and BCS/RCP guidelines included this alongside discussion which noted the assumption that dental procedures are associated with a risk of developing IE.

Non-dental procedures: the AHA guideline noted that conclusive links have not been demonstrated between the respiratory tract and IE and for GI and GU tract the possible association with IE has not been studied extensively. The BSAC guideline noted that there is no good epidemiological data on the impact of bacteraemia from non-dental procedures on the risk of developing endocarditis. The ESC guideline identified bacteraemia associated with respiratory, GI and GU procedures. The BCS/RCP guideline 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 and ESC 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. The AHA guideline 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 highlighted that the significance of both the magnitude and duration of bacteraemia is unknown. In contrast, the BCS/RCP guideline 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 an increased risk of developing IE

2.3.1 Overview

A nationwide prospective study of the epidemiology of bacterial endocarditis was completed in the Netherlands, this study considered antecedent procedures and use of prophylaxis (van der Meer, 1992 6811 /id). 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, 1995 1013 /id). In the other study the cardiac status of the control group was unknown (Strom, 2000 876 /id; Strom, 1998 5998 /id[o]). One case series considered a 28-year trend of IE associated with congenital heart disease (Takeda, 2005 4882 /id). A further paper used a survey of n = 2805 adults and applied the results to the adult

[o] One study reported in two papers, one for dental procedures and one for oral hygiene and nondental procedures.

population and estimated the risk of endocarditis with predisposing cardiac conditions undergoing dental procedures with or without antibiotic prophylaxis (Duval, 2006 10629 /id).

2.3.2 Dental and other interventional procedures associated with increased risk of IE in people with defined pre-existing cardiac conditions

Evidence review

The study (Level 2+) completed in the Netherlands (population 14.5 million) considered the epidemiology of bacterial endocarditis, using all suspected cases of BE (based on blood cultures) over a 2-year period (van der Meer, 1992 6811 /id). n = 149/427 (34.9%) had undergone a procedure[p] within 180 days of the onset of symptoms, with n = 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, CI 2.8 to 8.7).

A French case control study (Level 2+) considered n = 171 cases who were interviewed following diagnosis of IE[q] and the same number of matched controls (matched as regards age, sex and group of underlying cardiac conditions) (Lacassin, 1995 1013 /id). n = 8 (51.5%) of cases and n = 70 (41%) of controls had undergone at least one procedure[r]. Adjusted OR for the risk of IE related to a procedure was 1.6 (1.01 to 2.53, 95%CI), p<0.05. For all procedures the mean number of procedures was significantly higher in cases than controls (4.5 vs. 2.0, p < 0.05). The risk of IE increased with the number of procedures per case, RR for one procedure 1.2; 1.7 for two procedures; 3.6 for three or more procedures (p = 0.005).

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

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

A population based case-control study (Level 2+) which considered dental risk factors (Strom, 1998 5998 /id) and the risk factors with oral hygiene and non-dental procedures (Strom, 2000 876 /id), was undertaken in the USA, n = 273 cases. There was one control for each case 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% for both groups 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 ($p = 0.03$, though numbers were small, n = 6 cases and n = 0 controls). The n = 56 cases who were infected with dental flora compared with their controls 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, though when restricted to cases (and matched controls) who were infected with skin flora the OR for skin infections increased to 6.0 (1.3 to 27, $p = 0.019$). Following multivariate analysis only barium enema remained significant, OR 11.9 (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, nasal-oxygen therapy).

A Japanese case series (Level 3) considered a 28-year trend of IE associated with congenital heart disease (Takeda, 2005 4882 /id). Preceding events were documented in n = 61/183 patients. These events were dental procedures in n = 38, 21%, atopic dermatitis in n = 3, 2% and other in n = 10, 5%.

A study completed (Level 3) in France considered the estimated risk of endocarditis in adults with predisposing cardiac conditions (PCC) undergoing dental procedures with or without antibiotic prophylaxis (Duval, 2006 10629 /id). The authors discussed the difficulties with 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 this formula: risk = annual number of IE cases after at-risk dental procedures in adults with known PCCs /annual number of at-risk dental procedures in adults with known PCCs. The prevalence of PCC was n = 104 native valve (n = 12/15 dental procedures were unprotected) and n = 24 prosthetic valve (n = 2/4 dental procedures were unprotected). Applying these to the French population of 1999 showed an estimate of a known PCC in 3.3% (n = 1,287,296; 2.6 to 4%) of the 39million adults, with a rate of 2.1 procedures per subject per year (of these 62% were performed without antibiotic prophylaxis). n = 12/182 cases of IE occurred in adults with known PCC after at-risk dental procedures and were considered due to an oral microorganism (n = 10 unprotected). The estimated risk of IE after at-risk dental procedure in adults with known PCC was: 1 case per 46,000 (CI, 36,236 to 63,103) for unprotected at-risk dental procedures; 1 case per 54,300 (CI, 41,717 to 77,725) for unprotected at-risk dental procedures in those with native valve PCC; 1 case per 10,700 (CI, 6,000 to 25,149) for unprotected at-risk dental procedures in those with prosthetic valve PCC; 1 case per 149,000 (CI, 88,988 to 347,509) for protected at-risk dental procedures.

Evidence statement

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

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 IE. Therefore searches were completed to identify studies which considered the levels of bacteraemia associated with interventional procedures; this included dental procedures and non-dental interventional procedures. For bacteraemia related to dental procedures there were RCTs identified; however for bacteraemia related to other procedures the majority of the studies used an uncontrolled case series study design.

There were eight studies identified which 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, 2000 891 /id; Lucas, 2002 9668 /id; Roberts, 2000 460 /id; Roberts, 2006 2375 /id; Roberts, 1997 4116 /id; Roberts, 1998 2440 /id). While the majority of studies included considered bacteraemia levels at one or two time points following the procedure, one study did consider the duration of bacteraemia following dental extraction (Roberts, 2006 2375 /id). There was also a controlled study in children requiring dental extractions (Peterson, 1976 7927 /id), a case series which also considered bacteraemia following dental extraction in adults and children (Tomas, 2007 27 /id) and a retrospective theoretical analysis which considered the records of children with congenital disease having dento-gingival procedures (Al Karaawi, 2001 3435 /id).

There were sixteen studies which considered bacteraemia related to gastrointestinal procedures. There were also two controlled studies both of which considered upper endoscopic procedures (Sontheimer, 1991 4843 /id; Zuccaro, 1998 11644 /id). The remaining studies were predominantly case series studies (Barawi, 2001 11634 /id; Barragan Casas, 1999 1680 /id; el Baba, 1996 627 /id; Ho, 1991 11637 /id, 1991 829 /id; Kullman, 1992 796 /id; Kullman, 1995 1016 /id; Lo, 1994 4770 /id; London, 1986 952 /id; Low, 1987 930 /id; Melendez, 1991 828 /id; Mellow, 1976 1065 /id; Roudaut, 1993 4795 /id; Shull, 1975 1069 /id; Shyu, 1992 3820 /id, 1992 4805 /id; Weickert, 2006 42 /id).

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 which considered preoperative enema effects on prostatic ultrasound (Lindert, 2000 447 /id), a case series which considered bacteraemia during caesarean delivery (Boggess, 1996 6337 /id), a case series on extracorporeal shock wave lithotripsy (Kullman, 1995 1016 /id), a case series on bacteraemia during nasal septoplasty (Silk, 1991 4847 /id), a case series on bacteraemia related to fibreoptic bronchoscopy (Yigla, 1999 11640 /id) and a case series on bacteraemia during tonsillectomy (Lucas, 2002 9668 /id).

Evidence review

Dental

Six RCTs (Level 1+) considered paediatric patients referred for dental treatment at hospitals in London. One considered n = 155 referred for cleaning procedures under general anaesthetic, n = 52 in a toothbrushing group, n = 53 professional cleaning group, n = 50 scaling group, and n = 50 were a control group using data taken from a previous study (Lucas, 2000 891 /id). 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 n = 142 patients undergoing general anaesthesia receiving treatment in four groups, upper alginate impression, separator, fit/placement of band and archwire adjustment (Lucas, 2002 324 /id). 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 n = 735 children (nonmanipulation group, cleaning procedures, minimal manipulation group, conservative dentistry procedures, oral surgery group and the group having antibiotic prophylaxis) (Roberts, 1997 4116 /id). All procedures were associated with a bacteraemia, the highest association was found with intraligamental injection, the lowest was with a fast drill. Comparison of proportions compared with baseline, significant differences; 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% and mucoperiosteal flap 13.4 to 46.2%. No significant differences with dental examination, nasotracheal tube, slow drill and fast drill.

One RCT (Level 1+) considered bacteraemia associated with conservative dentistry in n = 257 children in five groups; rubber dam placement, slow drill, n = 47 fast drill, matrix band and wedge and a baseline group having no procedure (Roberts, 2000 460 /id). 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 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 ($p<0.0001$). There were no significant differences between: baseline vs. slow drill; baseline vs. fast drill; rubber dam placement vs. matrix band; slow drill vs. 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 children, n = 143 (Roberts, 1998 2440 /id). Positive blood cultures were identified in baseline (8.0%), buccal infiltration (15.6%), modified intraligimental (50.0%), conventional intraligamental (96.6%). There were significant differences between 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 ($p<0.0001$). There was no significant difference between baseline vs. buccal injection.

The final RCT (Level 1+) considered the duration of bacteraemia in n = 500 children after dental extraction (Roberts, 2006 2375 /id). The children were allocated to time groups which ranged from 10 sec to 1hr. The intensity of bacteraemia (cfu/6 ml sample) showed significant differences in the before extraction median and after extraction median for the time points at 10 sec ($p = 0.001$), 30sec ($p = 0.001$), 1 min ($p = 0.003$), 2 min ($p = 0.009$), 4 min ($p = 0.002$) and 7.5 min ($p = 0.002$). The differences were not significant for the before and after extraction medians for the 15 min, 45 min and 1hr time points[s]. The odds of having a positive culture were significantly greater in the post-extraction time than the pre-extraction time (OR > 1) at each time point up to and including a post-procedure time of 7.5min but not after this time point.

A controlled trial (Level 2+) in the USA considered the incidence of bacteraemia in paediatric patients following tooth extraction, n = 107 (Peterson, 1976 7927 /id). This study had four groups, group I extraction of healthy teeth for reasons other than disease, group II removal of teeth which

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

had diseased or necrotic pulps and associated abscesses, group III removal of permanent teeth for orthodontic reasons, group IV restorative dental treatment which served as a negative control. Positive cultures were identified in 35.7% 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 significant correlation found between the number of teeth extracted and the post-procedural blood culture.

One case series (Level 3) considered bacteraemia in adults and children at three time points following dental extractions in n = 53 patients in Spain (Tomas, 2007 27 /id). 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 dento-gingival manipulative procedure. This study considered theoretical calculated cumulative exposure derived from the following equation: intensity[t] x tally[u] x prevalence[v] x duration[w] = cumulative exposure in cfu/ml/procedure/year (Al Karaawi, 2001 3435 /id). 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 permanent tooth, and single extraction primary tooth.

Gastrointestinal

Two controlled studies (Level 2+) were identified, the first considered bacteraemia in n = 120 patients following operative upper GI endoscopy, with

[t] Number of cfu/ml blood.
[u] Average number of a given dentogingival manipulative procedures performed annually.
[v] The number of positive cultures expressed as a proportion.
[w] Length of bacteraemia, which is 15 mins.

a control group of n = 40 who had diagnostic endoscopy with or without sample biopsies (Sontheimer, 1991 4843 /id). 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 n = 103 of those with dysphagia having upper GI endoscopy and stricture dilation with a control group of n = 50 patients without dysphagia undergoing upper GI endoscopy for reasons unrelated to swallowing disorders (Zuccaro, 1998 11644 /id). 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 1min, 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 fourteen case series studies identified related to gastrointestinal procedures. These case studies considered bacteraemia following interventional gastrointestinal procedures; however the majority analysed only one or two post-procedure blood culture time points. Therefore assessment of the duration of intervention related bacteraemia is, accordingly, difficult.

1027 **Table 6 Bacteraemia associated with interventional procedures**

Reference	No. of patients	Procedure	Outcomes
(Barawi, 2001 11634 /id)	100	Endoscopic ultrasound guided FNA	No significant bacterial growth not considered related to contaminants Follow-up 1wk no infectious complications
(Barragan Casas, 1999 1680 /id)	102	n = 44 gastroscopy n = 30 colonoscopy n = 28 ERCP	Gastroscopy – positive cultures, n = 8 at 5min, n = 6 at 30min Colonscopy – positive cultures, n = 3 at 5min, n = 1at 30min ERCP – positive cultures, n = 4 at 5min, n = 9 at 30min
(el Baba, 1996 627 /id)	95 children	n = 68 oesogagastrod-uodenoscopy n = 29 colonoscopy n = 11 flexible sigmoidoscopy	n = 4 post endoscopy blood cultures were positive, none were indigenous oropharyngeal or GI flora Follow-up 72hrs after procedure those with positive culture were afebrile and without any evidence of sepsis
(Ho, 1991 11637 /id)	72	n = 36 emergency endoscopy n = 36 sclerotherapy groups	Emergency endoscopy n = 5 post-procedure positive blood cultures Sclerotherapy – elective EVS n = 5, emergency EVS n = 10 post-procedure positive blood cultures no significant differences between the post-endoscopy 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 post cultures, p = 0.03
(Kullman, 1992 796 /id)	180	n = 115 diagnostic ERCP n = 65 therapeutic ERCP	15% of diagnostic and 27% of therapeutic procedures had bacteraemia within 15min, no significant difference between the groups Follow-up 4 to 26mths no bacteraemic patients developed clinically overt endocarditis
(Lo, 1994 4770 /id)	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, 1986 952 /id)	50	Colonoscopy	In n = 2 the positive culture was considered to be directly related to the colonoscopy
(Low, 1987 930 /id)	270	n = 165 colonoscopy only n = 105 colonoscopy plus polypectomy	Colonoscopy only 4.1% blood cultures were positive at 10 or 15min, polypectomy group 3.6% positive at 30sec, 5 or 10min, there was no significant difference between the groups Follow-up, no patients developed clinical evidence of sepsis during the 24hr following

			the procedure
(Melendez, 1991 828 /id)	140	Transoesophgeal echocardiography (TOE)	Positive blood cultures in n = 2 within 5mins and n = 2 at 1hr, the relative risk of bacteraemia immediately after and 1hr 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 12wks no patients had developed BE or other infections requiring the administration of therapy
(Mellow, 1976 1065 /id)	100	Upper GI endoscopy	Positive blood cultures in n = 3 after endoscopy, no correlation between associated medical conditions, GI lesions, or endoscopic manipulation and post-endoscopy bacteraemia Follow-up, none of those with bacteraemia had any detectable symptoms of subsequent sepsis
(Roudaut, 1993 4795 /id)	82	TOE	2.4% had a single positive blood culture Follow-up, average 4mths, no signs of endocarditis detected
(Shull, 1975 1069 /id)	50	Upper GI endoscopy	Bacteraemia detected in 8% at 5 or 30min, no blood samples taken during the procedures were positive Follow-up of those with positive cultures showed no clinical manifestations of bacteraemia
(Shyu, 1992 3820 /id)	132	TOE	None of the blood samples taken after the procedure were positive, n = 1 patient had positive cultures 4hrs after the procedure Follow-up, no evidence of endocarditis in these patients
(Weickert, 2006 42 /id)	100	n = 50 conventional laparoscopy n = 50 minilaproscopy	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 and the other did not, n = 50 (Lindert, 2000 447 /id). n = 8 (16%) had positive blood cultures after biopsy,

enteric flora were identified in n = 5 (n = 7 who did not have the enema and n = 1 who did, p = 0.0003 for the difference). There was no correlation between positive 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.

Case series (Level 3) (see table 7)

Table 7 Bacteraemia associated with interventional procedures

Reference	Number of patients	Procedure	Blood cultures
(Boggess, 1996 6337 /id)	93	Caesarean delivery	14% bacteraemia after labour or rupture of membranes Positive blood cultures were associated with earlier median gestational age at delivery (<32wks, OR 13.9; 3.5 to 54.8), lower median birth weight (<2500g, OR 10.5; 2.8 to 39) and positive chorioamnionic membrane culture (OR 6.4; 1.7 to 24.7)
(Kullman, 1995 669 /id)	76	Extra corporeal shock wave lithotripsy (ESWL)	Positive blood cultures during ESWL n = 16, after 5min n = 12, after 20min n = 6, after 18hrs n = 3 During follow-up no patients developed sepsis or clinically overt endocarditis
(Silk, 1991 4847 /id)	50	Nasal septoplasty	None of the blood cultures showed bacterial growth
(Yigla, 1999 11640 /id)	200	Fibreoptic bronchoscopy	13% (n = 26) positive blood cultures, n = 13 at 0 and 20min, n = 13 at 20+min, defining true bacteraemia as those which two post-procedure 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, 2003 238 /id)	64	Tonsillectomy	27.3% of blood cultures taken within 2mins of tonsillectomy were positive, 6.5% of those taken at 15mins, 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 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 which did classify the bacteraemia did not use similar categories. One controlled study (Ho, 1991 11637 /id) did categorise positive blood cultures based on previous studies; into significant and non-significant; these categories were dependent on the micro-organisms isolated and related numbers of positive cultures. A second controlled study (Sontheimer, 1991 4843 /id) 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, 2000 456 /id). 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, 1997 4116 /id). One further study considered a comparison of transient bacteraemia between brushing with a conventional toothbrush and with an electric toothbrush (Bhanji, 2002 829 /id). Toothbrushing was associated with positive blood cultures in 46% of manual and 78% of those using the electric toothbrush, $p = 0.022$. There were no studies 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 defecation) were associated with bacteraemia.

Evidence statement

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

- *dental*
- *GI*
- *urological*
- *obstetric*
- *respiratory*
- *ENT.*

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

Evidence to recommendations

The Guideline Development Group noted that the evidence presented does not show any clear and consistent association between having a dental or other 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 Guideline Development Group noted that it is difficult to directly compare the level of bacteraemia between different dental procedures as the methodology of the bacteraemia studies was variable.

The Guideline Development Group considered that there are the 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 Guideline Development Group concluded that bacteraemia is associated with interventional procedures, toothbrushing and also occurs spontaneously in physiological activity (many included studies reported bacteraemia in pre-procedural blood samples).

The Guideline Development Group discussed the concept that an everyday oral activity - regular toothbrushing - may present a greater risk of IE than a single dental procedure because of the cumulative exposure to bacteraemia with oral flora. The Group considered that it was biologically implausible that a single dental procedure would lead to a greater risk of IE than regular toothbrushing.

Further discussion surrounded the organisms which have been implicated in the pathogenesis of IE and the most likely source of their origin, with particular reference to oral streptococci, staphylococcal and enterococci. The Guideline Development Group consensus was that the impact of enterococcal causation of IE is noteworthy as the outcome for those who develop IE from this organism (which is inherently more resistant to antibiotics) is deemed to be worse than with many other organisms.

The Guideline Development Group agreed that the evidence presented did identify bacteraemia arising from a range of non-dental interventional procedures. The Guideline Development Group concluded that as cases of IE occur with blood cultures positive to organisms which occur in the GU and GI tracts (for example enterococcus),then it logically follows that IE may occur following bacteraemias which arise from non-dental interventions. The Guideline Development Group also considered the lack of available evidence relating to bacteraemias arising from non-oral everyday activities. Their view was that there is no current proof for the hypothesis that activities such as defecation and urination cause a background level of bacteraemia that might account for a significant proportion of cases of IE.

Recommendation statement

The Guideline Development Group considered that recommendations on prophylaxis against IE could not be made solely based on the evidence relating to interventional procedures, the presence of post-interventional procedure bacteraemia and association with IE. 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 against IE

2.5.1 Introduction

Criteria for antibiotic prophylaxis against infection[x] have been developed and these include the following: that the health benefits must outweigh the antibiotic risks, the choice of antibiotic should be made on the single microorganism most likely to cause an infection, and that the cost-benefit ratio must be acceptable (Pallasch, 2003 144 /id).

Whether antibiotic prophylaxis is effective in reducing the incidence of 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 54 /id). The difficulty in determining whether antibiotics can reduce the incidence of a rare event (IE) has led to the use of post-procedure bacteraemia as a surrogate outcome measure in some studies of antibiotic effectiveness. However, as highlighted in section 2.5, there are problems in using bacteraemia as a valid surrogate outcome. A further problem is that the efficacy of prophylactic antibiotics is based on experimental studies done using animal models (Moreillon, 2004 141 /id) 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

[x] 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, 2006).

there has also been concern that their routine use may provoke the selection of resistant microorganisms (Brincat, 2006 93 /id).

Existing guidelines

The AHA guideline 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 (Wilson, 2007 521 /id). This guideline also noted the contradictory results with regard to the efficacy of topical antiseptics in reducing bacteraemia and that the body of evidence suggests no clear benefit. This guideline did not recommend prophylaxis for GI and genitourinary (GU) procedures; however, there was consideration was given to the recommendation that if antibiotics were being prescribed before a GI or GU procedure for other reasons then the chosen antibiotic(s) chosen should cover potential IE causing organisms.

The BSAC guideline 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 (Gould, 2006 6 /id). The ESC guideline 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 (Horstkotte, 2004 15 /id). This guideline noted that although the effectiveness of antibiotic prophylaxis has never been proven unequivocally in man, there is convincing evidence from clinical practice and experimental animal models that the strategy can be effective to prevent IE. The antibiotic prophylaxis recommended in both the BSAC and ESC guidelines aimed to reflect the potentially different infecting organisms between dental and non-dental procedures.

The BCS/RCP guideline noted that although doubts have been expressed about the value of antibiotic prophylaxis the following points – clinical experience documents IE following bacteraemia, bacteraemia occurs after various dental and instrumental procedures, that antibiotics are available that can kill potential causative organisms – mean it is prudent to offer prophylactic antibiotic therapy to individuals who are at higher risk of IE than the general

population (Advisory Group of the British Cardiac Society Clinical Practice Committee, 2004 22 /id). This guideline recommended the use of chlorhexidine hydrochloride 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 which considered penicillins for prophylaxis against bacterial endocarditis in dentistry (Oliver, 2004 134 /id). A study which considered the epidemiology of bacterial endocarditis identified those who had developed endocarditis who had and had not had antibiotic prophylaxis (van der Meer, 1992 6811 /id). There were two case control studies which considered procedures associated with IE (Lacassin, 1995 1013 /id) and risk factors for endocarditis (Strom, 2000 876 /id), these studies also identified and discussed antibiotic prophylaxis. An observational study considered two groups those who had and those who had not received prophylaxis (Horstkotte, 1987 531 /id). A study which estimated the risk of IE considered the potential impact with 100% prophylaxis (Duval, 2006 10629 /id).

Recommendation number 1.3.2.2

Antibiotic prophylaxis against IE is not recommended for patients at risk of IE undergoing dental procedures.

Recommendation number 1.3.2.3

Chlorhexidine mouthwash for prophylaxis against IE is not recommended for patients at risk of IE undergoing dental procedures.

Recommendation number 1.3.2.4

Patients at risk of IE should achieve and maintain high standards of oral health, this requires both:

- patient's responsibility and
- professional facilitation (with an emphasis on preventative dentistry).

Recommendation number 1.3.2.5

Antibiotic prophylaxis is recommended for patients at risk of IE undergoing endoscopic retrograde cholangiopancreatography (ERCP), manipulation of the biliary tract, and invasive oesophageal procedures and lower GI procedures.

Recommendation number 1.3.2.6

Antibiotic prophylaxis is recommended for patients at risk of IE for TURP, transrectal prostatic biopsy, lithotripsy and all urological procedures involving urethral manipulation except urethral catheterisation.

Recommendation number 1.3.2.7

Antibiotic prophylaxis to prevent IE is not recommended for patients at risk of IE (see exceptions in 1.3.2.5) undergoing:

- ear, nose and throat, upper respiratory tract and upper GI tract procedures
- bronchoscopy.

Recommendation number 1.3.2.8

Antibiotic prophylaxis to prevent IE is not recommended for patients at risk of IE undergoing obstetric and gynaecological procedures.

Recommendation number 1.3.2.9

Antimicrobial regimes should be modified to cover endocarditis-causing organisms when procedures are undertaken at a site of infection in patients at risk of IE.

Recommendation number 1.3.2.10

The following antibiotic regime should be used as prophylaxis against IE: amoxicillin plus gentamicin or for penicillin allergic patients teicoplanin plus gentamicin.

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 in dentistry (Oliver, 2004 134 /id). This review aimed to determine whether prophylactic penicillin administration compared with no such administration or placebo before invasive dental procedures in people at increased risk of BE influences mortality, serious illness or endocarditis incidence. This review did not search specifically to find papers on harms of the doses of amoxicillin. This review included one case control study (van der Meer, 1992 – 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 which 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 native valve endocarditis (van der Meer, 1992 1124 /id). Cases were patients with known cardiac disease in whom endocarditis developed within 180 days of a medical or dental procedure, n = 48. 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, n = 200. 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. [y]

A case control study (Level 2+) which involved cases and matched controls for procedures associated with infective endocarditis in adults (Lacassin, 1995 1013 /id) considered the protective efficacy of antibiotics. n = 8 cases of IE had occurred in those who had received an appropriate antibiotic prophylaxis, n = 4 with prosthetic valves and n = 4 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), n = 6 (23%) of cases vs. n = 6 (27%) of 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, 1992 6811 /id). Antibiotic prophylaxis had been administered to n = 8/48 (16.7%) of those with a native valve disease who known to have heart disease (n = 6 received 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 n = 9/16 (56.3%) of those with prosthetic valves (n = 1 received antibiotics in accordance with the Netherlands Heart Foundation guidelines, the antibiotics

[y] 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.

administered to the other patients could be considered to offer equivalent protection).

A population based case control study (Level 2+) which considered risk factors for infective endocarditis (Strom, 1998 5998 /id) 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% for 2 months; 1.1% and 1.1% for 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 with those who had undergone a procedure requiring endocarditis prophylaxis without having received any antibiotic regime, n = 533 (Horstkotte, 1987 531 /id). In those who received prophylaxis no cases of PVE were observed, whereas in those who had not received prophylaxis there were n = 6 cases, an incidence of 1.5 cases per 100 procedures (urological procedures 5.1%, oropharyngeal surgery 2.6%, gynaecological interventions 2.2%). n = 2/117 cases of PVE occurred after dental extraction without prophylaxis.

A study (Level 3) that estimated the risk of IE after an at-risk dental procedure considered that if antibiotics had been administered in 100% of at-risk dental procedures 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) n = 41 cases (95%CI 29 to 53) of IE would have been prevented in those with native valve conditions and n = 39 cases (95%CI 11 to 72) would have been prevented in those with prosthetic valve predisposing cardiac conditions (Duval, 2006 10629 /id).

Evidence statement

There is insufficient evidence to determine whether or not antibiotic prophylaxis in those at risk of developing IE 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 IE reduces the incidence of IE 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 (Level 1+) that addressed antibiotic prophylaxis and dental procedures. A Spanish RCT with n = 221 participants considered amoxicillin (2 g), clindamycin (600 mg), moxifloxacin (400 mg) and a control group taken orally 1 to 2 hours before anaesthesia induction for adult patients undergoing dental extractions under GA (Diz, 2006 1842 /id). There was a significant difference in the proportion of polymicrobial blood cultures in the control group (29%) vs. amoxicillin (0%) and vs. 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 post-procedure time points: - control vs. amoxicillin - control vs. moxifloxacin - amoxicillin vs. clindamycin - moxifloxacin vs. 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%	

An American RCT (Level 1+) with n = 100 participants compared amoxicillin elixir (50mg/kg) with a placebo taken 1 hour before intubation in children having dental treatment in the operating room (Lockhart, 2004 619 /id). 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, 15mins 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% vs. 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 vs. 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 ($p = 0.025$), 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 five studies are given in table 9, below.

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

Reference	Study type	Antibiotics	Bacteraemia	Differences
(Hall, 1993 2726 /id)	Controlled trial n = 60	penicillin (2g) amoxicillin (3g) placebo orally 1hr prior to dental extraction Level 1+	Pre-procedure; no growth During extraction; - 90% penicillin - 85% amoxicillin - 90% placebo 10mins 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, 1996 2578 /id)	RCT n = 38	erythromycin sterate (0.5g) clindamycin (0.3g) orally 1hr prior to dental extraction Level 1+	Pre-procedure; no growth During extraction; - 79% erythromycin - 84% clindamycin 10mins 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, 1996 4908 /id)	RCT n = 39	cefaclor (x2 0.5g) placebo (x2) orally 1hr before dental extraction Level 1+	Pre-procedure; no growth During extraction; - 79% cefaclor (streptococci 79%) - 85% placebo (streptococci 50%) 10mins extraction; - 53% cefaclor (streptococci 26%) - 47% placebo (streptococci 30%)	
(Roberts, 1987 528 /id)	RCT n = 108	amoxicillin (50mg/kg) control group orally 2hrs before surgery	Pre-procedure; samples negative 2mins after intubation; - n = 0/47 amoxicllin - n = 3/47 control Post-extraction; - n = 1/47	Post-extraction; control vs. amoxicillin, $p < 0.001$

			amoxicllin	
		Level 1+	- n = 18/47 control	
(Wahlmann, 1998581 /id)	RCT n = 59	cefuroxime (1.5g) placebo (0.9%NaCl) IV 10mins before multiple tooth extractions	10mins; - 23% cefuroxime - 79% control 30mins; - 20% cefuroxime - 69% control 10 or 30mins; - 33% cefuroxime - 86% control	Cefuroxime vs. placebo significant at 10mins, 30mins and 10 or30mins Duration of surgical procedure was not significant
		Level 1+		<6 or >10 teeth extracted not significant
(Shanson, 1985445 /id)	RCT n = 109 side effects study n = 82 bacteraemia study	erythromycin (1.5g) matched placebo orally 1hr before dental extraction Level 1+	Streptococcal bacteraemia; - 15% erythromycin - 43% control Side effects - 52% erythromycin vs. - 19% placebo	Erythromycin vs. control, p = 0.01

A retrospective analysis (Level 2+) was undertaken to consider the efficacy of prophylactic intravenous antibiotic regimens in the prevention of odontogenic bacteraemia in n = 92 children with severe congenital heart defects receiving dental treatment under GA (Roberts, 2002 2158 /id). 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 antibiotic groups 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

There were nine studies identified in relation to non-dental procedures and antibiotic prophylaxis. These included seven RCTs related to transurethral prostatectomy (Allan, 1985 977 /id), transrectal prostatic biopsy (Brewster, 1995 4118 /id) ERCP (Niederau, 1994 2662 /id; Sauter, 1990 2867 /id) transcervical resection or laser ablation of the endometrium (Bhattacharya, 1995 2602 /id) and sclerotherapy (Rolando, 1993 2719 /id; (Selby, 1994 5224 /id). Also identified were a meta-analysis which considered antibiotic prophylaxis with ERCP (Harris, 1999 2433 /id) and a systematic review which considered antibiotic prophylaxis with TURP (Qiang, 2005 1970 /id).

1406 **Table 10 non-dental procedures and antibiotic prophylaxis**

Reference	Study type	Antibiotics	Bacteraemia	Differences
(Allan, 1985 977 /id)	RCT n = 100	Mezlocillin (2g) Control group IV at about the time of induction of anaesthesia	Bacteraemia post-op; - 4% mezlocillin - 36% control	Post-op; mezlocillin vs. control, p<0.001 First day post-op and after catheter removal no significant difference between the groups
(Brewster, 1995 4118 /id)	RCT n = 111	Cefuroxime (1.5g) Piperacillin/tazobactam IV 20mins before procedure	Bacteraemia 48hrs; - n = 1 cefuroxime - n = 0 pip/tazo	
(Bhattacharya, 1995 2602 /id)	RCT	Augmentin 1.2g Control group IV at the induction of anaesthesia	Bacteraemia immediately following procedure; - 2% augmentin - 16% control	p<0.02
(Rolando, 1993 2719 /id)	RCT n = 97 (n = 115 procedures)	Imipenem/cilastatin Dextrose-saline control IV	Early bacteraemia; - 1.8% imipenem/cilastatin - 8.6% control	no significant difference between the groups
(Sauter, 1990 2867 /id)	RCT n = 96 (n = 100 procedures)	Cefotaxime 2g Control group IV 15min before procedure	Bacteraemia during and 5min; - 2% cefotaxime - 16% control	p<0.02
(Selby, 1994 5224 /id)	RCT n = 31 (n = 39 procedures)	Cefotaxime 1g Control group IV immediately before procedure	Bacteraemia 5mins, 4hrs, 24hrs - n = 1 at 5mins cefotaxime - n = 5 at 5mins, n = 2 at 4hrs control - n = 0 either group at 24hrs	
(Nieder	RCT	Cefotaxime (2g)	Bacteraemia, 15	

au, 1994 2662 /id)	n = 100	Control group IV 15mins before endoscopy	and 30mins; - n = 0 cefotaxime - n = 4 controls

A meta-analysis was completed, which included n = 7 RCTs that were placebo controlled and considered antibiotic prophylaxis in ERCP (Harris, 1999 2433 /id). Of these seven studies n = 4 reported bacteraemia, the RR risk for those receiving antibiotics compared with those receiving placebo was not significant.

The systematic review considered antibiotic prophylaxis for TURP in men with preoperative urine containing less than 100,000bacteria per ml; this included n = 28 studies (n = 10 placebo controlled, n = 18 with no treatment control group) (Qiang, 2005 1970 /id). This review found that antibiotic prophylaxis significantly decreased the frequency of post-operative bacteraemia (4.0% vs. 1.0%) in n = 10 placebo or no treatment control trials, RD -0.20 (-0.28 to -0.11, 95% CI).

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

There were six studies 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, 1998 252 /id; Lockhart, 1996 308 /id; Tomas, 2007 11632 /id), two RCTs that considered chlorhexidine and other oral topical rinses (Rahn, 1994 1847 /id; Jokinen, 1978 991 /id) and one case control study (MacFarlane, 1984 529 /id).

The first RCT (Level 1+) considered intraoral suture removal in those who needed the removal of a third molar, which would require at least 8 sutures, n = 71 (Brown, 1998 252 /id). Chlorhexidine 0.12% was used as a preprocedural rinse with a no-treatment control group. Pre-treatment blood samples were negative. Samples taken 90 seconds following suture removal had n = 4/31 in the chlorhexidine group and n = 2/24 control group had positive cultures; 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 308 /id). 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 adults and children undergoing dental extractions under GA and a comparative control group, n = 106. Following intubation the treatment group had their mouths filled with 0.2% chlorhexidine digluconate for 30seconds (Tomas, 2007 11632 /id). 9% in the chlorhexidine and 8% in the control group had positive blood cultures at baseline. There were significant differences between the bacteraemia rates in the chlorhexidine compared with the control groups at all time points; 30 seconds 79% vs. 96% ($p = 0.008$); 15min 30% vs. 64% ($p < 0.01$); 1hour 2% vs. 20% ($p = 0.005$). The risk of bacteraemia after dental extraction at 30 seconds was x1.21 (1.04 to 1.40, 95% CI) higher in the control group; at 15 minutes this was x2.12 (1.34 to 3.35, 95% CI); at 1 hour this was x10 (1.32 to 75.22, 95%CI).

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 those having treatment involving either intraligamental injection or elective extraction of a molar, n = 120 (Rahn, 1994 1847 /id). Pre-procedure blood samples were negative. Post-procedure bacteraemia was identified in n = 18 (45.0%) with chlorhexidine, n = 11

(27.5%) with povidone-iodine and n = 21 (52.5%) with controls; the difference between the povidone-iodine and the control groups was significant, p<0.05.

A fifth study (Level 1+) 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, n = 152. Participants were included for cleaning of the mouth or because of acute symptoms in the mouth or periodontal tissues, which indicated a need for dental extraction (Jokinen, 1978 991 /id). Positive cultures; iodine mouth rinses n = 21 (55%), operative filed isolation (n = 13 (34%), operative field isolation and iodine n = 12 (32%) and operative field and chlorhexidine n = 5 (13%), p = 0.05 between operative field and iodine and operative field and chlorhexidine.

The case control paper (Level 2+) considered the effect of irrigating the gingival crevice with three groups of participants, 1% chlorhexidine, 1% povidone-iodine, and normal saline, on the incidence of post-extraction bacteraemia, n = 60 participants (MacFarlane, 1984 529 /id). Pre-extraction blood cultures were negative. Post-extraction positive cultures; n = 5/20 in the chlorhexidine, n = 8/20 with povidone-iodine and n = 16 with the saline control. 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 infective endocarditis 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 HE literature

A literature review was conducted to identify cost-effectiveness evidence on antimicrobial prophylaxis against infective bacterial endocarditis 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. 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 Caviness et al (2004), considered only dental procedures. In addition, only Caviness et al 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 5.4 for full details).

Gould and Buckingham examined the cost effectiveness of penicillin prophylaxis in UK dental practice to prevent infective endocarditis. 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) 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 per cent. 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 co-workers (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 years 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.

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, 0.2-1.1). For the base case analyses, Agha et al used this pooled OR as a measure of the relative risk (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 (preventative 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. Average cost effectiveness ratios (ACERs) were estimated, that is, the cost effectiveness of one antibiotic prophylaxis strategy was compared

with no antibiotics only, and not to each other. In the base case, oral clarithromycin and oral cephalexin were associated with ACERs of $88,000 and $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), ACERs ranged from $38,000 - $199,000 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, ACERs ranged from $14,000 (oral cephalexin) to $500,000 (parenteral ampicillin) per QALY gained. Agha et al conclude that 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 cefalexin (a cephalosporin) as an alternative drug of choice.

The studies by Devereux et al (1994) and 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 post-dental 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

1590 older adults with MVP (50 years and older) at a cost of greater that
1591 US$1.5 million per life saved.

1592 Devereux et al (1994) assessed three prophylactic options for patients with
1593 MVP with or without a mitral regurgitant murmur: oral amoxicillin, oral
1594 erythromycin and intravenous or intramuscular ampicillin. Their analysis
1595 estimated that amoxicillin and ampicillin would have an efficacy of 80% and
1596 erythromycin of 60%. Severe allergic reactions to oral amoxicillin were
1597 estimated to occur with a frequency of 0.9 per million patients. For intravenous
1598 ampicillin, this was assumed to be higher: 15 per million. As per the study by
1599 Clemens and Ransohoff, Devereux et al estimated a cost per year of life
1600 saved and took into account of the costs of chronic sequelae of IE. It was
1601 found that the cost effectiveness of antibiotic prophylaxis for all MVP patients
1602 ranged from $20,000 per year of life saved for the oral regimens to a net loss
1603 of life using intravenous ampicillin secondary to fatal anaphylaxis. In a
1604 sensitivity analysis that restricted the population to one of MVP patients with
1605 systolic murmur, average cost effectiveness ratios for the oral regimens were
1606 around $3000; the cost per life year saved for IV ampicillin versus no
1607 prophylaxis was around $800,000.

1608 Caviness et al (2004) examined a paediatric population of 0 to 24 months who
1609 have moderate-risk cardiac lesions requiring bacterial endocarditis
1610 prophylaxis, present to an emergency department with fever and require urine
1611 collection to evaluate the possibility of an underlying UTI. According to AHA
1612 guidelines at that time, moderate-risk cardiac lesions include most congenital
1613 cardiac malformations, acquired valvular dysfunction, hypertrophic
1614 cardiomyopathy, and mitral valve prolapse with valvular regurgitation and/or
1615 thickened leaflets. Only two antibiotics were considered - amoxicillin and
1616 vancomycin - and these were assumed to be equally effective in preventing
1617 bacteraemia. The model relied on adult data to a large extent due to an
1618 apparent paucity of evidence from paediatric populations. The prophylactic
1619 efficacy of antibiotics (assumed to be 89% in both cases) was determined
1620 from one trial (Allan and Kumar, 1985) and the analyses of Bor and
1621 Himmelstein (1984) and Clemens and Ransohoff (1984). On the basis of the

data presented in the text, unprotected antibiotic prophylaxis leads to approximately 7 to 8 cases of IE per million children. Quality of life weights were obtained from the Years of Healthy Life Measure.

The results produced by the Caviness et al model suggests that antibiotic prophylaxis is extremely cost ineffective, and potentially leads to a net lost of life. Excluding antibiotic related deaths, it was found that the cost effectiveness of amoxicillin was $10 million per QALY gained ($70 million per BE case prevented). In the case of vancomycin, the average cost effectiveness of prophylaxis versus no prophylaxis was $13 million per QALY gained ($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 (e.g. 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 infective endocarditis and the additional future costs of antibiotic prophylaxis.

De novo economic evaluation

Aims

The de novo economic evaluation aimed to estimate the cost-effectiveness of antibiotic prophylaxis for infective bacterial endocarditis in adults with predisposing cardiac conditions undergoing dental procedures. No model was developed to consider the cost effectiveness of antimicrobial prophylaxis for individuals undergoing other interventional procedures.

In the model, eight 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).

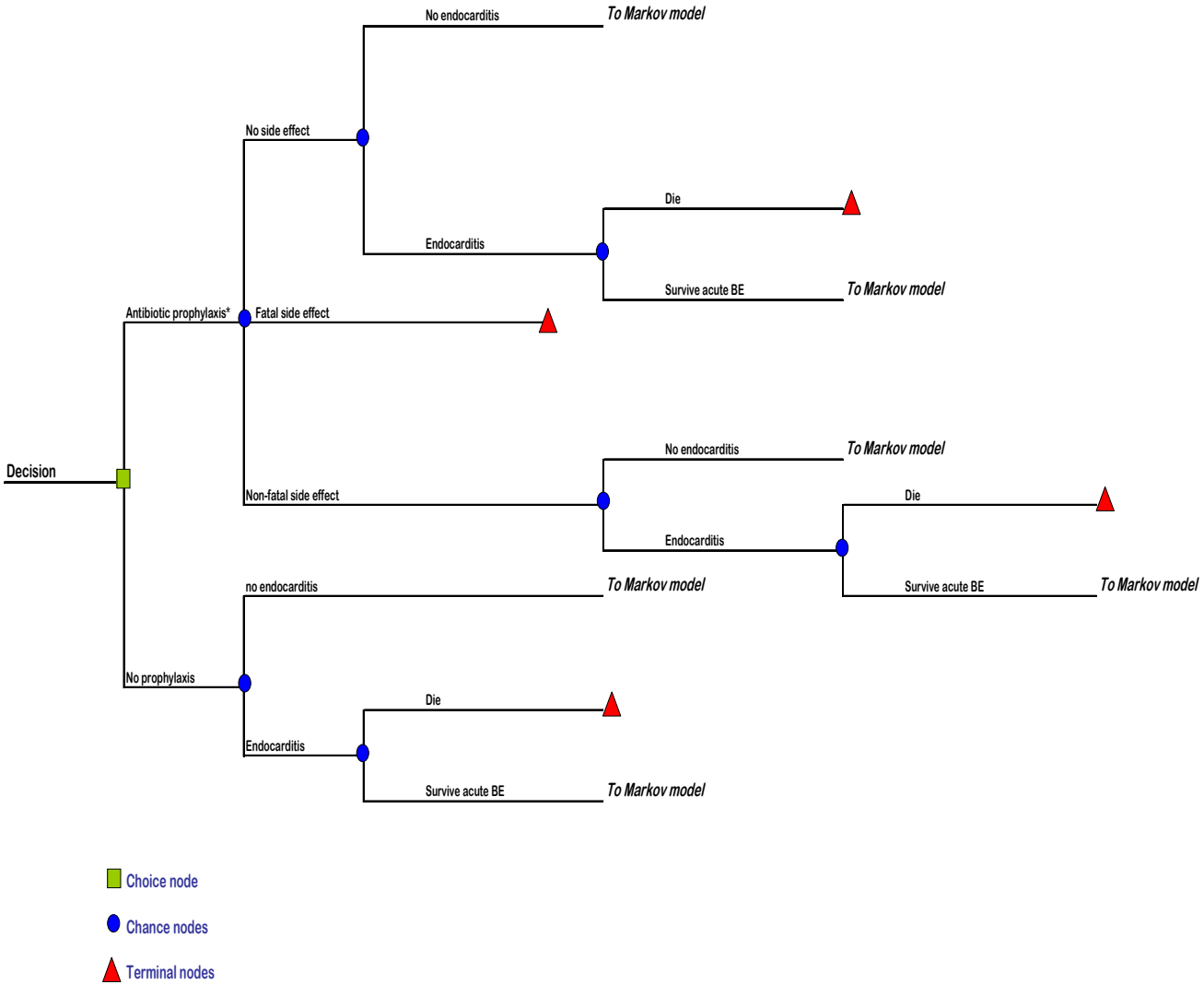
Table11 Antibacterial prophylaxis options (based on section 5.1, table 2 of adult BNF [54])

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 5
Dental procedures under general anaesthesia		
No special risk (including pts 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 5
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

Method

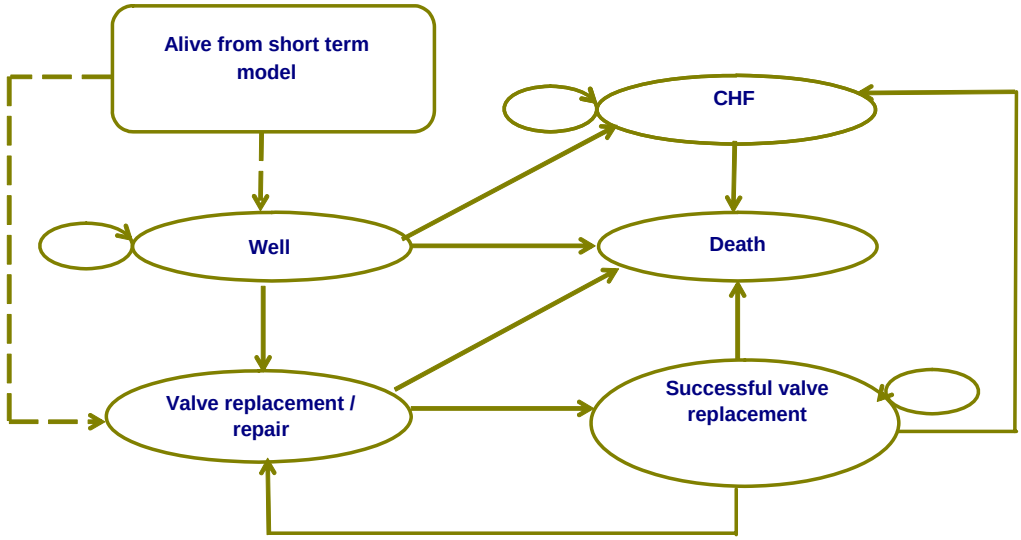
The economic evaluation was based on the one developed by Agha et al. It consists of a decision tree representing the short term (3-month) consequences for at risk patients undergoing a dental procedure requiring a course of antibiotic prophylaxis (as per current recommendations). In addition, a 5-state 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 (55 years), and follows a hypothetical cohort of 10 million individuals from a given starting age until death. Cycle length was set at 1 year incremental analysis was conducted for any mutually exclusive options. In addition, simple deterministic sensitivity analyses were used to explore the contribution of individual parameters to overall uncertainty in the cost effectiveness estimates.

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 estimation of risk for developing IE was based on data presented in the French survey by Duval et al (2006). Duval et al estimated risk using 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).

This equation formed the basis of the risk calculation. Using Duval's French 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)

The base case estimate for this model was 22 per million. This happens to be the exact base case estimate used by Agha et al, using the same algorithm, although with different input parameters into the equation.

1723 **Table 12 Summary of model epidemiological parameters, values and sources**

Parameter	Base case	Lower	Upper	Source/comment
Estimated risk of IE following a dental procedure	22 per million	18 per million	93 per million	Duval et al (2006). See text.
Efficacy of prophylaxis	0.5	0.25	0.75	Assumed (see text)
Probability of mortality from acute endocarditis – native valves	0.164	Fixed		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	Fixed		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	Fixed		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	Fixed		Tornos et al (1992)
Annual probability of valve replacement, years 1 to 10 (non endocarditis cases)	0.004	Fixed		Zuppiroli et al (1995)
Probability of valve replacement, years 1 to 10 (endocarditis cases)	0.013	Fixed		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	Fixed		Zuppiroli et al (1995)
Probability of death from valve surgery.	0.082	Fixed		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	0.02	Fixed		deShazo and Kemp (1997); cited in Agha et al (2005)
Probability of non fatal hypersensitivity to clindamycin	0.004	Fixed		Mazur et al (1999), Lee et al (2000); cited in Agha et al (2005)
Probability of non fatal hypersensitivity to vancomycin	0.007	Fixed		Lee et al (2000); cited in Agha et al
Probability of non fatal hypersensitivity to gentamicin	0.003	Fixed		Lee et al (2000); cited in Agha et al
Probability of non fatal hypersensitivity to teicoplanin	0.007	Fixed		Assumed same as vancomycin
Probability of fatal anaphylaxis from amoxicillin	20 per million	0.9 per million	40 per million	Idsoe et al (1968), Ahlstedt (1984); cited in Agha et al (2005)
Probability of fatal anaphylaxis from clindamycin	0	0	5 per million	Mazur et al (1999)
Probability of fatal anaphylaxis from vancomycin, gentamicin and teicoplanin	0	0	5 per million	Assumed as per clindamycin

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

Table 13 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. 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, between 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 analysis, a base case estimate of 20 per million was applied to all penicillin containing antibiotic strategies. 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 assumes a risk of fatal anaphylaxis of zero.

In terms of non fatal allergic reactions, the estimates cited in Agha et al (2005) were applied in the present analysis. The data in Lee et al (2000) cited by Agha et al, was used to estimate the non fatal risks for vancomycin and gentamicin. In the case of teicoplanin, it was assumed that non fatal hypersensitivity reactions would occur with the same probability as that assigned to vancomycin.

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 14 Utility weights used in the model

Health states	Estimate	Source / comment
Well	0.930	Kirsch and McGuire, 2001. It was assumed that all patients will be in NYHA class I
Valve replacement / repair needed	0.525	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	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	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	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.

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).

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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;	£121.27	Fixed	Adult BNF, September 2007 (Number 54); includes administration costs (see below)
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	£124.21	Fixed	Adult BNF, September 2007 (Number 54); includes administration costs (see below)
IV vanco 1g over at least 100 minutes then IV gentamicin 120mg at induction or 15 min before procedure.	£139.05	Fixed	Adult BNF, September 2007 (Number 54); includes administration costs (see below)
IV teicoplanin 400 mg plus gentamicin 120 mg at induction or 15 min before procedure	£158.56	Fixed	Adult BNF, September 2007 (Number 54); includes administration costs (see below)
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	£129.30	Fixed	Adult BNF, September 2007 (Number 54); includes administration costs (see below). Cost estimate based on oral clindamycin being used post procedure.
Secondary care and outpatient costs			
Hospitalisation cost for endocarditis	£7,013	Up to £10,125 for patients prosthetic valve endocarditis	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 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	Fixed	Non-elective cost. National Schedule of Reference Costs

			2005-6 for NHS trusts. (Based on HRG E03 description – "Cardiac Valve Procedures")
Fatal anaphylaxis	£450	Fixed	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)	£2,340	Fixed	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)	£2,875	Fixed	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	Fixed	National Schedule of Reference Costs 2005-6 for NHS trusts; Adult outpatient follow-up attendance data (TOPS FUA)
Anticoagulation services	£134	Fixed	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	£120	Fixed	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	Fixed	Assumed a maintenance dose of warfarin of 6 mg per day. Unit costs of warfarin from BNF 54
Annual drug cost for patients with heart failure	£247.61	Fixed	Based on resource use estimates for patients in NYHA class III (Fox et al 2006; Technology Appraisal assessment report)
Cost for non fatal allergic reaction	£25	Fixed	PSSRU 2005/6. GP consultation lasting 10 minutes

Results

Tables 16 and 17 provide the base case results from the short term model. If ten million patients underwent prophylaxis, an estimated 110 cases of IE are prevented and deaths due to BE are reduced from 36 to 18. However, in the case of the amoxicillin containing strategies, there is a competing risk of fatal anaphylaxis (20 per million), the consequence of which leads to an overall net increase in mortality. These antibiotic strategies are subject to simple dominance: they are less effective and more costly than a policy of no prophylaxis.

Table 16 Short term health outcomes (base case analysis)

Antibiotic strategy	BE cases	BE cases prevented	BE deaths	Deaths caused by anaphylaxis
No antibiotic	220	NA	36	0
Oral amoxicillin (strategy 1)	110	110	18	200
Oral clindamycin (strategy 2)	110	110	18	0
IV amoxicillin then oral amoxicillin (strategy 3)	110	110	18	200
Oral amoxicillin before and after (strategy 4)	110	110	18	200
IV amoxicillin, IV gent then oral amoxicillin (strategy 5)	110	110	18	200
IV vanco and IV gent (strategy 6)	110	110	18	0
IV teicoplanin and IV gent (strategy 7)	110	110	18	0
IV clindamycin (strategy 8)	110	110	18	0

Table 17 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	£0.00	£2,417,288.37	£2,417,288.37	NA
Oral amoxicillin (strategy 1)	£6,342,857.14	£6,303,544.18	£12,646,401.33	not effective
Oral clindamycin (strategy 2)	£38,383,333.33	£2,208,644.18	£40,591,977.52	£2,116,114
IV amoxicillin then oral amoxicillin (strategy 3)	£1,212,657,142.86	£6,303,544.18	£1,218,960,687.04	not effective
Oral amoxicillin before and after (strategy 4)	£12,685,714.29	£6,303,544.18	£18,989,258.47	not effective
IV amoxicillin, IV gent then oral amoxicillin (strategy 5)	£1,242,057,142.86	£7,053,529.18	£1,249,110,672.04	not effective
IV vanco and IV gent (strategy 6)	£1,390,500,000.00	£3,708,644.18	£1,394,208,644.18	£77,150,297
IV teicoplanin and IV gent (strategy 7)	£1,585,600,000.00	£3,708,644.18	£1,589,308,644.18	£87,965,153
IV clindamycin (strategy 8)	£1,293,000,000.00	£2,208,644.18	£1,295,208,644.18	£71,662,492

Tables 18a (10 years) and 18b (55 years) provide estimates derived from the long term model of the average cost per QALY for the various antibiotic prophylactic options. These estimates exclude the costs and potential benefits of ongoing antibiotic use. Tables 19a and 19b 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 (55 year time horizon), the no antibiotic prophylaxis option generated a mean 15.25354 QALYs per person. For the non amoxicillin containing antibiotic options, the QALY gain was of the order of only 0.00006. This is equivalent to an extra half an hour of quality adjusted time. If the potential benefits of ongoing prophylaxis are included, this QALY gain increases to 0.0005, equivalent to approximately 4.5 hours of quality adjusted time.

Table 18a Ten year average 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	Average cost effectiveness ratio (versus no antibiotics)
No antibiotic	£788	7.53405234	NA
Oral amoxicillin (strategy 1)	£789	7.53392571	dominated
Oral clindamycin (strategy 2)	£793	7.53407640	£237,397
IV amoxicillin then oral amoxicillin (strategy 3)	£970	7.53392571	dominated
Oral amoxicillin before and after (strategy 4)	£790	7.53392571	dominated
IV amoxicillin, IV gent then oral amoxicillin (strategy 5)	£975	7.53392571	dominated
IV vanco and IV gent (strategy 6)	£996	7.53407640	£8,678,361
IV teicoplanin and IV gent (strategy 7)	£1,026	7.53407640	£9,894,977
IV clindamycin (strategy 8)	£982	7.53407640	£8,061,011

Table 18b Lifetime (55 year time horizon) average 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	Average cost effectiveness ratio (versus no antibiotics)
No antibiotic	£3,230	15.25354006	NA
Oral amoxicillin (strategy 1)	£3,231	15.25329067	dominated
Oral clindamycin (strategy 2)	£3,236	15.25359574	£102,364
IV amoxicillin then oral amoxicillin (strategy 3)	£3,412	15.25329067	dominated
Oral amoxicillin before and after (strategy 4)	£3,232	15.25329067	dominated
IV amoxicillin, IV gent then oral amoxicillin (strategy 5)	£3,417	15.25329067	dominated
IV vanco and IV gent (strategy 6)	£3,439	15.25359574	£3,748,463
IV teicoplanin and IV gent (strategy 7)	£3,468	15.25359574	£4,273,984
IV clindamycin (strategy 8)	£3,424	15.25359574	£3,481,797

Table 19a Ten year average 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	Average cost effectiveness ratio (versus no antibiotics)
No antibiotic	£789	7.53388433	NA
Oral amoxicillin (strategy 1)	£803	7.53291048	dominated
Oral clindamycin (strategy 2)	£842	7.53399239	£487,503
IV amoxicillin then oral amoxicillin (strategy 3)	£2,447	7.53291048	dominated
Oral amoxicillin before and after (strategy 4)	£812	7.53291048	dominated
IV amoxicillin, IV gent then oral amoxicillin (strategy 5)	£2,488	7.53291048	dominated
IV vanco and IV gent (strategy 6)	£2,687	7.53399239	£17,564,419
IV teicoplanin and IV	£2,953	7.53399239	£20,026,144

gent (strategy 7)			
IV clindamycin (strategy 8)	£2,553	7.53399239	£16,317,957

Table 19b Lifetime (55 year time horizon) average 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	Average cost effectiveness ratio (versus no antibiotics)
No antibiotic	£3,233	15.25263435	NA
Oral amoxicillin (strategy 1)	£3,266	15.24781862	dominated
Oral clindamycin (strategy 2)	£3,377	15.25314288	£283,175
IV amoxicillin then oral amoxicillin (strategy 3)	£7,738	15.24781862	dominated
Oral amoxicillin before and after (strategy 4)	£3,290	15.24781862	dominated
IV amoxicillin, IV gent then oral amoxicillin (strategy 5)	£7,849	15.24781862	dominated
IV vanco and IV gent (strategy 6)	£8,395	15.25314288	£10,151,104
IV teicoplanin and IV gent (strategy 7)	£9,119	15.25314288	£11,573,982
IV clindamycin (strategy 8)	£8,030	15.25314288	£9,433,186

Sensitivity analysis

A number of sensitivity analyses were undertaken. One analysis explored the impact of increasing the risk of developing IE following an unprotected dental procedure to 93 per million, the estimated risk for individuals with a prosthetic valve (Duval et al, 2006). In this instance, 928 cases of IE are expected to develop under a policy of no prophylaxis, which is reduced by half with prophylaxis. Acute endocarditis deaths are reduced from 212 to 106 with antibiotic prophylaxis, although for strategies containing amoxicillin there is a net increase in mortality. Cost per IE death prevented was approximately £310,000 for oral clindamycin (strategy 2). For non-dominated strategies, the

cost per IE death prevented in the short term analysis was in excess of £12 million.

Table 20 provides the lifetime average cost effectiveness ratios for the various antibiotic strategies under this scenario (excluding estimated costs and potential benefits of future antibiotic prophylaxis). Table 21 provides the same results but includes an estimate of the recurring costs and potential benefits of future prophylaxis.

Table 20 10-year and lifetime (55-year time horizon) average cost effectiveness ratios (antibiotics versus no antibiotics) for a population of individuals with prosthetic valves. Estimated hospitalisation costs of prosthetic valve endocarditis Excluding estimated costs and potential benefits of future antibiotic prophylaxis.

	10 years	**55 years**
Antibiotic strategy	**Average cost effectiveness ratio (antibiotic vs. "No antibiotic")**	
No antibiotic	NA	NA
Oral amoxicillin (strategy 1)	dominated	Dominated
Oral clindamycin (strategy 2)	£41,648	£18,213
IV amoxicillin then oral amoxicillin (strategy 3)	dominated	Dominated
Oral amoxicillin before and after (strategy 4)	dominated	Dominated
IV amoxicillin, IV gent then oral amoxicillin (strategy 5)	dominated	Dominated
IV vanco and IV gent (strategy 6)	£1,780,459	£784,288
IV teicoplanin and IV gent (strategy 7)	£2,031,078	£894,704
IV clindamycin (strategy 8)	£1,653,287	£728,259

Table 21 10-year and lifetime (55 year time horizon) average cost effectiveness ratios (antibiotics versus no antibiotics) for a population of individuals with prosthetic valves. Analysis includes estimated costs and potential benefits of future antibiotic prophylaxis. Estimated hospitalisation

costs of prosthetic valve endocarditis were used. All other parameters are as per base case analysis.

	10 years	55 years
Antibiotic strategy	**Average cost effectiveness ratio (antibiotic vs. "No antibiotic")**	
No antibiotic	NA	NA
Oral amoxicillin (strategy 1)	dominated	Dominated
Oral clindamycin (strategy 2)	£65,833	£41,744
IV amoxicillin then oral amoxicillin (strategy 3)	dominated	Dominated
Oral amoxicillin before and after (strategy 4)	dominated	Dominated
IV amoxicillin, IV gent then oral amoxicillin (strategy 5)	dominated	Dominated
IV vanco and IV gent (strategy 6)	£2,621,695	£1,555,217
IV teicoplanin and IV gent (strategy 7)	£2,990,122	£1,773,438
IV clindamycin (strategy 8)	£2,435,047	£1,445,044

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 55-year average cost effectiveness ratio for oral clindamycin (strategy 2) at a starting age of 20 years (male) is around £266,751 per QALY. (Amoxicillin containing strategies are dominated, and IV regimens generate cost effectiveness ratios in excess of £8 million per QALY.)

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)

average cost effectiveness ratio for strategy 2 fell from £283,175 per QALY to £277,267. When the estimated risk of developing IE was additionally raised to 93 per million, the average cost effectiveness ratio of strategy 2 falls very slightly from £41,744 to £41,180 per QALY.

Tables 22 and 23 provide the incremental cost effectiveness ratios obtained as a result of varying a number of key parameters: antibiotic effectiveness, frequency of fatal anaphylactic reactions to amoxicillin, and the level of risk of developing IE following an unprotected dental procedure (all PCCs versus individuals with prosthetic valves only). Only the incremental results from strategies 1 and 2 are presented. Note: these strategies are directly compared with each other. In other words, the analysis assumes that it is possible to choose between the two strategies, ignoring the possibility that a patient may have an established allergy to penicillin or had received more than a single dose of a penicillin in the previous month.

Table 22 55-year ICERs excluding long-term costs and benefits of prophylaxis. Base case highlighted in bold. Strategies are dominated through simple dominance (the strategy is more costly and less effective than no antibiotics) or through extended dominance.

		All PCC – 22 per million risk			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	£19,892.23	£35,560.49	£113,049.60	£205.67	£2,463.11	£9,757.28
	AB strategy 2	£306,544.99	£306,544.99	£306,544.99	£306,544.99	£306,544.99	£306,544.99
10	AB strategy 1	dominated	dominated	dominated	£228.68	£5,298.40	dominated
	AB strategy 2	£67,002.63	£102,364.45	£208,455.69	£27,739.25	£27,739.25	£40,502.68
20	AB strategy 1	dominated	dominated	dominated	£333.60	dominated	dominated
	AB strategy 2	£67,002.63	£102,364.45	£208,455.69	£13,952.15	£18,213.48	£40,502.68
40	AB strategy 1	dominated	dominated	dominated	dominated	dominated	dominated
	AB strategy 2	£67,002.63	£102,364.45	£208,455.69	£10,783.84	£18,213.48	£40,502.68

Table 23 55-year ICERs for strageies 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.

		All PCC – 22 per million risk			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	£63,061	£127,926	£2,449,637	£4,317	£9,595	£27,308
	AB strategy 2	£457,357	£457,359	£457,360	£435,158	£435,161	£435,164
10	AB strategy 1	Dominated	dominated	dominated	£9,048	£54,142	dominated
	AB strategy 2	£186,941	£283,175	£571,881	£39,371	£39,371	£88,929
20	AB strategy 1	dominated	dominated	dominated	dominated	dominated	dominated
	AB strategy 2	£186,941	£283,175	£571,881	£26,016	£41,744	£88,929
40	AB strategy 1	dominated	dominated	dominated	dominated	dominated	dominated
	AB strategy 2	£186,941	£283,175	£571,881	£26,016	£41,744	£88,929

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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 estimated with uncertainty – the risk of fatal anaphylaxis as it principally relates to amoxicillin, and the risk of developing IE following a particular dental procedure. Taking into account recurring costs of antibiotic prophylaxis, as well as its potential benefits, the model developed for this guideline appears to indicate that oral amoxicillin (strategy 1) can be highly cost effective when the risk of developing IE following a dental procedure was set at 93 per million (the Duval et al [2006] estimated risk for an individual with a prosthetic valve). The present modelling also shows that IV administered antibiotics are not cost effective under any of the scenarios explored in the model. However, the estimation of cost effectiveness is based on a set of assumptions – not least with respect to the risk of developing IE and also antibiotic effectiveness – that are arguably over optimistic with respect adopting a policy of antibiotic prophylaxis, even in individuals at 'high risk'.

Base case assumptions in the model assumed a risk of developing IE of 22 per million procedures. Taking into account the long term costs and potential benefits of ongoing prophylaxis, even when the risk of fatal anaphylaxis is 0.9 per million and antibiotic effectiveness is 75%, the incremental cost effectiveness ratio is around £63,000 per QALY (table 23).

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. In addition, the model does not take into account the impact of potentially increasing the risk of antibiotic resistant pathogens secondary to widespread and ongoing dental prophylaxis.

It is arguable that the estimated risks of endocarditis following a dental procedure used in the present analysis over inflate the actual risk by a wide margin. In the case of all individuals with a PCC, the risk equation assumes that approximately 5% of all PCC 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 base case 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 used in the base case risk equation. Using these data, the estimated risk of developing IE from a dental procedure is about 0.8 cases per million. Under these circumstances, it is highly unlikely that antibiotic prophylaxis would be cost effective.

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 predicts a scenario whereby prophylaxis with oral amoxicillin and oral clindamycin can be highly cost effective options only if certain key assumptions are made regarding the level of risk of developing IE following a dental procedure, the frequency of fatal anaphylactic reactions to amoxicillin, and the level of antibiotic efficacy. Prophylactic antibiotic strategies involving IV administration are not cost effective under all scenarios explored in the present analysis.

Evidence to recommendations

Dental

The Guideline Development Group 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. They also noted that cases of IE have been documented despite antibiotic prophylaxis for dental procedures, which indicates that, even if the case for antibiotic efficacy was proven, its effectiveness is less than 100%. This observation is supported by the findings of the bacteraemia studies that show that prophylactic antibiotics given before a dental procedure reduce, but do not eliminate, bacteraemia.

The Guideline Development Group considered that antibiotic prophylaxis is not a risk free intervention and that although antibiotic related anaphylaxis is a rare event it is nonetheless potentially fatal when it occurs and therefore the possibility of anaphylaxis needs acknowledgement. The occurrence of other adverse effects of antibiotic usage, including the risk of increasing antibiotic resistance, was also noted.

The Guideline Development Group felt that regular tooth-brushing may present a greater risk of IE than a single dental procedure because of cumulative 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 tooth-brushing.

The GDG considered that the presented cost effectiveness analyses demonstrated that the adverse consequences of penicillin use in patients at increased 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 the de novo economic analysis and in some of the previous cost effectiveness studies. The GDG therefore concluded that offering antibiotic prophylaxis prior to dental procedures is not clinically beneficial and was associated with a risk of harm (anaphylactic reaction to antibiotics, notably penicillins).

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

The Guideline Development Group 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 Guideline Development Group noted that the maintenance of good oral health would be assisted with an emphasis on preventative dentistry.

Non-dental

The Guideline Development Group considered that there 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 findings of the bacteraemia studies show that prophylactic antibiotics given before non-dental procedures reduce, but do not eliminate, bacteraemia which suggests that even if the case for antibiotic efficacy was proven, its effectiveness would be likely to be less than 100%.

The Guideline Development Group considered that antibiotic prophylaxis is not a risk free intervention and that although antibiotic related anaphylaxis is a

rare event it is nonetheless potentially fatal when it occurs. Therefore the possibility of anaphylaxis needs acknowledgement. The occurrence of other adverse effects of antibiotic usage, including the risk of increasing antibiotic resistance, was also noted.

The Guideline Development Group 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 Guideline Development Group considered that two important pieces of evidence that are absent from the non-dental interventional procedure literature. First, there is a lack of published evidence to support the hypothesis that non-oral daily activities (for example, urination, defecation) lead to a cumulative exposure to non-oral flora. It is therefore not possible to 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 defecation. Second, there is a lack of evidence to allow a formal assessment of the risks and benefits of giving antibiotics for non-dental procedures using economic modelling.

The Guideline Development Group therefore decided that a cautious approach is required regarding antibiotic prophylaxis for non-dental interventional procedures.

The Guideline Development Group's consensus opinion was that prophylaxis against infective endocarditis is indicated when the procedure is likely to result in a bacteraemia from organisms not usually identified in the oropharnygeal tract (for example enterococci). They considered that the following groups of procedures fall into this category: ERCP, manipulation of the biliary tract and invasive oesophageal procedures and lower GI procedures; transurethral resection of prostate (TURP), transrectal prostatic biopsy, lithotripsy and all urological procedures involving urethral manipulation except urethral catheterisation.

The Guideline Development Group's consensus opinion was that prophylaxis against infective endocarditis is not indicated for obstetric and gynaecological procedures.

The Guideline Development Group considered that there is insufficient evidence to make a recommendation for antibiotic prophylaxis on urethral catheterisation and catheter removal.

The Guideline Development Group's consensus opinion was that prophylaxis against infective endocarditis is not indicated when the procedure is likely to result in a bacteraemia from organisms usually identified in the oropharyngeal tract. The Group considered that the following groups of procedures fell into this category: ENT, upper GI tract and upper respiratory tract and bronchoscopy.

The Guideline Development Group considered that when antibiotics are recommended for prophylaxis the regimen should cover organisms that are known to be potential causes IE. This was considered likely to be particular issue with procedures being carried out at a site of infection when antibiotic prophylaxis may be indicated to prevent both surgical site infection and IE.

It was also considered important that, if appropriate, a regimen should be chosen that was already in widely used in clinical practice in the UK to facilitate implementation of the guidance. It was noted that this regimen may need to change in future in line with likely changes in causative organisms for IE and that prescribers should consult the most recent version of the BNF for detailed advice on antibiotic to be used, including advice on the dosage, timing and route of administration. It should be noted that detailed guidance on dosage, timing and route of administration is outside the scope of this guideline (appendix 5.1.

2.6 Patient perspectives on prophylaxis against IE

2.6.1 Introduction

Until publication of the recent AHA (Wilson, 2007 521 /id) and BSAC (Gould, 2006 6 /id) guidelines, antibiotic prophylaxis was universally prescribed to

cover dental and other interventional procedures in patients at increased risk of 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 under the more restrictive position adopted by the AHA (Wilson, 2007 521 /id) and BSAC (Gould, 2006 6 /id). The information and support needs for such patients are likely to be significant as 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 IE

Recommendation number 1.3.2.11

Patients at risk of IE should receive clear and consistent information about IE including (a) the likely benefits and risks of antibiotic prophylaxis and (b) the specific symptoms that may indicate that a healthcare professional should consider a diagnosis of IE.

Recommendation number 1.3.2.12

Patients at risk of IE should receive information about the importance of maintaining good oral health.

Recommendation number 1.3.2.13

Patients at risk of IE should be informed of potential risks of undergoing medical and non medical invasive procedures (such as body piercing or tattooing).

Evidence review

The search in this area identified seventeen studies that considered the current knowledge of patients (or their families) about their cardiac conditions, knowledge about infective endocarditis and the procedures for which antibiotics are used or attitudes towards dental treatment (Balmer, 2003 678 /id; Barreira, 2002 51 /id; Bulat, 2003 46 /id; Cetta, 1995 115 /id; Cetta, 1993 125 /id; Cetta, 1993 126 /id; Chessa, 2005 17 /id; Cheuk, 2004 36 /id; da Silva, 2002 59 /id; De Geest, 1990 156 /id; Kantoch, 1997 89 /id; Leviner, 1991 586 /id; Moons, 2001 698 /id; Saunders, 1997 436 /id; Seto, 2000 73 /id; Sholler, 1984 217 /id; Stucki, 2003 47 /id). However, these studies did not consider the specific issues around prophylaxis against infective endocarditis which patients (and their families/carers) may have. Consequently these papers have not been included.

Evidence to recommendations

The Guideline Development Group 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 Guideline Development Group. The Guideline Development Group also re-emphasised the need for information and support to help achieve and maintain good oral health.

The Guideline Development Group further discussed the need for those with defined pre-existing cardiac conditions being 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 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 IE (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.

Antibiotic prophylaxis against IE (see section 2.2)

- What is the clinical and cost effectiveness of antibiotic prophylaxis against IE in patients undergoing non-dental interventional procedures? It is considered that it is impractical to perform a randomised controlled trial to answer this question and that a well designed observational study is the optimal study design. Such research should:
  - use a population based case-control design
  - use cases and controls with pre-existing cardiac conditions
  - have a sufficient sample size to minimise the risk of a type 2 error.

Interventional procedures and IE (see section 2.3)

- Which non-dental interventional procedures are associated with an increased risk of developing IE? Such research should:
  - use a population-based case-control study design
  - use cases and controls with pre-existing cardiac conditions
  - have a sufficient sample size to minimise the risk of a type 2 error.

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

3 Methods

3.1 Aim and scope of the guideline

3.1.1 Scope

NICE guidelines are developed in accordance with a scope that defines what the guideline will and will not cover (see appendix 5.1). The scope of this guideline is available from www.nice.org.uk/NICEtoadddetails

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 increased risk of infective endocarditis who may require antimicrobial prophylaxis before an interventional procedure.

3.1.2 Guideline objectives

Clinical guidelines are defined as 'systematically developed statements to assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances' (Institute of Medicine Committee to Advise the Public Health Service on Clinical Practice Guidelines - Field MJ and Lohr KN eds. 1990). The aim of this guideline is to provide systematically developed recommendations to guide healthcare professionals on the use of antimicrobial prophylaxis against IE in adults and children undergoing defined interventional procedures (both dental and non-dental).

3.1.3 Areas covered by this guideline

This guideline provides guidance on:

- patients in primary dental care, primary medical care, secondary care and community settings, specifically:
  - adults and children with known underlying structural cardiac defects, including those who have previously had IE
  - adults and children who have previously had IE (irrespective of whether they have a known underlying cardiac defect).

3.1.4 Areas outside the remit of this guideline

This guideline does not address care that should be provided to:

- people at increased risk of IE who do not have structural cardiac defects (such as intravenous drug users).

3.1.5 Disclaimer

The Guideline Development Group assumes that healthcare professionals will use general medical knowledge and clinical judgement in applying the general principles and specific recommendations of this document to the management of individual patients. Recommendations may not be appropriate in all circumstances. Decisions to adopt any particular recommendation must be made by the practitioner in light of the circumstances presented by individual patients and available resources. Clinicians will need to share appropriately the information within this guideline to enable patients to participate in the decision making to the extent that they are able and willing.

3.2 Contributors

3.2.1 The Guideline Development Group

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

The members of the 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 Dental Paediatrics

Professor Kate Gould – Professor of Microbiology

Dr Bernard Prendergast – Consultant Cardiologist

Mr Ian Eardley – Consultant Urologist

Professor Mark Kilby – Professor of Maternal and Fetal Medicine

Dr Andrew Klein – Consultant Anaesthetist

Dr Pallav Shah – Consultant Chest Physician

Dr Miles Alison – Consultant Gastro-enterologist

Mr Gerald McGarry – Consultant Otorhinolaryngologist (ENT surgeon)

Ms Alison Pottle – Cardiac Nurse

3.2.2 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

3.2.3 Acknowledgements

[To be inserted into final guideline]

3.3 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 'the Institute') in 'The guidelines manual: an overview for stakeholders, the public and the NHS' (available at: www.nice.org.uk) . As noted in section 1.4.2, the interim process guide for the short clinical guideline programme has been the subject of public consultation and the revised version will be incorporated into 'The guidelines manual' 2008 update.

3.3.1 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 facilitated an overview of the issues likely to be covered by the guideline – the clinical need for the guideline and antimicrobial chemoprophylaxis against infective endocarditis in adults and children undergoing defined interventional procedures (dental and non-dental) – 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.

3.3.2 Forming and running the Short Clinical Guideline Development Group

The short clinical guideline on antimicrobial prophylaxis for infective endocarditis 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. Development took 4 months and the Guideline Development Group met on three occasions every 4-6 weeks.

3.3.3 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 5.2.

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 5.4.

3.3.4 Developing recommendations

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

3.3.5 Literature search

The key clinical questions 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 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 and in consultation with the Guidelines Development Group. 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 Guidelines 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 2007 and September 2007. Full details of the systematic search, including the sources searched and the MEDLINE strategies for each clinical question are presented in appendix 5.3.

3.3.6 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, where 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 text 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' (2006) by NICE (available from www.nice.org.uk). 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.

3.3.7 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 under way 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 24.

Table 24 Levels of evidence for intervention studies.
Reproduced with permission from the Scottish Intercollegiate Guidelines Network.

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*
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.

3.3.8 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 they 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.

3.3.9 Health economics

An economic evaluation aims to integrate data on the benefits (ideally in terms of quality adjusted life years, or 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 if 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 infective endocarditis in acutely ill patients was 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 at-risk dental procedures.

Given the potentially large resource implications of antibiotic prophylaxis – it has been estimated that approximately 3% of the population have a pre-disposing 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.

3.3.10 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 accepted, 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.

3.3.11 Audit methods

The guideline recommendations have been used to develop clinical audit criteria for use in practice. An audit criterion can be defined as ‘a systematically developed statement that can be used to assess the appropriateness of specific healthcare decisions, services and outcomes’ (Institute of Medicine - Field MJ and Lohr KN eds. 1992). 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.

3.3.12 Scheduled review of this guideline

The guidance has been developed in accordance with the NICE guideline development process for short clinical guidelines. This includes 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 will be collated and presented anonymously for consideration by the Guideline Development Group. All comments will be considered systematically by the Guideline Development Group and the Short Clinical Guideline Technical Team will record the agreed responses.

This guideline will be considered for an update by the Short Clinical Guidelines Technical Team following the current process (chapter 15 of 'The guidelines manual'). 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.

3.4 Declarations

3.4.1 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: [to be inserted].

3.4.2 Declarations of interest

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