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# **Prophylaxis against infective endocarditis**

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

## **NICE clinical guideline 64**

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

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## Foreword

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

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

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

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

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

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

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

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

Professor David Wray  
Guideline Development Group Chair

## ***Patient-centred care***

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

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

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

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

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

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

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

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

# 1 Summary

## 1.1 *List of all recommendations*

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

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

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

#### **Patient advice**

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

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



## **Prophylaxis against infective endocarditis**

1.1.3 Antibiotic prophylaxis against infective endocarditis is not recommended:

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

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

## **Infection**

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

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

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

## **1.2 Overview**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

### **1.2.2 The NICE short clinical guideline programme**

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

For a full explanation of the process, see [www.nice.org.uk/guidelinesmanual](http://www.nice.org.uk/guidelinesmanual).

### **1.2.3 Using this guideline**

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

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

### **1.2.4 Using recommendations and supporting evidence**

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

## **2 Evidence review and recommendations**

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

#### **2.1.1 Introduction**

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

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

#### **Guidelines in the area**

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

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

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

### **2.1.2 Overview**

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

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

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

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

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

#### **Recommendation number 1.1.1**

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

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

#### **Evidence review**

##### *Congenital heart disease*

#### **a) Aortic stenosis, pulmonary stenosis, ventricular septal defect**

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



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

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

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

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

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

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

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

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

**c) Repair of major congenital heart defects**

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

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

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<sup>4</sup> 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 <sup>a</sup>	7.2
	Pulmonary atresia <sup>a</sup>	6.4
	Un-operated VSD	3.8
Moderate-to-low	Primum ASD with cleft mitral valve <sup>a</sup>	1.8
	Coarctation of the aorta <sup>a</sup>	1.2
	Complete atrioventricular septal defect <sup>a</sup>	1.0
	Tetralogy of Fallot <sup>a</sup>	0.7
	Dextrotransposition of the great arteries <sup>a</sup>	0.7
	VSD <sup>a</sup> (no cases occurred with closed VSD in the absence of other abnormalities)	0.6
No documented risk	ASD*	0
	Patent ductus arteriosus <sup>a</sup>	0
	Pulmonic stenosis <sup>a</sup>	0

<sup>a</sup> 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<sup>5</sup>. The incidence appeared to increase more rapidly after 5 years, and by 25 years the cumulative incidence was 13.3% (standard error [SE] 3.8%). Of those with aortic stenosis, 28 (16%) had aortic valve replacement; for prosthetic valves there were three cases of IE (10-year incidence 26%), for native valves there were 10 cases of IE (10-year incidence 5%). IE in other underlying conditions following surgery: coarctation

<sup>5</sup> This excludes those with isolated supra- or subvalvular aortic stenosis in whom there were no cases of IE.

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

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

#### *Case-control studies*<sup>6</sup>

##### **a) Valvular disease**

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

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

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

<sup>7</sup> Adjusted for socioeconomic status variables (ethnic group, education, occupation, health insurance status, and dental insurance status).

**Table 2 Risk of IE with valvular disease**

<b>Risk factor</b>	<b>Cases (n = 273)</b>	<b>Controls (n = 273)</b>	<b>Adjusted OR<sup>8</sup> (95% CI)</b>
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 <sup>a</sup>	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)

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

### **b) Mitral valve prolapse**

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

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<sup>8</sup> 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**

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

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

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

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

A further case–control study (Level 2+), in Australia, considered MVP and BE (Hickey et al. 1985). There were three age-, sex- and date of echocardiography-matched controls for each case; 56 cases were selected from those admitted with BE, and 168 controls were selected from inpatients who did not have BE and underwent an echocardiography during the study period<sup>10</sup>. 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.

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<sup>9</sup> Controls with antecedent heart disease were excluded.

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

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

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



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

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

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

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

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

#### Prosthetic valve

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

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

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

## **Evidence statements**

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

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

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

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

#### **Evidence review**

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

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

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

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

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

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

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

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

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

#### *Case series*

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



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

<b>Reference</b>	<b>Study/dates/location</b>	<b>Relevant results</b>
Bouza et al. 2001	Prospective study  March 1994 to October 1996  Spain  n = 109 patients	Mortality:  IE related mortality was 25.7% (total 109 patients): <ul style="list-style-type: none"><li>• 25% (n = 13) with NVE</li><li>• 100% (n = 6) with early PVE</li><li>• 25% (n = 3) with late PVE.</li></ul> Early PVE was significantly related to mortality (with multivariate analysis)  Valve replacement: Required in a total of n = 25: <ul style="list-style-type: none"><li>• 16 (30.7%) of those with NVE</li><li>• 2 (33%) of those with early PVE</li><li>• 6 (50%) of those with late PVE</li></ul>
Chu et al. 2004	Case review  1997 to 2002  New Zealand  n = 62 patients	Mortality:  Overall n = 20: <ul style="list-style-type: none"><li>• 11 (55%) with NVE</li><li>• 6 (30.0%) with PVE</li></ul>
Dyson et al. 1999	Epidemiological review  March 1987 to March 1996  Wales  n = 125 patients	Mortality:  Overall n = 21: <ul style="list-style-type: none"><li>• 9 (12.3%) with NVE</li><li>• 12 (24.5%) with PVE</li></ul>

Gentry and Khoshdel 1989	Consecutive case review  1983 to 1989  USA  n = 94 patients	Therapeutic failure <sup>12</sup> :  Overall failure 24% (14% death; 11% relapse): <ul style="list-style-type: none"> <li>• NVE failure was 28% (17% death; 11% relapse)</li> <li>• PVE failure was 20% (10% death; 10% relapse)</li> </ul>
Mansur et al. 2001	Case series  Mean follow-up 6.1 years for survivors, 3.7 for those who died  Brazil  n = 420 adult and paediatric patients	Relapse <sup>13</sup> :  Overall n = 14: <ul style="list-style-type: none"> <li>• Prosthetic valve n = 7 (50%)</li> <li>• Valvular heart disease n = 2</li> <li>• Congenital heart disease n = 1</li> <li>• Cardiac pacemaker n = 1</li> <li>• No known cardiac disease n = 3</li> </ul> Valve replacement:  PVE was a risk factor for having valve replacement (risk ratio 1.61, p = 0.0099)  n = 76/116 (64%) complicated PVE <sup>14</sup>
Calderwood et al. 1986	Case series/review  1975 to 1982  USA  n = 116 with PVE	Mortality  n = 27 (23%) during initial hospitalisation  Significantly lower with coagulase-negative staphylococci (OR < 1)   Complications: <ul style="list-style-type: none"> <li>• 89 discharged</li> </ul>

<sup>12</sup> Defined as relapse caused by the same organism or as in-hospital death.

<sup>13</sup> 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.

<sup>14</sup> Complicated PVE was defined as infection associated with any of the following; a new or increasing murmur of prosthetic valve dysfunction; new or worsening CHF related to dysfunction of the prosthesis; fever for 10 or more days during antibiotic therapy; new or progressive abnormalities of cardiac condition.

		<ul style="list-style-type: none"> <li>• 71 had mild or no CHF</li> <li>• 13 moderate CHF</li> <li>• n = 5 severe CHF</li> </ul>
		<p>Relapse:</p> <p>n = 11 (12%) (not significantly affected by valve site or infecting organism)</p>
Habib et al. 2005	Consecutive case series	<p>Mortality:</p> <p>n = 22 (21%) died in-hospital</p> <p>32 month mean follow-up; n = 61 (58%) survival</p>
	January 1991 to March 2003	
	France	<p>Significantly associated with in-hospital mortality; severe comorbidity (p = 0.05), renal failure (p = 0.05), moderate-to-severe regurgitation (p = 0.006), staphylococcal infection (p = 0.001), occurrence of any complication (p = 0.05)</p>
	n = 104 with PVE	<p>Predictors of in-hospital death; severe heart failure (OR 5.5, 95% CI 1.9 to 16.1), <i>S. aureus</i> infection (OR 6.1, 95% CI 1.9 to 19.2)</p>
		<p>Complications:</p> <p>Similar between early and late endocarditis</p>
Sett et al. 1993	Retrospective review	<p>PVE incidence:</p> <p>n = 56/3200 (1.8%)</p>
	1975 to 1988	
	Canada	<p>Mortality overall n = 18 (32%):</p> <ul style="list-style-type: none"> <li>• early PVE 75%</li> <li>• late PVE 25%<sup>15</sup></li> </ul>
	n = 3200 with porcine bioprosthesis	<p>Predictors of death; renal status, presence of ongoing sepsis, mode of treatment, presence of</p>

<sup>15</sup> Early endocarditis was within 60 days of surgery, late was after 60 days.

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

	n = 188 paediatric and adults with CHD	
Martin et al. 1997	Retrospective review 1958 to 1992	Mortality: 13 (18%) died during initial hospitalisation
	USA	Complications: <ul style="list-style-type: none"> <li>• 30 (41%) recovered with no complications</li> <li>• 30 (41%) had complications</li> </ul>
	n = 73 paediatric patients	

### **Evidence statements**

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

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

### **Evidence to recommendations**

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

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

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

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

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

## **2.2 *Bacteraemia: interventional procedures and infective endocarditis***

### **2.2.1 Introduction**

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

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

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

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

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

## **2.2.2 Existing guidelines**

### **Interventional procedures**

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

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

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

### **Bacteraemia**

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



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

## **2.3 *Interventional procedures associated with risk of developing infective endocarditis***

### **2.3.1 Overview**

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

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<sup>16</sup> One study reported in two papers, one for dental procedures and one for oral hygiene and non-dental procedures.

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

#### **Evidence review**

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

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

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

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<sup>17</sup> The questionnaire listed procedures for which antibiotic prophylaxis is needed, according to the recommendations of the Netherlands Heart Foundation.

<sup>18</sup> Information reported in the interviews was verified with the cited practitioner.

<sup>19</sup> Interviewees were asked regarding all procedures involving cutaneous and mucosal surfaces within the previous 3 months.

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

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

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

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

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

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

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

### **Evidence statement**

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

## **2.4 *Levels of bacteraemia associated with interventional procedures and everyday activities***

### **2.4.1 Overview**

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

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

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

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

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

## **Evidence review**

### *Dental*

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

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

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

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

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

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

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

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

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<sup>20</sup> The 30-minute difference was not determined due to a lack of difference between before and after procedure values.



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

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

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

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

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<sup>21</sup> Number of colony forming units (CFU)/ml blood.

<sup>22</sup> Average number of a given dentogingival manipulative procedure performed annually.

<sup>23</sup> The number of positive cultures expressed as a proportion.

<sup>24</sup> Length of bacteraemia, which is 15 minutes.

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

### *Gastrointestinal*

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

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

**Table 6 Bacteraemia associated with interventional procedures**

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

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

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

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

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

*Case series (Level 3) (see table 7)*

**Table 7 Bacteraemia associated with interventional procedures**

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

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

### *Significant bacteraemia*

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

### *Levels of bacteraemia associated with everyday activities*

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



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

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

### **Evidence statements**

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

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

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

### **Evidence to recommendations**

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

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

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

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

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

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

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

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

### **Recommendation statement**

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

## **2.5      *Antibiotic prophylaxis to prevent infective endocarditis***

### **2.5.1      Introduction**

Criteria for antibiotic prophylaxis against infection<sup>25</sup> have been developed and these include the following: the health benefits must outweigh the antibiotic

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

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

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

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

### **Existing guidelines**

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

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

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

### **2.5.2 Overview**

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

### **Recommendation number 1.1.2**

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

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

### **Recommendation number 1.1.3**

Antibiotic prophylaxis against infective endocarditis is not recommended:

- for people undergoing dental procedures
- for people undergoing non-dental procedures at the following sites<sup>26</sup>:
  - upper and lower gastrointestinal tract
  - genitourinary tract; this includes urological, gynaecological and obstetric procedures, and childbirth
  - upper and lower respiratory tract; this includes ear, nose and throat procedures and bronchoscopy

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

**Recommendation number 1.1.4**

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

**Recommendation number 1.1.5**

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

**Recommendation number 1.1.6**

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

**2.5.3 Antibiotic prophylaxis given to those at risk before a defined interventional procedure****Evidence review***Procedures*

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

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

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

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

### *Bacteraemia*

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

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



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

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

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

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

### **Evidence statement**

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

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

##### **Evidence review**

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

### **Evidence statement**

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

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

##### **Evidence review**

###### *Dental procedures*

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

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

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

<b>Bacter- aemia</b>	<b>Amoxi- cillin</b>	<b>Clinda- mycin</b>	<b>Moxi- floxacin</b>	<b>Control</b>	<b>Differences</b>
Baseline	5%	12.5%	7.5%	9.4%	Significant differences all postprocedure time points: <ul style="list-style-type: none"> <li>• control versus amoxicillin</li> <li>• control versus moxifloxacin</li> <li>• amoxicillin versus clindamycin</li> <li>• moxifloxacin versus clindamycin</li> </ul>
30 seconds	46.4%	85.1%	56.9%	96.2%	
15 minutes	10.7%	70.4%	24.1%	64.2%	
1 hour	3.7%	22.2%	7.1%	20%	

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

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

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

Reference	Study type	Antibiotics	Bacteraemia	Differences
Hall et al. 1993	Controlled trial  n = 60	Penicillin (2 g) Amoxicillin (3 g) Placebo  Orally 1 hour before dental extraction  Level 1+	Preprocedure: no growth During extraction: <ul style="list-style-type: none"> <li>• 90% penicillin</li> <li>• 85% amoxicillin</li> <li>• 90% placebo</li> </ul> 10 minutes after surgery: <ul style="list-style-type: none"> <li>• 70% penicillin</li> <li>• 60% amoxicillin</li> <li>• 80% placebo</li> </ul>	No significant difference in the incidence or magnitude of bacteraemia, viridans streptococci, or anaerobic bacteria among the three groups at any time point
Hall et al. 1996a	RCT  n = 38	Erythromycin stearate (0.5 g) clindamycin (0.3 g)  Orally 1 hour prior to dental extraction  Level 1+	Preprocedure: no growth During extraction: <ul style="list-style-type: none"> <li>• 79% erythromycin</li> <li>• 84% clindamycin</li> </ul> 10 minutes extraction: <ul style="list-style-type: none"> <li>• 58% erythromycin</li> <li>• 53% clindamycin</li> </ul>	No significant difference in total bacteraemia, bacteraemia with viridans streptococci or anaerobic bacteraemia between the two groups at any time point
Hall et al. 1996b	RCT  n = 39	Cefaclor (0.5 g x 2) placebo (x2)  Orally 1 hour before dental extraction  Level 1+	Preprocedure: no growth During extraction: <ul style="list-style-type: none"> <li>• 79% cefaclor (streptococci 79%)</li> <li>• 85% placebo (streptococci 50%)</li> </ul>	

			10 minutes after extraction:	
			<ul style="list-style-type: none"> <li>• 53% cefaclor (streptococci 26%)</li> <li>• 47% placebo (streptococci 30%)</li> </ul>	
Roberts et al. 1987	RCT n = 108	Amoxicillin (50 mg/kg) control group  Orally 2 hours before surgery  Level 1+	Preprocedure: samples negative 2 minutes after intubation:  <ul style="list-style-type: none"> <li>• n = 0/47 amoxicillin</li> <li>• n = 3/47 control</li> </ul>	Postextraction; control versus amoxicillin, p < 0.001
Wahlmann et al. 1999	RCT n = 59	Cefuroxime (1.5 g) placebo (0.9% NaCl)  IV 10 minutes before multiple tooth extractions  Level 1+	10 minutes:  <ul style="list-style-type: none"> <li>• 23% cefuroxime</li> <li>• 79% control</li> </ul> 30 minutes:  <ul style="list-style-type: none"> <li>• 20% cefuroxime</li> <li>• 69% control</li> </ul> 10 or 30 minutes:  <ul style="list-style-type: none"> <li>• 33% cefuroxime</li> <li>• 86% control</li> </ul>	Cefuroxime versus placebo significant at 10 minutes, 30 minutes and 10 or 30 minutes  Duration of surgical procedure was not significant
Shanson 1985	RCT	Erythromycin (1.5 g) matched placebo	Streptococcal bacteraemia;	Erythromycin versus control,

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

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

### **Evidence statements**

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

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

### *Non-dental procedures*

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

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

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

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



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

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

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

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

### **Evidence statements**

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

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

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

### **Evidence review**

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

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

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

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

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

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

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

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

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

### **Evidence statements**

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

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

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

### **Health economics**

#### *Published health economics literature*

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

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

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

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

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

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

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

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

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

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

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

Clemens and Ransohoff compared oral and parenteral penicillin regimens with no prophylaxis. Their analysis estimated a risk of 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 older adults with MVP (50 years and older) at a cost of greater than US\$1.3 million per spared year of life.

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

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

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

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



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

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

#### *De novo economic evaluation*

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

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

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

## **Evidence to recommendations**

### *Dental*

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

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

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

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

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

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

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

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

#### *Non-dental*

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

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

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

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

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

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

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

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

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

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

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

## **2.6 *Patient perspectives on prophylaxis against infective endocarditis***

### **2.6.1 Introduction**

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

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

#### **Evidence review**

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

## **Evidence to recommendations**

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

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

## **2.7 Research recommendations**

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

### **Cardiac conditions and infective endocarditis (see section 2.1)**

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

### **Interventional procedures and infective endocarditis (see section 2.3)**

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

## **3 Glossary and abbreviations**

### **3.1 Glossary**

#### **Case–control study**

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

#### **Cohort study**

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

#### **Confidence interval**

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

#### **Economic evaluation**

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

#### **Guideline Development Group**

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



**Generalisability**

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

**Heterogeneity**

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

**Odds ratio**

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

**Quality-adjusted life year (QALY)**

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

**Randomised controlled trial**

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

**Relative risk**

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

**Sensitivity (of a test)**

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

**Systematic review**

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

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

### **3.2      *Abbreviations***

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

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

## **4 Methods**

### **4.1 *Aim and scope of the guideline***

#### **4.1.1 Scope**

NICE guidelines are developed in accordance with a scope that defines what the guideline will and will not cover (see appendix 1). The scope of this guideline is available from:

<http://www.nice.org.uk/guidance/index.jsp?action=download&o=37136>

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

### **4.2 *Development methods***

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

#### **4.2.1 Developing the guideline scope**

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

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

The draft scope was the subject of public consultation.

#### **4.2.2 Forming and running the Short Clinical Guideline Development Group**

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

#### **4.2.3 Developing key clinical questions**

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

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

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

#### **4.2.4 Developing recommendations**

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

#### **4.2.5 Literature search**

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

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

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

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

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

#### **4.2.6 Reviewing the evidence**

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

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

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

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

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

#### **4.2.7 Grading the evidence**

##### **Intervention studies**

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

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

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

**Table 11 Levels of evidence for intervention studies.**

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<b>Level of evidence</b>	<b>Type of evidence</b>
1 <sup>++</sup>	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1 <sup>+</sup>	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1 <sup>-</sup>	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias <sup>a</sup>



2 <sup>++</sup>	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 <sup>+</sup>	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 <sup>–</sup>	Case–control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal <sup>a</sup>
3	Non-analytic studies (for example, case reports, case series)
4	Expert opinion, formal consensus
<sup>a</sup> Studies with a level of evidence ‘–’ should not be used as a basis for making a recommendation	

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

#### 4.2.8 Evidence to recommendations

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

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

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

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

#### **4.2.9 Health economics**

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

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

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

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

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

#### **4.2.10 Consultation**

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

#### **4.2.11 Piloting and implementation**

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

#### **4.2.12 Audit methods**

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

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

#### **4.2.13 Scheduled review of this guideline**

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

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

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

## **5 Contributors**

### **5.1 *The Guideline Development Group***

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

The members of the Guideline Development Group are listed below.

Professor David Wray (Chair) – Professor of Oral Medicine

Mr Danny Keenan – Consultant Cardiothoracic Surgeon

Dr Deborah Franklin – Consultant Paediatric Dentist

Dr John Gibbs – Consultant Cardiologist

Dr Jonathan Sandoe – Consultant Microbiologist

Dr Kathy Orr – Consultant Microbiologist

Dr Martin Fulford – General Dental Practitioner

Dr Nicholas Brooks – Consultant Cardiologist

Mr Nick Cooley – Antibiotic Pharmacist

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

Ms Suzannah Power – Patient representative

Ms Anne Keatley-Clarke – Patient representative

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

Professor Graham Roberts – Professor of Paediatric Dentistry

Professor Kate Gould – Professor of Microbiology

Dr Bernard Prendergast – Consultant Cardiologist

Mr Ian Eardley – Consultant Urologist

Professor Mark Kilby – Professor of Maternal and Foetal Medicine

Dr Andrew Klein – Consultant Anaesthetist

Dr Pallav Shah – Consultant Chest Physician

Dr Miles Alison – Consultant Gastroenterologist

Mr Gerald McGarry – Consultant Otorhinolaryngologist (ENT surgeon)

Ms Alison Pottle – Cardiac Nurse

### **5.1.1 The Short Clinical Guidelines Technical Team**

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

Dr Tim Stokes – Guideline Lead and Associate Director

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Roberta Richey – Technical Analyst

Michael Heath – Project Manager

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Lynda Ayiku – Information Specialist

Nicole Elliott – Commissioning Manager

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### **5.1.2 Guideline Review Panel A**

- Robert Walker
- Ailsa Donnelly

- John Harley
- John Young

### **5.1.3 List of stakeholders**

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

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



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

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

## **5.2        *Declarations***

### **5.2.1      Authorship and citation**

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

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

### **5.2.2      Declarations of interest**

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

## **6 Appendices**

Available as a separate document:

**6.1 *Appendix 1 – The scope***

**6.2 *Appendix 2 – Key clinical questions***

**6.3 *Appendix 3 – Search strategies***

**6.4 *Appendix 4 – Evidence flow charts and evidence tables***

**6.5 *Appendix 5 – References***

**6.6 *Appendix 6 – De novo economic analysis***

**6.7 *Appendix 7 – Health economics evidence tables***