Antibiotics for the prophylaxis of bacterial endocarditis in dentistry (Review)

Oliver R, Roberts GJ, Hooper L, Worthington HV

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2009, Issue 2

http://www.thecochranelibrary.com

TABLE OF CONTENTS

[Intervention Review]

Antibiotics for the prophylaxis of bacterial endocarditis in dentistry

Richard Oliver[1], Graham J Roberts[2], Lee Hooper[3], Helen V Worthington[4]

[1]Department of Oral and Maxillofacial Surgery, School of Dentistry, The University of Manchester, Manchester, UK. [2]Department of Paediatric Dentistry, Eastman Dental Institute, London, UK. [3]School of Medicine, Health Policy & Practice, University of East Anglia, Norwich, UK. [4]Cochrane Oral Health Group, MANDEC, School of Dentistry, The University of Manchester, Manchester, UK

Contact address: Richard Oliver, Department of Oral and Maxillofacial Surgery, School of Dentistry, The University of Manchester, Higher Cambridge Street, Manchester, M15 6FH, UK. richard.j.oliver@manchester.ac.uk. (Editorial group: Cochrane Oral Health Group.)

Cochrane Database of Systematic Reviews, Issue 2, 2009 (Status in this issue: *Unchanged*)

DOI: 10.1002/14651858.CD003813.pub3
This version first published online: 8 October 2008 in Issue 4, 2008.
Last assessed as up-to-date: 23 July 2008. (Help document - Dates and Statuses explained)

This record should be cited as: Oliver R, Roberts GJ, Hooper L, Worthington HV. Antibiotics for the prophylaxis of bacterial endocarditis in dentistry. *Cochrane Database of Systematic Reviews* 2008, Issue 4. Art. No.: CD003813. DOI: 10.1002/14651858.CD003813.pub3.

ABSTRACT

Background

Infective endocarditis is a severe infection arising in the lining of the heart with a high mortality rate.

Many dental procedures cause bacteraemia and it was believed that this may lead to bacterial endocarditis (BE) in a few people. Guidelines in many countries have recommended that prior to invasive dental procedures antibiotics are administered to people at high risk of endocarditis. However, recent guidance by the National Institute for Health and Clinical Excellence (NICE) in England and Wales has recommended that antibiotics are not required.

Objectives

To determine whether prophylactic antibiotic administration compared to no such administration or placebo before invasive dental procedures in people at increased risk of BE influences mortality, serious illness or endocarditis incidence.

Search strategy

The search strategy from the previous review was expanded and run on MEDLINE (1950 to June 2008) and adapted for use on the Cochrane Oral Health, Heart and Infectious Diseases Groups' Trials Registers, as well as the following databases: CENTRAL (*The Cochrane Library* 2008, Issue 2); EMBASE (1980 to June 2008); and the *meta*Register of Controlled Trials (to June 2008).

Selection criteria

Due to the low incidence of BE it was anticipated that few if any trials would be located. For this reason, cohort and case-control studies were included where suitably matched control or comparison groups had been studied. The intervention was the administration of antibiotic compared to no such administration before a dental procedure in people with an increased risk of BE. Cohort studies would need to follow those at increased risk and assess outcomes following any invasive dental procedures, grouping by whether prophylaxis was received. Included case-control studies would need to match people who had developed endocarditis (and who were known to

be at increased risk before undergoing an invasive dental procedure preceding the onset of endocarditis) with those at similar risk but who had not developed endocarditis. Outcomes of interest were: mortality or serious adverse event requiring hospital admission; development of endocarditis following any dental procedure in a defined time period; development of endocarditis due to other non-dental causes; any recorded adverse events to the antibiotics; and cost implications of the antibiotic provision for the care of those patients who develop endocarditis.

Data collection and analysis

Two review authors independently selected studies for inclusion, then assessed quality and extracted data from the included study.

Main results

No randomised controlled trials (RCTs), controlled clinical trials (CCTs) or cohort studies were included. One case-control study met the inclusion criteria. It collected all the cases of endocarditis in The Netherlands over 2 years, finding a total of 24 people who developed endocarditis within 180 days of an invasive dental procedure, definitely requiring prophylaxis according to current guidelines and who were at increased risk of endocarditis due to a pre-existing cardiac problem. This study included participants who died because of the endocarditis (using proxys). Controls attended local cardiology outpatient clinics for similar cardiac problems, had undergone an invasive dental procedure within the past 180 days and were matched by age with the cases. No significant effect of penicillin prophylaxis on the incidence of endocarditis could be seen. No data were found on other outcomes.

Authors' conclusions

There remains no evidence about whether penicillin prophylaxis is effective or ineffective against bacterial endocarditis in people at risk who are about to undergo an invasive dental procedure. There is a lack of evidence to support previously published guidelines in this area. It is not clear whether the potential harms and costs of antibiotic administration outweigh any beneficial effect. Ethically practitioners need to discuss the potential benefits and harms of antibiotic prophylaxis with their patients before a decision is made about administration.

PLAIN LANGUAGE SUMMARY

Antibiotics for the prophylaxis of bacterial endocarditis in dentistry

There is no evidence about whether antibiotic prophylaxis is effective or ineffective against bacterial endocarditis in people at risk who are about to undergo an invasive dental procedure.

There is a lack of evidence to support previously published guidelines in this area. It is not clear whether the potential harms and costs of antibiotic administration outweigh any beneficial effect. Ethically practitioners need to discuss the potential benefits and harms of antibiotic prophylaxis with their patients before a decision is made about administration.

BACKGROUND

Infective endocarditis is a rare disease caused by infected vegetations (growths) which often occurs on previously damaged or congenitally malformed cardiac valves or endocardium (heart lining). There is a generally accepted incidence of approximately 10 per 100,000 of the population per year. It is a life-threatening condition with a mortality of up to 30% even with antibiotic therapy (Delahaye 1995; Netzer 2000; Verheul 1993). The infecting organisms are usually bacteria but less commonly are fungi, particularly of the Candida species, which may enter the blood via a number of portals. Bacterial endocarditis (BE) is infective endocarditis caused by bacteria which enter the blood (bacteraemia). Bacteria may enter the blood through a variety of portals especially mucosal surfaces. The gingiva and periodontal ligament which surrounds all teeth is almost constantly a degree of inflammation and as such a potential point of entry for bacteria within the blood. Indeed, it has been demonstrated that everyday activities such as toothbrushing cause bacteraemia (Lucas 2000; Roberts 1999).

Dentistry and endocarditis

The incidence of BE is low and the proportion of cases arising as a result of dental treatment is arguable, estimated to be as low

as 4% (Gendron 2000; Gunneroth 1984) and as high as 64% of cases of BE (Bennis 1995). Although dental procedures are commonly implicated in the causation of endocarditis, the number of cases where the temporal relationship can be demonstrated ranges between only 4% and 7.5% of cases (Gendron 2000).

Most dental procedures cause bacteraemia and it was believed that this may lead to BE. There has been a well established practice of administering antibiotics to patients who are at risk of developing BE prior to procedures during which a bacteraemia may develop and guidelines were published recommending this practice (Dajani 1997; EWP 1993). The rationale for this is that a high circulating dose of antibiotic will prevent the development of an infected vegetation on damaged endocardium and thus prevent endocarditis. However, since this review was first published, both the UK (Gould 2006) and the USA (Wilson 2007) have issued updated guidelines which saw a radical sea-change moving away from giving antibiotics to all at risk patients to only advising antibiotics are given to high risk patients. In England and Wales, the National Institute for Health and Clinical Excellence (NICE) recently published guidance on the topic with the bottom line that no antibiotics were required for any interventional procedure (dental or other surgical site) (NICE 2008).

People at risk

In the past the majority of patients who developed endocarditis had a known pre-existing cardiac defect; more recently this trend has shifted with nearly half of the cases of endocarditis having no known previous cardiac disease (Hoen 2002; Hoen 2006). Some patients with no known heart disease may also develop endocarditis, particularly children up to the age of 2 years and intravenous drug users (Durack 1994). Common cardiac conditions at risk include previous endocarditis, prosthetic heart valves, valvular stenosis, ventricular septal defect and valvular damage following rheumatic fever. Some of these conditions have a higher risk of developing endocarditis, namely previous endocarditis and prosthetic heart valves (Durack 1994). In the recent NICE guidance (NICE 2008), it was decided not to stratify levels of risk as this has lead to some confusion particularly among dentists, patients were either considered at risk or not.

The above conditions either cause changes in the surface of the heart lining (endocardium) or changes in the blood flow which damage the endocardium and enables organisms in the blood to adhere and multiply forming bacterial vegetations. This leads to a severe systemic illness as well as direct effects on the functioning of the heart. Fragments of the vegetations may break away and become lodged elsewhere in the circulation (embolism).

Natural history

Without antibiotic therapy, infective endocarditis is fatal (Durack 1994). The most common and important complication of endocarditis is heart failure due to the direct effects of the proliferating vegetations on the heart valves which are eventually destroyed. Embolism of fragments of the vegetation can damage organs and tissues including the brain, lung, coronary arteries, spleen and the extremities of the limbs (Durack 1994).

Antibiotics

Despite antibiotics remaining relatively successful in the treatment of infective endocarditis, the incidence of the disease has not altered significantly; nor has the use of prophylactic antibiotics in individuals at risk of BE altered the incidence (Durack 1994), however this is against a background of a dramatic rise in the numbers of people receiving artificial valves and pacemakers.

Some authorities have questioned the routine use of antibiotics for endocarditis prophylaxis (Strom 1998), arguing that the adverse effects of antibiotics may outweigh the potential benefits. For example, one study stated that patients receiving penicillin were 5 times more likely to die from an anaphylactic (allergic) reaction than from endocarditis (Bor 1984), however this study only considered people with mitral valve prolapse who are not at greatly increased risk of endocarditis. The overprescription of antibiotics by the whole medical and veterinary professions has resulted in the emergence of resistance of many organisms to the traditional therapeutic antibiotics available (SMAC 1997). This is now a major problem globally but the single use of antibiotic for prophylaxis is unlikely to have contributed greatly to this.

A preliminary review of the available literature indicated that the most widely used antibiotics for the prevention of endocarditis are penicillins. Published guidelines recommend a single pre-operative dose (2 g or 3 g) sometimes with a subsequent dose post-operatively (Dajani 1997; EWP 1993). The original version of the review was limited to penicillins since these were by far the most widely used antibiotic for endocarditis prophylaxis. However, in this update, the scope has been extended to all antibiotics.

OBJECTIVES

Primary objective

To determine whether prophylactic antibiotic administration compared to no such administration or placebo before invasive dental procedures in people at risk or at high risk of bacterial endocarditis (BE) influences mortality, serious illness or endocarditis incidence.

Secondary objectives

To determine whether the effect of dental antibiotic prophylaxis differs from no such administration or placebo in people with different cardiac conditions predisposing to raised risk of endocarditis, and in people undergoing different high risk dental procedures, on the effectiveness of antibiotic prophylaxis in people at high risk.

Harms

If there was no evidence from randomised controlled trials or cohort studies on whether prophylactic antibiotic affected mortality or serious illness, and there was evidence from these or case-control studies suggesting that prophylaxis with antibiotic reduced incidence of endocarditis, then the following would have also been assessed: whether the harms of prophylaxis with single antibiotic dose such as penicillin (amoxicillin 2 g or 3 g) before invasive dental procedures compared with no antibiotic or placebo in people at high risk of endocarditis did not differ from the benefits in prevention of endocarditis.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and controlled clinical trials (CCTs) would be included where available. Due to the low incidence of bacterial endocarditis (BE) it was anticipated that few such trials would be found. Cohort and case-control studies were included where suitably matched control or comparison groups had been studied.

Types of participants

RCTs and CCTs

Studies must have included adults or children or both who had any of the following pre-existing cardiac defects (i.e. patients known to be at risk): congenital heart defects, a history of rheumatic fever, and those at high risk with prosthetic heart valves (tissue and mechanical), or who had had endocarditis previously. People with pacemakers (and no other risk factors) were excluded.

The dental procedures which the patients may have undergone in the studies included: supragingival and subgingival scaling of teeth, extensive restorations of teeth, endodontics, oral surgery including dental extractions. Procedures performed under local and general anaesthetic were considered.

Types of interventions

RCTs and CCTs

The prime intervention assessed was the administration of an antibiotic, compared with no such administration or placebo, before a dental procedure. Studies in which an antibiotic was administered post-operatively were included if this was part of a protocol in which the antibiotic was administered pre-operatively. The antibiotics could be administered by oral, intravenous or intramuscular routes but not topical.
Co-interventions may have included the following procedures: the use of mouthwash pre-operatively or the mechanical cleaning of teeth.

Types of outcome measures

RCTs and CCTs

The primary outcome measures were.
(1) Mortality or serious adverse events (from any cause) requiring hospital admission.
(2) The development of endocarditis following any dental procedure in a defined time period.
(3) The development of endocarditis due to other non-dental causes.
The secondary outcome measures were.
(1) Any recorded adverse events to the antibiotics.
(2) Cost implications of antibiotic provision for prophylaxis compared with the cost of care of those extra patients who develop endocarditis.
Assessment of harms would have included all studies where potentially serious (such as would be expected to result in hospitalisation) or fatal side effects of a single antibiotic dose had been reported or assessed. Studies included would have been any studies already included in the review, as well as randomised controlled trials, cohort studies, case-control studies, uncontrolled trials, case series and case reports.

Characteristics of included cohort studies and case-control studies

Cohort studies to be included would fulfil the following criteria: Participants were people at high risk of endocarditis (as above). Their progress was followed (no minimum time period) and invasive dental procedures carried out, use (or not) of prophylactic antibiotics at these visits and occurrence or not of BE, death or serious illness were recorded (as a minimum). It would have been possible to compare incidence of BE, death or serious illness in

those who received invasive dental procedures with and without antibiotics.

Case-control studies included fulfilled the following criteria:

The groups compared included a group of people at high risk of endocarditis who do develop BE, and a group of people at high risk of endocarditis who do not develop BE. Information was provided on the numbers of people in each group who had undergone invasive dental procedures within a (stated) set period, and the numbers who had received antibiotic prophylaxis concomitant with that dentistry. Post-hoc it was decided that studies which excluded cases when they died due to endocarditis would be excluded as around 20% of people who contract endocarditis will die of it and these participants may be different from those who do not die.

Search methods for identification of studies

A comprehensive search of the literature was performed. Articles in languages other than English were only excluded if they could not be translated into English.

The search strategy from the original review was developed on MEDLINE (1950 to June 2008) and adapted for use on the Cochrane Oral Health, Heart and Infectious Diseases Groups' Trials Registers, as well as the following databases: Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2008, Issue 2); EMBASE (OVID) (1980 to June 2008); and the *meta*Register of Controlled Trials (http:/ / www.controlled-trials.com/) (June 2008). *See* Appendix 1; Appendix 2; and Appendix 3.

It was decided that, if harms of treatment were assessed, a search specifically to find papers on harms of the doses of amoxicillin or other antibiotics commonly recommended in previous US and UK guidelines (Dajani 1997; EWP 1993; Gould 2006; Wilson 2007) would be run on MEDLINE and EMBASE, and references suggested in *Meyler's Side Effects of Drugs* (Aronson 2006) collected, but this was not carried out.

Data collection and analysis

Inclusion/exclusion criteria

Study titles and abstracts obtained from the search were screened for inclusion independently by two review authors. The review authors were not blinded to the authors, institution or journal. Full text papers retrieved were similarly screened for inclusion independently by two review authors. The inclusion criteria were as stated above. Disagreements over inclusion were resolved by discussion; if agreement could still not be reached it was intended that the paper would be taken to a third party, but this did not occur.

Data extraction

Data and quality information were extracted by two review authors independently onto a custom designed data collection form. Briefly, in addition to bibliographic details of the paper, the key items of data were the study design, country of origin, details of the antibiotic intervention, study population details including risk factors and type of dental procedure. The outcome data collected from randomised controlled trials (RCTs) and controlled clinical trials (CCTs) included number of deaths; number of hospital admissions; the number of serious illnesses that would be expected to result in hospital admission; the number of cases of endocarditis; any other adverse events noted; and the number of people originally randomised to each group. The outcome data collected from cohort studies would have included the same information as for RCTs plus adjusted odds ratios or risk ratios and information on which factors were adjusted for. The outcome data collected from case-control studies included the adjusted odds ratio of a person at high risk of endocarditis having had antibiotic prophylaxis before invasive dentistry before either developing endocarditis (cases) or not (controls). Authors were contacted for further details of their studies, as well as to assess inclusion where necessary.

Assessment of study quality

Included studies were ranked according to study design: RCT, CCT, cohort, case-control. Analysis of quality was based on the assessment of Downs and Black (Downs 1998), and included external validity (representativeness of the populations studied) and internal validity (blinding, validity of outcome measures, similarity of the groups compared, similarity of timing, randomisation, allocation concealment and losses to follow up). Where data appeared ambiguous or incomplete, the study authors would have been contacted.

Data analysis

It was planned that data on the number of patients with each outcome event, by allocated treatment group (RCTs) or quantile (cohort studies) would be sought. We aimed to calculate a pooled estimate of the treatment effect for each outcome (separately) across RCTs, CCTs, cohort studies and case-control studies in random-effects meta-analysis, as an odds ratio (the ratio of odds in the prophylaxis group to the odds in the no prophylaxis group), since the odds ratio is the only good measure of association that works across prospective studies and case-control studies (Fleiss 1981). Heterogeneity between trial results was to be tested for using a standard Chi^2 test, and considered significant where $P < 0.1$. For case-control studies it was planned that the odds of antibiotic prophylaxis before dental treatment in the previous 3 months for cases and controls would not be pooled with data from other types of studies. It was planned that if harm data were collected they would be tabulated according to study design, but not pooled.

For amoxicillin, if sufficient data were available, then the interventions of 2 g and 3 g amoxicillin would be considered separately.

Also, if appropriate, subgrouping would be used to explore the effects of different underlying causes of at risk and high risk status for endocarditis, and of different invasive dental techniques.
It was also planned that sensitivity analysis would be carried out on any pooled analyses, removing studies where there appeared to be significant differences in risk factors for endocarditis between the groups compared and where this had not been adequately adjusted for.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.
In the original search for the review a total of 980 references were initially identified by the above search strategy. The updated search in 2008 revealed an additional 70 references. Assessment of the titles and abstracts, where available, resulted in 118 references; all of which were obtained in full text. A further 83 were rejected since they were clearly discussion papers, editorials or guidelines. A total of 35 references were assessed for inclusion in duplicate. Of these full papers, 34 were eventually excluded (*see* Characteristics of excluded studies for further details). In particular, one potentially useful cohort study was identified but excluded as it was not possible to separate out those who received prophylaxis or not before dental treatment (Gersony 1977). Several case-control studies were identified where only some of the cases were at high risk from endocarditis before dental treatment (Strom 1998B; Strom 2000). It was evident that there were many review articles, commentaries and guidelines but few primary studies.
No randomised controlled trials (RCTs) were identified, nor were any other controlled trials (quasi-randomised, historically controlled) or cohort studies identified. Three case-control studies were initially included (Imperiale 1990; Lacassin 1995; Van der Meer 1992) however on discussion with editors of the Cochrane Oral Health Group it was decided that two of these, Imperiale 1990 and Lacassin 1995, might have been severely biased and so should be excluded. In these studies people with endocarditis ('cases') who died, about 20% of potential cases in both studies, were not included. Excluding this group, whose characteristics may have been very different from those cases who survived endocarditis, from the cases, but not from the controls (where many fewer people are likely to have died), will have made the characteristics of the two groups very different. Thus only one case-control study was included in this review, Van der Meer 1992.
The Van der Meer 1992 study collected details of all of the 349 people who developed definite native-valve endocarditis in The Netherlands over a 2-year period (1st November 1986 to 1st November 1988). Cases were eligible if they had previously had congenital heart disease, coarctation of the aorta, rheumatic or other valvular dysfunction, or mitral valve prolapse with mitral regurgitation. They had to have undergone a medical or dental procedure that required prophylaxis within 180 days of the onset of symptoms of endocarditis. Proxy responders (spouses or general practitioners) were used where cases were too ill to be interviewed or had died.
Controls had not been diagnosed with endocarditis but had one of the cardiac conditions and were outpatients at cardiology departments of one of five hospitals. Controls were matched for age (within the same 5-year age category) and had undergone a medical or dental procedure within 180 days of their interview. A random sample of potential controls was drawn, and where there were at least four controls per case all were contacted. Where there were fewer than four controls a further random sample was drawn.
For both groups all information about invasive procedures and use of prophylaxis was checked with medical or dental specialists and pharmacists.

Risk of bias in included studies

The included study used a case-control design.

External validity

Good (included all people with a pre-existing cardiac risk who developed endocarditis within Holland over a given period, and had had relevant dental interventions within 180 days, controls were people with similar pre-existing cardiac risk factors from several hospitals).

Internal validity

- Blinding - not done (as this was not an intervention study).
- Validity of outcome measures - good. (Endocarditis was defined by the diagnostic criteria of Von Reyn 1981, and it was checked that controls had not developed endocarditis. Appropriateness of antibiotic prophylaxis was checked with medical, dental and pharmacy staff, and assessed against The Netherlands Heart Foundation recommendations, 6 of 8 cases and 15 of 26 controls were administered prophylaxis in keeping with these recommendations, and the remaining 2 of 8 cases and 11 of 26 controls were administered prophylaxis which were considered equivalent (though the exact criteria for equivalence were not described.))
- Similarity of the groups compared - unclear (type of cardiac risk factor, sex not described for the subgroup who had had a dental procedure, and type of dental intervention appears different in the cases and controls, but cases and controls matched for age).

- Similarity of timing - good (both groups were required to have undergone invasive dental techniques within 180 days of onset of symptoms/interview and data are split by time period for both groups).
- Randomisation - not done (this is an observational study, it is entirely possible that as the dentist is deciding whether to give prophylaxis or not on the basis of the information held about the patient in front of him or her that those patients appearing frailer may have been more likely to receive prophylaxis).
- Allocation concealment - not done (this is an observational study).
- Losses to follow up - moderate (cases who were very ill or who died were included via use of proxy responders, however this did not occur for the 53/889 controls who died).

Overall the observational and retrospective nature of the design conferred a substantial risk of bias.

Effects of interventions

In the included case-control study (Van der Meer 1992) of the 349 people with definite native-valve endocarditis, 197 had previous heart disease (proxy responders were interviewed for 10 of these). Of these 54 had undergone a medical or dental procedure with an indication for prophylaxis within the past 180 days, of whom in six a causal relationship was ruled out as it was unlikely that the agent isolated from the blood originated in the area of the procedure. Of the 48 people with endocarditis left, 44 had undergone dental procedure which the paper identified as having a definite (24) or possible (20) indication for prophylaxis (none of these cases had used a proxy responder). Indications for definite prophylaxis were dental extractions and dental root work, while indications for possible prophylaxis were defined as dental scaling.

Of 889 potential controls who were sent an introductory letter, 689 were ineligible (53 had died, 29 had a prosthetic heart valve, 62 could not be located, 102 could not be contacted by phone and 418 had not undergone an invasive dental or medical procedure within the past 180 days), the remaining 200 were interviewed by phone 2 to 5 days later. 181 of these controls had undergone a dental procedure with definite (79) or possible (102) indication for prophylaxis.

Seven of 24 cases and 16 of 79 controls had had appropriate prophylaxis for a dental procedure requiring definite prophylaxis within 180 days.

The characteristics of the cases and controls were not well described as those who had received a dental procedure (rather than a medical one) were not separated out in the publication (the separated data were provided by Professor Van der Meer). The median time between a dental procedure requiring definite prophylaxis and onset of endocarditis was 10 days in the cases, and the median time between a dental procedure requiring definite prophylaxis and interview was 71 days in controls (data missing for 12 controls). The procedure was apical surgery in 1 case (4%) and 1 control (1%), dental avulsion in 1 case (4%) and 12 controls (15%), dental extraction in 9 cases (38%) and 15 controls (19%), dental abscess in 1 case (4%) and 1 control (1%), removal of subgingival calculus in 3 cases (13%) and 8 controls (33%), removal of calculus plus polishing of teeth in 6 cases (25%) and 34 controls (43%), root canal therapy in 3 cases (13%) and 8 controls (10%).

Including the cases and controls undergoing either definite or possible indication for prophylaxis, and including the 4 cases and 19 controls who underwent a non-dental indication, 69% of cases were male, 55% of controls. The median age of this larger group was 41 years for cases and 40 for controls (controls were age-matched).

Seven of 21 cases and 9 of 46 controls had had appropriate prophylaxis for a dental procedure requiring definite prophylaxis within 90 days. Seven of 44 cases and 17 of 181 controls had had appropriate prophylaxis for a dental procedure requiring definite or possible prophylaxis within 180 days. Seven of 32 cases and 9 of 100 controls had had appropriate prophylaxis for a dental procedure requiring definite or possible prophylaxis within 90 days. No information was presented on the adjunctive use of mouthwash.

In each of these ways of assessing the data the proportion of those receiving prophylaxis was greater in the cases than in the controls. Translating the data so that we assess the odds of developing endocarditis in those receiving prophylaxis compared with those not receiving prophylaxis we find an odds ratio (OR) which is not significantly different from one for any of the groupings (OR 1.62, 95% confidence interval (CI) 0.57 to 4.57 for those with a definite indication for prophylaxis over 180 days). Similarly, if we include the data from the two excluded case-control studies (Imperiale 1990; Lacassin 1995) that were originally included in this review (between the three studies 59 participants developed endocarditis of 67 people receiving appropriate prophylaxis and 148 people not receiving prophylaxis) we still find no significant protection of prophylaxis against endocarditis ($OR_{random-effects}$ 0.56, 95% CI 0.15 to 2.15).

Only four cases developed endocarditis following non-dental medical interventions (within the past 180 days and with pre-existing cardiac indications for the use of prophylaxis), so assessment of the effects of prophylaxis in these cases was not possible.

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.

No studies were located that assessed mortality, serious adverse events requiring hospital admission, other adverse events or cost implications of treatment.

Because no significant protective effect of antibiotic prophylaxis was seen against endocarditis, we did not do a wide ranging search to pool information on the potential harmful effects of antibiotic prophylaxis, as pre-specified in the protocol.

DISCUSSION

The previous version of this review was confined to penicillins for the prophylaxis of endocarditis in dentistry. This update has extended the search to include all antibiotics but no further studies were identified in addition to the ones in the original review.

The one included case-control study, which included all of the people in The Netherlands who developed endocarditis following an invasive dental procedure while at known cardiac risk over a 2-year period (24 individuals who underwent a procedure definitely requiring prophylaxis, and a further 20 which may possibly have required prophylaxis), provides no conclusive evidence about whether antibiotic prophylaxis is effective or ineffective against bacterial endocarditis in such high risk individuals about to undergo an invasive dental procedure.

There are currently insufficient primary data to know whether antibiotic prophylaxis before invasive dental procedures in people at high risk of endocarditis does actually prevent endocarditis, deaths or other serious illness. As the usefulness of prophylaxis could not be established, we have not examined, in detail, the harms of antibiotic administration; this would be a systematic review in itself. Such a review would, however, be extremely valuable and could potentially be used by a wide-spectrum of research workers and other systematic reviews. In the absence of a systematic review on the harms of penicillins, the most authoritative source is *Meyler's Side Effects of Drugs* (Aronson 2006).

The range of potential side effects from the administration of antibiotics is vast, largely with a hypersensitive aetiology but some direct toxic effects may also occur. All four types of hypersensitivity reaction have been reported with the use of penicillins including the most severe reaction, anaphylactic shock, and other type I reactions including allergic bronchial obstruction, allergic rhinitis and angio-oedema; haemolytic anaemia, type II, has been recorded; drug fever, a type III reaction and the delayed type hypersensitivity (type IV) of allergic dermatitis (Aronson 2006). Hypersensitivity reactions are reported to occur in between 1% and 10% of patients treated (Aronson 2006); the incidence of anaphylaxis is between 1 in 2500 and 1 in 10,000 and is fatal in about 10% of those affected (Grahame-Smith 2002). Additional reactions reported in association with penicillins include erythema multiforme, fixed drug eruptions and pemphigus vulgaris (Aronson 2006). However, the lesser reactions may be due to courses of penicillins which are not usually given for endocarditis prophylaxis and there is evidence that some of the side effects are dose- and time-dependent (Aronson 2006). A hospital based case-control study from Europe and India estimated the incidence of anaphylaxis related to oral amoxicillin to be relatively low at 6 cases per 10,000 and intermediate for parentally administered penicillin at 32 cases per 10,000 (Kaufman 2003), and is likely to be lower in doses administered orally for one or two doses (Aronson 2006). A recent report of a UK survey of fatal anaphylaxis after oral amoxicillin by the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK who monitor adverse drug reactions reported to them concluded that there had been only one reported case of fatal anaphylaxis with oral amoxicillin in 35 years (Lee 2007). Furthermore, this was following a course of 250 mg amixicillin and there are no reported cases of fatal anaphylaxis with a single 3 g dose used for prophylaxis.

On current available data we cannot accurately assess either the presence or size of any beneficial effect of antibiotic prophylaxis in people at cardiac risk who undergo invasive dentistry, nor the scale of the potential side effects, so it is not possible to clearly assess the balance of risk and benefit.

For the original version of this review we canvassed opinion among some healthcare workers with an interest in evidence based care and a separate group of dentists who had attended an evidence based practice course. Those healthcare workers and dentists who were blinded to the details of the intervention and condition, but shown the level of evidence and the non-significant odds ratio, stated that in this circumstance they would attempt to seek out further evidence (randomised controlled trials (RCTs), cohort studies etc) and/or involve their patients in the decision about whether to use the intervention. However, those dentists who were not blinded, who were told that the topic was endocarditis prophylaxis using penicillin, stated that they would use prophylaxis despite the paucity of evidence and cited medico-legal reasons for this decision. It will be interesting how the National Institute for Health and Clinical Excellence (NICE) guideline (NICE 2008) is adhered to by not just dentists but other healthcare professionals to which it applies. A recent study examined the legal situation of claimants contracting endocarditis against dentists who had recently treated them (Martin 2007). The authors concluded that as long as dentists adhere to current published guidelines there is little course for redress and it is eminently defensable in a court of law.

It would be useful to have evidence about the usefulness of antibiotic prophylaxis of endocarditis in dentistry from higher levels of evidence. As the incidence of endocarditis is so low, a randomised controlled trial, run over 2 years, would require approximately 60,000 patients with a cardiac risk factor for endocarditis to be included (a cohort study over 10 years would require approximately 18,000 patients). Such a trial would require an intense international effort.

A larger, well conducted case-control study might be more feasible but would still require a large effort and multicentre participation. If including every endocarditis case in The Netherlands for 2 years produces only 24 appropriate cases then the area or time span covered will be very large indeed. Selection of appropriate controls is probably the most challenging aspect; ideally, as in Van der Meer's study, they would have had dental treatment in a predefined time

and be matched very closely for sex, age and type of cardiac risk factor. Additionally, neither cases nor controls should be excluded for death or serious illness (use of proxy respondents would be ideal and this will require retrospective identification of controls as well as ongoing prospective identification of cases), and dental records would be available and be explicit about the use (or not) of prophylaxis. Full details would be collected on other factors which may compound the risk such as general well being, coexisting medical problems, socio-economic status and oral health status.

The effects of the NICE guidance on the incidence of endocarditis in the UK are going to be monitored using the Hospital Episode Statistics (HES). Tracked over a number of years and compared with the pre-NICE guideline era the incidence of endocarditis might be one method to answer this conundrum in an albeit rather crude fashion.

Another, underexplored area is the cost of prophylaxis both in terms of finance and health. The financial cost to health services of providing large quantities of prophylactic antibiotics must be weighed against the cost of treating patients who develop endocarditis, which although significant, occurs in many fewer patients than those potentially at risk. The health costs need considering, particularly the potential harms of the administration of antibiotics compared to the development of endocarditis. The involvement of health economists would be beneficial. This was explored in depth in the recent NICE guidance.

Despite the varying guidelines produced over the years and the recent significant change recommended by NICE, it is important for medical and dental practitioners to remember that patients remain at risk from developing endocarditis. Many patients will develop endocarditis with organisms that have originated from the oral cavity. Whilst there is no evidence that dental treatment is directly related to the development of the disease or not, nor that prophylactic antibiotics can prevent the development of the disease or not, it would appear logical to recommend that the higest level of oral health should be achieved and maintained in at risk patients.

AUTHORS' CONCLUSIONS

Implications for practice

There remains no evidence that antibiotic prophylaxis is either effective or ineffective against bacterial endocarditis in people at risk who are about to undergo an invasive dental procedure which is reflected in recent guidance. There is a lack of evidence to support the previously published guidelines in this area. It is not clear whether the potential harms and costs of penicillin administration outweigh any beneficial effect.

Implications for research

A randomised controlled trial (RCT) would only be feasible in extensive areas of very centralised and organised health care, due to the large numbers of participants with risk factors for endocarditis required. A well designed multicentre cohort or case-control study is possible but would still require a very large and co-ordinated effort, and a great deal of attention would need to be paid to recruiting suitable control participants. These will be most feasible to perform in an area where registers exist so that it is possible to identify all people with current risk factors for endocarditis, randomise or follow their dental histories in detail and identify outcomes completely and accurately.

A systematic review of the harms and costs associated with antibiotic use is needed, and such a review may be useful to assess harms for systematic reviews of a number of different interventions. It would be important to assess the effects of type of antibiotic, route of administration, dose, previous history of reaction and duration of use on the side effects and adverse events experienced by people on antibiotic therapy.

ACKNOWLEDGEMENTS

Our gratitude goes to Dr Van der Meer (Academic Medical Center, University of Amsterdam) for splitting his data into people who had or had not had a relevant dental intervention, and to Dr Imperiale (Yale University School of Medicine) for his helpful information on his study. Thanks also to the Cochrane Non-Randomised Methods Group, and the Harms subgroup, for support, discussion and ideas about the review. We are grateful to Emma Tavender and Luisa Fernandez of the Cochrane Oral Health Group for excellent support, Sylvia Bickley (Cochrane Oral Health Group), Margaret Burke (Cochrane Heart Group) and Vittoria Lutje (Cochrane Infectious Diseases Group) for kindly searching their specialist registers for us, and Marco Esposito, Helen Worthington, Sylvia Bickley, Jan Clarkson, Paul Coulthard, Jayne Harrison, David Rickard, Robin Richardson, Jan van der Meer, Robin Seymour and Jeremy Bagg for constructive comments on the manuscript.

REFERENCES

References to studies included in this review

Van der Meer 1992 *{published and unpublished data}*

Van der Meer JTM, van Wijk W, Thompson J, Vandenbroucke JP, Valkenburg HA, Michel MF. Efficacy of antibiotic prophylaxis for prevention of native-valve endocarditis. *Lancet* 1992;**339**(8786): 135–9.

References to studies excluded from this review

Al-Karaawi 2001 *{published data only}*

Al Karaawi ZM, Lucas VS, Gelbier M, Roberts GJ. Dental procedures in children with severe congenital heart disease: A theoretical analysis of prophylaxis and non-prophylaxis procedures. *Heart* 2001;**85**(1): 66–8.

Anonymous 1992 *{published data only}*

Anonymous. Prophylaxis of infectious endocarditis. *Medecine et Maladies Infectieuses* 1992;**22**(Suppl Apr):1–12.

Archard 1966 *{published data only}*

Archard HO, Roberts WC. Bacterial endocarditis after dental procedures in patients with aortic valve prostheses. *Journal of the American Dental Association* 1966;**72**:648–2.

Bayliss 1983 *{published data only}*

Bayliss R, Clarke C, Oakley C. The teeth and infective endocarditis. *British Heart Journal* 1983;**50**(6):506–12.

Bennis 1995 *{published data only}*

Bennis A, Zahraoui M, Izzouzi L, Soulami S, Mehadji BA, Tahiri A, et al.Bacterial endocarditis in Morocco. *Annales de Cardiologie et D'Angeiologie* 1995;**44**(7):339–44.

Bhat 1996 *{published data only}*

Bhat AW, Jalal S, John V, Bhat AM. Infective endocarditis in infants and children. *Indian Journal of Pediatrics* 1996;**63**(2):204–9.

Biron 1997 *{published data only}*

Biron CR. Despite diligent staff, infective endocarditis surfaces during periodontal treatment. [erratum appears in RDH 1997 Jun;17 (6):67]. *RDH* 1997;**17**(3):42–8.

Bonhomme 1992 *{published data only}*

Bonhomme I, Briancon S, Fagnani F. Exploratory economic appraisal of prophylaxis of infective endocarditis. *Medecine et Maladies Infectieuses* 1992;**22**(Spec Iss Dec):1084–91.

Caretta 1988 *{published data only}*

Caretta Q, Chiarini F, Di Rocco V, Brandimarte C, Biggio S, Alessandri N, et al.[Anti-infectious prophylaxis in patients at risk for endocarditis in the treatment of the oral cavity. Importance of the antibiotic combination]. [Italian]. *Cardiologia* 1988;**33**(6):577–81.

Clemens 1982 *{published data only}*

Clemens JD, Horwitz RI, Jaffe CC. A controlled evaluation of the risk of bacterial endocarditis in persons with mitral-valve prolapse. *New England Journal of Medicine* 1982;**307**(13):776–81.

Conner 1967 *{published data only}*

Conner HD, Haberman S, Collings CK, Winford TE. Bacteremias following periodontal scaling in patients with healthy appearing gingiva. *Journal of Periodontology* 1967;**38**(6):466–72.

Gersony 1977 *{published data only}*

Gersony WM, Hayes CJ. Bacterial endocarditis in patients with pulmonary stenosis, aortic stenosis, or ventricular septal defect. *Circulation* 1977;**56**(Suppl 1):I84–7.

Herr 1976 *{published data only}*

Herr HB. [Fever after dental treatment]. [German]. *Schweizerische Rundschau fur Medizin Praxis* 1976;**65**(38):1152–4.

Hess 1983 *{published data only}*

Hess J, Holloway Y, Dankert J. Incidence of postextraction bacteremia under penicillin cover in children with cardiac disease. *Pediatrics* 1983;**71**(4):554–8.

Horstkotte 1986 *{published data only}*

* Horstkotte D, Friedrichs W, Pippert H, Bircks W, Loogen F. Benefits of endocarditis prevention in patients with prosthetic heart valves [Nutzen der endokarditisprophlaxe bei pateinten mit prothetischen herzklappen]. *Zeitschrift fur Kardiologie* 1986;**75**(1):8–11.

Horstkotte D, Rosin H, Friedrichs W, Loogen F. Contribution for choosing the optimal prophylaxis of bacterial endocarditis. *European Heart Journal* 1987;**8**(Supplement J):379–81.

Imperiale 1990 *{published data only}*

Imperiale TF. Effectiveness of antibiotic prophylaxis for postdental infective endocarditis. *Cardiology Board Review* 1991;**8**(3):18–27.

* Imperiale TF, Horwitz RI. Does prophylaxis prevent postdental infective endocarditis? A controlled evaluation of protective efficacy. *American Journal of Medicine* 1990;**88**(2):131–6.

Khairat 1966 *{published data only}*

Khairat O. An effective antibiotic cover for the prevention of endocarditis following dental and other post-operative bacteraemias. *Journal of Clinical Pathology* 1966;**19**(6):561–6.

Lacassin 1995 *{published data only}*

Hoen B, Lacassin F, Briancon S, Selton-Suty C, Goulet V, Delahaye F, et al.Procedures at risk for infective endocarditis [Gestes a risque d'endocardite infectieuse. Une enquete cas–temoins]. *Medecine et Malades Infectieuses* 1992;**22**:1010–22.

* Lacassin F, Hoen B, Leport C, Selton-Suty C, Delahaye F, Goulet V, et al.Procedures associated with infective endocarditis in adults - A case control study. *European Heart Journal* 1995;**16**(12):1968–74.

Lauridson 1984 *{published data only}*

Lauridson JR, Rainer WG, Merrick TA. The dental patient with artificial heart valves.The importance of antibiotic prophylaxis prior to dental surgery. *Journal of the Colorado Dental Association* 1984;**62** (5):5–6.

Lecointre 1981 *{published data only}*

Lecointre C, Aupois R. [Prevention using antibiotics of infectious endocarditis after tooth extraction]. [French]. *Chirurgien-Dentiste de France* 1981;**51**(126):41–2.

McGowan 1978 *{published data only}*

McGowan DA. Failure of prophylaxis of infective endocarditis following dental treatment. *Journal of Antimicrobial Chemotherapy* 1978;**4**(6):486–8.

McGowan 1982 *{published data only}*

McGowan DA. Endodontics and infective endocarditis. *International Endodontic Journal* 1982;**15**(3):127–31.

Pogrel 1975 *{published data only}*

Pogrel MA, Welsby PD. The dentist and prevention of infective endocarditis. *British Dental Journal* 1975;**139**(1):12–6.

Rahn 1988 *{published data only}*

Rahn R, Shah PM, Schafer V, Muggenthaler F, Frenkel G, Knothe H. [Oral endocarditis prophylaxis in dental-surgery operations]. [German]. *Schweizer Monatsschrift fur Zahnmedizin* 1988;**98**(5):478–81.

Rahn 1993 *{published data only}*

Rahn R. Review presentation on povidone-iodine antisepsis in the oral cavity. [Review]. *Postgraduate Medical Journal* 1993;**69**(Suppl 3):S4–S9.

Shanson 1980 *{published data only}*

Shanson DC, Ashford RF, Singh J. High-dose oral amoxycillin for preventing endocarditis. *British Medical Journal* 1980;**280**(6212): 446.

Strom 1998B *{published data only}*

Strom BL, Abrutyn E, Berlin JA, Kinman JL, Feldman RS, Stolley PD, et al.Dental and cardiac risk factors for infective endocarditis: A population-based, case-control study. *Annals of Internal Medicine* 1998;**129**(10):761–9.

Strom 2000 *{published data only}*

Strom BL, Abrutyn E, Berlin JA, Kinman JL, Feldman RS, Stolley PD, et al.Risk factors for infective endocarditis: oral hygiene and nondental exposures. *Circulation* 2000;**102**(23):2842–8.

Tozer 1966 *{published data only}*

Tozer RA, Boutflower S, Gillespie WA. Antibiotics for prevention of bacterial endocarditis during dental treatment. *Lancet* 1966;**1** (7439):686–8.

Tzukert 1984 *{published data only}*

Tzukert A, Leviner E. Prevention of infective endocarditis in dental care: not by antibiotics alone. *Lancet* 1984;**1**(8387):1190–1.

Tzukert 1986 *{published data only}*

Tzukert AA, Leviner E, Sela M. Prevention of infective endocarditis: not by antibiotics alone. A 7-year follow-up of 90 dental patients. *Oral Surgery, Oral Medicine, Oral Pathology* 1986;**62**(4):385–8.

Van der Meer 1992a *{published data only}*

Van der Meer JT, Thompson J, Valkenburg HA, Michel MF. Epidemiology of bacterial endocarditis in The Netherlands. II. Antecedent procedures and use of prophylaxis. *Archives of Internal Medicine* 1992;**152**(9):1869–73.

Woodman 1985 *{published data only}*

Woodman AJ, Vidic J, Newman HN, Marsh PD. Effect of repeated high dose prophylaxis with amoxycillin on the resident oral flora of adult volunteers. *Journal of Medical Microbiology* 1985;**19**(1):15–23.

Yoshimura 1985 *{published data only}*

Yoshimura Y, Kishimoto H, Matsuura R, Oka M, Matsumoto K. Dental extraction in patients with prosthetic heart valves: antibiotic prophylaxis of prosthetic valve endocarditis. *Journal of the Osaka University Dental School* 1985;**25**:153–9.

Additional references

Aronson 2006

Aronson JK. In: Aronson JK editor(s). *Meyler's side effects of drugs*. 15th Edition. Amsterdam: Elsevier Science, 2006.

Bor 1984

Bor DH, Himmelstein DU. Endocarditis prophylaxis for patients with mitral valve prolapse. A quantitative analysis. *American Journal of Medicine* 1984;**76**:711–7.

Dajani 1997

Dajani AS, Taubert KA, Wilson W, Bolger AF, Bayer A, Ferrieri P, et al.Prevention of bacterial endocarditis - Recommendations by the American Heart Association. *JAMA* 1997;**277**(22):1794–801.

Delahaye 1995

Delahaye F, Ecochard R, Degevigney G, Barjhoux C, Malquarti V, Saradarian W, et al.The long-term prognosis of infective endocarditis. *European Heart Journal* 1995;**16**:48–53.

Downs 1998

Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *Journal of Epidemiology and Community Health* 1998;**52**:377–84.

Durack 1994

Durack DT. Infective and noninfective endocarditis. In: Schlant R, Alexander RW editor(s). *The heart: Arteries and veins*. 8th Edition. New York: McGraw-Hill, 1994:1681–709.

EWP 1993

Endocarditis Working Party of the British Society of Antimicrobial Chemotherapy. Recommendations for endocarditis prophylaxis. *Journal of Antimicrobial Chemotherapy* 1993;**31**:437–8.

Fleiss 1981

Fleiss JL. Sampling method II: prospective and retrospective studies. *Statistical methods for rates and proportions*. New York: John Wiley and Sons, 1981:83–99.

Gendron 2000

Gendron R, Grenier D, Maheu-Robert LF. The oral cavity as a reservoir of bacterial pathogens for focal infections. *Microbes and Infection* 2000;**2**(8):897–906.

Gould 2006

Gould FK, Elliott TS, Foweraker J, Fulford M, Perry JD, Roberts GJ, et al.Guidelines for the prevention of endocarditis: report of the Working Party of the British Society for Antimicrobial Chemotherapy. *Journal of Antimicrobial Chemotherapy* 2006;**57**(6):1035–42.

Grahame-Smith 2002

Grahame-Smith DG, Aronson JK. Penicillins. In: Grahame-Smith DG, Aronson JK editor(s). *Oxford textbook of clinical pharmacology and drug therapy*. 3rd Edition. Oxford: Oxford University Press, 2002:569–71.

Gunneroth 1984

Gunneroth WG. How important are dental procedures as a cause of infective endocarditis?. *American Journal of Cardiology* 1984;**54**(7): 797–801.

Hoen 2002

Hoen B, Alla F, Selton-Suty C, Beguinot I, Bouvet A, Briancon S, et al.Changing profile of infective endocarditis. Results of a 1-year survey in France. *JAMA* 2002;**288**(1):75–81.

Hoen 2006

Hoen B. Epidemiology and antibiotic treatment of infective endocarditis: an update. *Heart* 2006;**92**(11):1694–700.

Kaufman 2003

Kaufman DW, Kelly JP. Risk of anaphylaxis in a hospital population in relation to the use of various drugs: an international study. *Pharmacoepidemiology and Drug Safety* 2003;**12**(195):202.

Lee 2007

Lee P, Shanson D. Results of a UK survey of fatal anaphylaxis after oral amoxicillin. *Journal of Antimicrobial Chemotherapy* 2007;**60**(5): 1172–3.

Lucas 2000

Lucas V, Roberts GJ. Odontogenic bacteremia following tooth cleaning procedures in children. *Pediatric Dentistry* 2000;**22**(2):96–100.

Martin 2007

Martin MV, Longman LP, Forde MP, Butterworth ML. Infective endocarditis and dentistry: the legal basis for an association. British Dental Journal 2007; Vol. 203, issue 1:E1.

Netzer 2000

Netzer ROM, Zollinger E, Seiler C, Cerny A. Infective endocarditis: clinical spectrum, presentation and outcome. An analysis of 212 cases 1980-1995. *Heart* 2000;**84**(1):25–30.

NICE 2008

National Institute for Health and Clinical Excellence. Prophylaxis against infective endocarditis: antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures. NICE Clinical Guideline No 64. London: National Institute for Health and Clinical Excellence, 2008.

Oakley 1987

Oakley CM. Controversies in the prophylaxis of infective endocarditis. *Journal of Antimicrobial Chemotherapy* 1987;**20**(Suppl A):99–104.

Roberts 1999

Roberts GJ. Dentists are innocent! "Everyday" bacteremia is the real culprit: A review and assessment of the evidence that dental surgical procedures are a principal cause of bacterial endocarditis in children. *Pediatric Cardiology* 1999;**20**(5):317–25.

SMAC 1997

Standing Medical Advisory Committee. *The path of least resistance*. London: Department of Health, 1997.

Strom 1998

Strom BL, Abrutyn E, Berlin JA, Kinman JL, Feldman RS, Stolley PD, et al.Dental and cardiac risk factors for infective endocarditis. A population-based, case-control study. *Annals of Internal Medicine* 1998;**129**:761–9.

Verheul 1993

Verheul HA, Vandenbrink RBA, Vanvreeland T, Moulijn AC, Duren DR, Dunning AJ. Effects of changes in management of active infective endocarditis on outcome in a 25-year period. *American Journal of Cardiology* 1993;**72**(9):682–7.

Von Reyn 1981

Von Reyn CF, Levy BS, Arbeit RD, Friedland G, Crumpacker CS. Infective endocarditis: an analysis based on strict case definitions. *Annals of Internal Medicine* 1981;**94**:505–18.

Wilson 2007

Wilson W, Taubert KA, Gewitz M, Lockhart PB, Baddour LM, Levison M, et al.Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation* 2007;**116**(15):1736–54.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Van der Meer 1992

Methods	Case-control study. External validity: good. Internal validity: Blinding - not done. Validity of outcome measures - good. Similarity of the groups compared - unclear. Similarity of timing - good. Randomisation - not done. Allocation concealment - not done. Losses to follow up - moderate.
Participants	All of the 349 people who developed definite native-valve endocarditis in The Netherlands over a 2-year period (1st November 1986 to 1st November 1988) were collected. Cases were eligible if they had previously had congenital heart disease, coarctation of the aorta, rheumatic or other valvular dysfunction, or mitral valve prolapse with mitral regurgitation. Proxy responders (spouses or general practitioners) were used where cases were too ill to be interviewed or had died. Controls had not been diagnosed with endocarditis but had 1 of the cardiac conditions and were outpatients at cardiology departments of 1 of 5 hospitals. Controls were matched for age (within the same 5-year age category). A random sample of potential controls was drawn, and where there were at least 4 controls per case all were contacted. Where there were fewer than 4 controls a further random sample was drawn.
Interventions	Cases and controls had to have undergone a medical or dental procedure that required prophylaxis within 180 days of the onset of symptoms of endocarditis (cases) or of their interview (controls). 6 of 24 (25%) cases and 34 of 79 (43%) controls undergoing a dental procedure with definite indication for prophylaxis had removal of calculus plus polishing of teeth, 9 of 24 (38%) cases and 15 of 79 (19%) controls had a dental extraction, 1 case and 1 control had apical surgery, 1 case and 1 control had dental extraction, 1 (4%) case and 12 (15%) controls had dental avulsion, 3 (13%) cases and 8 (10%) controls had removal of subgingival calculus, 3 (13%) cases and 8 (10%) controls had root canal therapy. Median time from dental procedure to onset of endocarditis in cases was 10 days, range 0 to 175 days (and for the 7 who received antibiotics median time to onset was 18 days, range 7 to 60). Median time from dental procedure to interview in controls was 71 days, range 0 to 179 (12 missing values ignored), and for the controls who received antibiotics a median of 83 days, range 5 to 151 (1 missing value ignored). For both groups all information about invasive procedures and use of prophylaxis was checked with medical or dental specialists and pharmacists.
Outcomes	Of 349 people with definite native-valve endocarditis, 197 had previous heart disease (10 proxy responders). Of these, 54 had undergone a medical or dental procedure with an indication for prophylaxis within the past 180 days, of whom in 6 a causal relationship was ruled out as it was unlikely that the agent isolated from the blood originated in the area of the procedure. Of the 48 people with endocarditis left, 44 had undergone dental procedure with a definite (24) or possible (20) indication for prophylaxis (none of these cases had used a proxy responder). Of 889 potential controls who were sent an introductory letter 689 were ineligible (53 had died, 29 had a prosthetic heart valve, 62 could not be located, 102 could not be contacted by phone and 418 had not undergone an invasive

Van der Meer 1992 (*Continued*)

	dental or medical procedure within the past 180 days), the remaining 200 were interviewed by phone 2 to 5 days later. 181 of these controls had undergone a dental procedure with definite (79) or possible (102) indication for prophylaxis. 7 of 24 cases and 16 of 79 controls had had appropriate prophylaxis for a dental procedure requiring definite prophylaxis within 180 days.
Notes	The published paper provides data on participants who had both medical and dental invasive procedures. The author kindly separated out those who had had invasive dental interventions.

Characteristics of excluded studies *[ordered by study ID]*

Al-Karaawi 2001	Retrospective analysis of cumulative exposure to bacteraemia following various dental procedures in children with severe congenital heart disease but no cases of endocarditis.
Anonymous 1992	Economic analysis of the cost-effectiveness of using prophylactic antibiotics using same data as Bonhomme 1992.
Archard 1966	2 case studies of high risk patients developing endocarditis after dental treatment with antibiotic prophylaxis, not RCT, CCT, cohort or case-control.
Bayliss 1983	Not all cases at risk and no controls.
Bennis 1995	No control group.
Bhat 1996	Retrospective analysis of 28 cases of endocarditis. No controls.
Biron 1997	Case report.
Bonhomme 1992	Economic analysis of the cost-effectiveness of using prophylactic antibiotics based on published data.
Caretta 1988	No control group.
Clemens 1982	Assessment of the effect of mitral valve prolapse on risk of endocarditis (rather than assessment of the effect of prophylaxis), case-control design.
Conner 1967	Participants not at high risk of endocarditis.
Gersony 1977	Cohort study but it was not stated how many patients had preceding dental treatment, only two cases with preceding dental treatment and no prophylaxis.

(*Continued*)

Herr 1976	Case report (German).
Hess 1983	All children with cardiac disease received antibiotic prophylaxis before dental extraction, no controls.
Horstkotte 1986	Retrospective study of a group of people at high risk of endocarditis who had had appropriate prophylaxis for medical and dental interventions, and a group of people at similar risk who did not have appropriate prophylaxis for such interventions. It is not possible to ascertain how many of the cases or controls had had dental interventions, and the source of the 2 groups is unclear.
Imperiale 1990	Case-control study: People with endocarditis (cases) who died were excluded, although the mortality rate in the cases was much higher (20%) than was likely in the control group, thus making the 2 groups incomparable.
Khairat 1966	CCT, but participants not at high risk of endocarditis and no relevant outcomes measured.
Lacassin 1995	Case-control study: People with endocarditis (cases) who died were excluded, although the mortality rate in the cases was much higher (20%) than was likely in the control group, thus making the 2 groups incomparable.
Lauridson 1984	Case reports.
Lecointre 1981	Cohort study of patients having dental extractions but all patients received antibiotics.
McGowan 1978	Letter on failures of prophylaxis on a case by case basis, not RCT, CCT, cohort or case-control design.
McGowan 1982	Case reports, not RCT, CCT, cohort or case-control design.
Pogrel 1975	Retrospective study of cases of endocarditis but no controls.
Rahn 1988	Serological study of bacteraemia following penicillin V administration and tooth extraction.
Rahn 1993	Not an assessment of penicillin prophylaxis (concerned with adjunctive use of antiseptic solution).
Shanson 1980	No at risk patients. Examined serum levels of amoxycillin in healthy volunteers.
Strom 1998B	Case-control study based in the USA of 273 hospital patients with endocarditis. Not all the cases (38%) or controls (6%) had a previously known risk for endocarditis.
Strom 2000	Case-control study of same patient group as Strom 1998B. Not all the cases or controls were at known risk of endocarditis.
Tozer 1966	No dental interventions, and participants not at high risk of endocarditis.
Tzukert 1984	Same group of patients as Tzukert 1986.

(*Continued*)

Tzukert 1986	High risk participants undergoing dental procedures all received a regimen that included antibiotic prophylaxis, no control group.
Van der Meer 1992a	Epidemiological study of endocarditis in The Netherlands. No controls.
Woodman 1985	Basic science research paper.
Yoshimura 1985	Cohort study of 17 patients undergoing dental extractions but all received antibiotics.

CCT: controlled clinical trial
RCT: randomised controlled trial

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. MEDLINE search strategy

1. exp Endocarditis/
2. endocardi$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
3. (ABE or SABE).ab,ti.
4. (acute-endocarditis or subacute-endocarditis or bacterial-endocarditis).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
5. or/1-4
6. dent$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
7. exp Dental Prophylaxis/
8. exp Dentistry, Operative/
9. exp Endodontics/
10. exp Oral Surgical Procedures/
11. ((oral$ or tooth or teeth) adj5 (surg$ or extract$ or restor$ or invas$ or scaling$ or polish$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
12. or/6-11
13. Antibiotic Prophylaxis/
14. (antimicrobial$ or anti-microbial$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
15. exp Anti-Bacterial Agents/
16. (antibiotics or lactam).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
17. exp Penicillins/
18. amox?cillin$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
19. (augmentin$ or ampicillin$ or "penicillin v" or "penicillin-vor pen v" or pen-v or "penicillin g" or penicillin-g or amoxil$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
20. (amoyl$ or co-amox$ or coamox$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
21. (antibacterial$ or anti-bacterial$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
22. (Acedapsone or alamethicin or amdinocillin or amikacin or amoxicillin or "amphotericin B" or ampicillin or anisomycin or "antimycin A" or arsphenamine or Aurodox or Azithromycin or Azlocillin or Aztreonam or Bacitracin or Bacteriocins or Bambermycins or beta-Lactams or "Bongkrekic Acid" or "Brefeldin A" or "Butirosin Sulfate" or Calcimycin or Candicidin or "Capreomycin Sulfate" or Carbenicillin or Carfecillin or Cefaclor or Cefadroxil or Cefamandole or Cefatrizine or Cefazolin or Cefixime or Cefmenoxime or Cefmetazole or Cefonicid or Cefoperazone or Cefotaxime or Cefotetan or Cefotiam or Cefoxitin or Cefsulodin or Ceftazidime or Ceftizoxime or Ceftriaxone or Cefuroxime or Cephacetrile or Cephalexin or Cephaloglycin or Cephaloridine or Cephalosporins or Cephalothin or Cephamycins or Cephapirin or Cephradine or Chloramphenicol or Chlortetracycline or Citrinin or Clarithromycin or "Clavulanic Acid" or "Clavulanic Acids" or Clindamycin or Clofazimine or Cloxacillin or Colistin or Cyclacillin or Cycloserine or Dactinomycin or Dapsone or Daptomycin or Demeclocycline or Dibekacin or Dicloxacillin or "Dihydrostreptomycin Sulfate" or Diketopiperazines or Distamycins or Doxycycline or Echinomycin or Edeine or Enviomycin or Erythromycin or "Erythromycin Estolate" or "Erythromycin Ethylsuccinate" or Ethambutol or Ethionamide or Filipin or Floxacillin or Fluoroquinolones or Fosfomycin or Framycetin or "Fusidic Acid" or Gentamicins or Gramicidin or "Hygromycin B" or Imipenem or Isoniazid or Josamycin or Kanamycin or Kitasamycin or Lactams or Lasalocid or Leucomycins or Lincomycin or Lucensomycin or Lymecycline or Mepartricin or Methacycline or Methicillin or Mezlocillin or Mikamycin or Minocycline or Miocamycin or Moxalactam or Mupirocin or Mycobacillin or Nafcillin or Natamycin or Nebramycin or Neomycin or Netilmicin or Netropsin or Nigericin or Nisin or Norfloxacin or Novobiocin or Nystatin or Ofloxacin or Oleandomycin or Oligomycins or Oxacillin or Oxytetracycline or "p-Aminosalicylic Acid" or Paromomycin or "Penicillanic Acid" or "Penicillic Acid" or "Penicillin G" or "Penicillin G Benzathine" or "Penicillin G Procaine" or "Penicillin V"

or Piperacillin or Pivampicillin or "Polymyxin B" or Polymyxins or Pristinamycin or Prodigiosin or Prothionamide or Pyrazinamide or Ribostamycin or Rifabutin or Rifampin or Rifamycins or Ristocetin or Rolitetracycline or Roxarsone or Roxithromycin or Rutamycin or Sirolimus or Sisomicin or Spectinomycin or Spiramycin or "Streptogramin A" or "Streptogramin Group A" or "Streptogramin Group B" or Streptogramins or Streptomycin or Streptovaricin or Sulbactam or Sulbenicillin or Sulfameter or Sulfamethoxypyridazine or Talampicillin or Teicoplanin or Tetracycline or Thalidomide or Thiamphenicol or Thienamycins or Thioacetazone or Thiostrepton or Ticarcillin or Tobramycin or Troleandomycin or Tunicamycin or Tylosin or Tyrocidine or Tyrothricin or Valinomycin or Vancomycin or "Vernamycin B" or Viomycin or Virginiamycin).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
23. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24. 5 and 12 and 23

Appendix 2. CENTRAL search strategy

#1 Exp ENDOCARDITIS
#2 endocardi*
#3 "ABE or SABE (Title, abstract or keywords)
#4 acute-endocarditis or subacute-endocarditis or bacterial-endocarditis
#5 #1 or #2 or #3 or #4
#6 dent* (Title, abstract or keywords)
#7 Exp DENTAL PROPHYLAXIS
#8 Exp DENTISTRY, OPERATIVE
#9 ExP ENDODONTICS
#10 Exp ORAL SURGICAL PROCEDURES
#11 oral* NEAR surg* (in ti)
#12 oral* NEAR surg* (in ab)
#13 oral* NEAR surg* (in ky)
#14 oral* NEAR extract* (in ti)
#15 oral* NEAR extract* (in ab)
#16 oral* NEAR extract* (in ky)
#17 oral* NEAR restor* (in ti)
#18 oral* NEAR restor* (in ab)
#19 oral* NEAR restor* (in ky)
#20 oral* NEAR invas* (in ti)
#21 oral* NEAR invas* (in ab)
#22 oral* NEAR invas* (in ky)
#23 oral* NEAR scaling (in ti)
#24 oral* NEAR scaling (in ab)
#25 oral* NEAR scaling (in ky)
#26 oral* NEAR polish* (in ti)
#27 oral* NEAR polish* (in ab)
#28 oral* NEAR polish* (in ky)
#29 tooth NEAR surg* (in ti)
#30 tooth NEAR surg* (in ab)
#31 tooth NEAR surg* (in ky)
#32 tooth NEAR extract* (in ti)
#33 tooth NEAR extract* (in ab)
#34 tooth NEAR extract* (in ky)
#35 tooth NEAR restor* (in ti)
#36 tooth NEAR restor* (in ab)
#37 tooth NEAR restor* (in ky)
#38 tooth NEAR invas* (in ti)
#39 tooth NEAR invas* (in ab)

#40 tooth NEAR invas* (in ky)
#41 tooth NEAR scaling (in ti)
#42 tooth NEAR scaling (in ab)
#43 tooth NEAR scaling (in ky)
#44 tooth NEAR polish* (in ti)
#45 tooth NEAR polish* (in ab)
#46 tooth NEAR polish* (in ky)
#47 teeth NEAR surg* (in ti)
#48 teeth NEAR surg* (in ab)
#49 teeth NEAR surg* (in ky)
#50 teeth NEAR extract* (in ti)
#51 teeth NEAR extract* (in ab)
#52 teeth NEAR extract* (in ky)
#53 teeth NEAR restor* (in ti)
#54 teeth NEAR restor* (in ab)
#55 teeth NEAR restor* (in ky)
#56 teeth NEAR invas* (in ti)
#57 teeth NEAR invas* (in ab)
#58 teeth NEAR invas* (in ky)
#59 teeth NEAR scaling (in ti)
#60 teeth NEAR scaling (in ab)
#61 teeth NEAR scaling (in ky)
#62 teeth NEAR polish* (in ti)
#63 teeth NEAR polish* (in ab)
#64 teeth NEAR polish* (in ky)
#65 #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64
#66 ANTIBIOTIC PROPHYLAXIS/
#67 antimicrobial* or anti-microbial*
#68 Exp ANTI-BACTERIAL AGENTS/
#69 Exp PENICILLINS
#70 antibiotic* AND lactam (ti, ab, ky)
#71 antibiotic* or anti-biot* (ti, ab, ky)
#72amox?cillin* (ti, ab, ky)
#73 augmentin* or "pen v" or "pen g" or amoxil*
#74 amoyl* or coamox* or coamox* (ti, ab, ky)
#75 antibacterial* or anti-bacterial*
#76 Acedapsone or alamethicin or amdinocillin or amikacin or amoxicillin or "amphotericin B" or ampicillin or anisomycin or "antimycin A" or arsphenamine or Aurodox or Azithromycin or Azlocillin or Aztreonam or Bacitracin or Bacteriocins or Bambermycins or beta-Lactams or "Bongkrekic Acid" or "Brefeldin A" or "Butirosin Sulfate" or Calcimycin or Candicidin or "Capreomycin Sulfate" or Carbenicillin or Carfecillin or Cefaclor or Cefadroxil or Cefamandole or Cefatrizine or Cefazolin or Cefixime or Cefmenoxime or Cefmetazole or Cefonicid or Cefoperazone or Cefotaxime or Cefotetan or Cefotiam or Cefoxitin or Cefsulodin or Ceftazidime or Ceftizoxime or Ceftriaxone or Cefuroxime or Cephacetrile or Cephalexin or Cephaloglycin or Cephaloridine or Cephalosporins or Cephalothin or Cephamycins or Cephapirin or Cephradine or Chloramphenicol or Chlortetracycline or Citrinin or Clarithromycin or "Clavulanic Acid" or "Clavulanic Acids" or Clindamycin or Clofazimine or Cloxacillin or Colistin or Cyclacillin or Cycloserine or Dactinomycin or Dapsone or Daptomycin or Demeclocycline or Dibekacin or Dicloxacillin or "Dihydrostreptomycin Sulfate" or Diketopiperazines or Distamycins or Doxycycline or Echinomycin or Edeine or Enviomycin or Erythromycin or "Erythromycin Estolate" or "Erythromycin Ethylsuccinate" or Ethambutol or Ethionamide or Filipin or Floxacillin or Fluoroquinolones or Fosfomycin or Framycetin or "Fusidic Acid" or Gentamicins or Gramicidin or "Hygromycin B" or Imipenem or Isoniazid or Josamycin or Kanamycin or Kitasamycin or Lactams or Lasalocid or Leucomycins or Lincomycin or Lucensomycin or Lymecycline or Mepartricin or Methacycline or Methicillin or Mezlocillin or Mikamycin or Minocycline or Miocamycin or Moxalactam or Mupirocin or Mycobacillin

or Nafcillin or Natamycin or Nebramycin or Neomycin or Netilmicin or Netropsin or Nigericin or Nisin or Norfloxacin or Novobiocin or Nystatin or Ofloxacin or Oleandomycin or Oligomycins or Oxacillin or Oxytetracycline or "p-Aminosalicylic Acid" or Paromomycin or "Penicillanic Acid" or "Penicillic Acid" or "Penicillin G" or "Penicillin G Benzathine" or "Penicillin G Procaine" or "Penicillin V" or Piperacillin or Pivampicillin or "Polymyxin B" or Polymyxins or Pristinamycin or Prodigiosin or Prothionamide or Pyrazinamide or Ribostamycin or Rifabutin or Rifampin or Rifamycins or Ristocetin or Rolitetracycline or Roxarsone or Roxithromycin or Rutamycin or Sirolimus or Sisomicin or Spectinomycin or Spiramycin or "Streptogramin A" or "Streptogramin Group A" or "Streptogramin Group B" or Streptogramins or Streptomycin or Streptovaricin or Sulbactam or Sulbenicillin or Sulfameter or Sulfamethoxypyridazine or Talampicillin or Teicoplanin or Tetracycline or Thalidomide or Thiamphenicol or Thienamycins or Thioacetazone or Thiostrepton or Ticarcillin or Tobramycin or Troleandomycin or Tunicamycin or Tylosin or Tyrocidine or Tyrothricin or Valinomycin or Vancomycin or "Vernamycin B" or Viomycin or Virginiamycin
#77 #66 or #67 or #68 or #69 or #70 or #71 or #72 or #73 or#74 or #75 or #76
#78 #5 AND #65 AND #77

Appendix 3. EMBASE search strategy

1. exp Endocarditis/
2. endocardi$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
3. (ABE or SABE).ab,ti.
4. (acute-endocarditis or subacute-endocarditis or bacterial-endocarditis).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
5. or/1-4
6. dent$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
7. ("Dental Prophylaxis" or "oral prophylaxis").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
8. Dental Surgery/
9. Endodontics/
10. Oral Surgery/
11. ((oral$ or tooth or teeth) adj5 (surg$ or extract$ or restor$ or invas$ or scaling$ or polish$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
12. or/6-11
13. Antibiotic Prophylaxis/
14. (antimicrobial$ or anti-microbial$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
15. exp Antibiotic Agent/
16. (antibiotics or lactam).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
17. exp Penicillins/
18. amox?cillin$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
19. (augmentin$ or ampicillin$ or "penicillin v" or "penicillin-vor pen v" or pen-v or "penicillin g" or penicillin-g or amoxil$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
20. (amoyl$ or co-amox$ or coamox$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
21. (antibacterial$ or anti-bacterial$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
22. (Acedapsone or alamethicin or amdinocillin or amikacin or amoxicillin or "amphotericin B" or ampicillin or anisomycin or "antimycin A" or arsphenamine or Aurodox or Azithromycin or Azlocillin or Aztreonam or Bacitracin or Bacteriocins or Bambermycins or beta-Lactams or "Bongkrekic Acid" or "Brefeldin A" or "Butirosin Sulfate" or Calcimycin or Candicidin or "Capreomycin Sulfate" or Carbenicillin or Carfecillin or Cefaclor or Cefadroxil or Cefamandole or Cefatrizine or Cefazolin or Cefixime or Cefmenoxime or Cefmetazole or Cefonicid or Cefoperazone or Cefotaxime or Cefotetan or Cefotiam or Cefoxitin or Cefsulodin or Ceftazidime or

Ceftizoxime or Ceftriaxone or Cefuroxime or Cephacetrile or Cephalexin or Cephaloglycin or Cephaloridine or Cephalosporins or Cephalothin or Cephamycins or Cephapirin or Cephradine or Chloramphenicol or Chlortetracycline or Citrinin or Clarithromycin or "Clavulanic Acid" or "Clavulanic Acids" or Clindamycin or Clofazimine or Cloxacillin or Colistin or Cyclacillin or Cycloserine or Dactinomycin or Dapsone or Daptomycin or Demeclocycline or Dibekacin or Dicloxacillin or "Dihydrostreptomycin Sulfate" or Diketopiperazines or Distamycins or Doxycycline or Echinomycin or Edeine or Enviomycin or Erythromycin or "Erythromycin Estolate" or "Erythromycin Ethylsuccinate" or Ethambutol or Ethionamide or Filipin or Floxacillin or Fluoroquinolones or Fosfomycin or Framycetin or "Fusidic Acid" or Gentamicins or Gramicidin or "Hygromycin B" or Imipenem or Isoniazid or Josamycin or Kanamycin or Kitasamycin or Lactams or Lasalocid or Leucomycins or Lincomycin or Lucensomycin or Lymecycline or Mepartricin or Methacycline or Methicillin or Mezlocillin or Mikamycin or Minocycline or Miocamycin or Moxalactam or Mupirocin or Mycobacillin or Nafcillin or Natamycin or Nebramycin or Neomycin or Netilmicin or Netropsin or Nigericin or Nisin or Norfloxacin or Novobiocin or Nystatin or Ofloxacin or Oleandomycin or Oligomycins or Oxacillin or Oxytetracycline or "p-Aminosalicylic Acid" or Paromomycin or "Penicillanic Acid" or "Penicillic Acid" or "Penicillin G" or "Penicillin G Benzathine" or "Penicillin G Procaine" or "Penicillin V" or Piperacillin or Pivampicillin or "Polymyxin B" or Polymyxins or Pristinamycin or Prodigiosin or Prothionamide or Pyrazinamide or Ribostamycin or Rifabutin or Rifampin or Rifamycins or Ristocetin or Rolitetracycline or Roxarsone or Roxithromycin or Rutamycin or Sirolimus or Sisomicin or Spectinomycin or Spiramycin or "Streptogramin A" or "Streptogramin Group A" or "Streptogramin Group B" or Streptogramins or Streptomycin or Streptovaricin or Sulbactam or Sulbenicillin or Sulfameter or Sulfamethoxypyridazine or Talampicillin or Teicoplanin or Tetracycline or Thalidomide or Thiamphenicol or Thienamycins or Thioacetazone or Thiostrepton or Ticarcillin or Tobramycin or Troleandomycin or Tunicamycin or Tylosin or Tyrocidine or Tyrothricin or Valinomycin or Vancomycin or "Vernamycin B" or Viomycin or Virginiamycin or adicillin or "6 aminopenicillanic Acid" or amenopenicillin or apalcillin or aspoxicillin or azidocillin or bacampicillin or bacmeccillinam or carimdacillin or epicillin or flucloxacillin or flumoxil or fomidacillin or furbenicillin or fuzlocillin or hetacillin or isopenicillin or lenampicillin or mecillinan or metampicillin or meticillin or mezlocillin or miraxid or optocillin or penamecillin or "penicillin K" or "penicilloic Acid" or pheneticillin or "procaine penicillin" or quinacillin or retacillin or tameticillin or temocillin or triplopen or ureidopenicillin).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
23. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24. 5 and 12 and 23

WHAT'S NEW

Last assessed as up-to-date: 23 July 2008.

24 July 2008	New search has been performed	Search updated to June 2008.
24 July 2008	New citation required but conclusions have not changed	Review updated and scope expanded to include all antibiotics and not just penicillins. Change in authors.
24 June 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 3, 2002

Review first published: Issue 2, 2004

CONTRIBUTIONS OF AUTHORS

Richard Oliver: Initiated the review, involved with the design and writing of the protocol, searching, duplication of assessment of titles and abstracts, inclusion/exclusion of full text papers, data extraction and quality assessment of included studies, data analysis and interpretation.

Lee Hooper: Lee was involved in the design of the first published version of the review, writing of the protocol, searching, duplication of assessment of titles and abstracts, inclusion/exclusion of full text papers, data extraction and quality assessment of included studies, data analysis and interpretation.

Graham Roberts: Provided background information for the protocol and review.

Helen Worthington: Provided methodological and statistical support.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Central Manchester and Manchester Children's University Hospitals NHS Trust, UK.
- The University of Manchester, UK.
- Eastman Dental Institute, UK.

External sources

- Department of Health Cochrane Review Incentive Scheme 2007, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

*Antibiotic Prophylaxis; Dental Care [*adverse effects]; Dentistry; Endocarditis, Bacterial [etiology; *prevention & control]; Penicillins [*therapeutic use]

MeSH check words

Humans