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Antibiotic prophylaxis for infective endocarditis: a systematic review and meta-analysis

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Abstract:	Objective The use of antibiotic prophylaxis for prevention of infective endocarditis is controversial. In recent years, guidelines to cardiologists and dentists have advised restriction of antibiotic prophylaxis (AP) to high risk groups (in Europe and the USA), or against its use at all (in the UK). The objective of this systematic review was to appraise the evidence for use of AP for prevention of bacteraemia or infective endocarditis in patients undergoing dental procedures. Methods We conducted electronic searches in Medline, Embase, Cochrane Library and ISI Web of Science. We assessed the methodological characteristics of included studies using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria for observational studies, and the Cochrane Risk of Bias Tool for trials. Two reviewers independently determined the eligibility of studies, assessed the methodology of included studies and extracted the data.

Results
We identified 178 eligible studies, of which 36 were included in the review. This included 10 time-trend studies, 5 observational studies and 21 trials. All trials identified used bacteraemia as an endpoint, rather than infective endocarditis. One time-trend study suggests that total AP restriction may be associated with a rising incidence of infective endocarditis, while data on the consequences of relative AP restriction are conflicting. Meta-analysis of trials indicates that AP is effective in reducing the incidence of bacteraemia (risk ratio 0.53, 95% CI 0.49-0.57, $p < 0.01$), but case control studies suggest this may not translate to a statistically significant protective effect against infective endocarditis in patients at low risk of disease.

Conclusions
The evidence base for the use of antibiotic prophylaxis is limited, heterogeneous and the methodological quality of many studies is poor. Post-procedural bacteraemia is not a good surrogate endpoint for infective endocarditis. Given the logistical challenges of a randomised trial, high quality case control studies would help to evaluate the role of dental procedures in causing infective endocarditis, and the efficacy of antibiotic prophylaxis in its prevention.

Title

Antibiotic prophylaxis for infective endocarditis in patients undergoing dental procedures: a systematic review and meta-analysis

Authors

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Abstract

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Methods

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Key words
Endocarditis
Antibiotic prophylaxis
Systematic review

Abbreviations
ACC/AHA - American College of Cardiology/American Heart Association
AP – antibiotic prophylaxis
ESC – European Society for Cardiology
IE – infective endocarditis
NICE – National Institute for Health and Care Excellence (UK)
NVE – native valve infective endocarditis
PVE – prosthetic valve infective endocarditis
RCT – randomized controlled trial
UK – United Kingdom
USA – United States of America
VGS – viridans group streptococci

Introduction

Infective endocarditis is a rare but life-threatening disease.[1] Despite trends towards multidisciplinary 'heart team' care and early surgery, 1-year mortality approaches 30%.[2] In patients with prosthetic heart valves, rheumatic and congenital heart disease, the risk of acquiring infective endocarditis is thought to be 10-50 fold higher than that of the general population.[3] Effective strategies for prevention of both community and healthcare-acquired infective endocarditis in at-risk groups are required.[4]

The oral cavity was identified as a major portal of entry for bacteria in 1909 by Thomas Horder.[5] Oral streptococci are commensal flora of the oropharynx and account for 10-30% of cases of infective endocarditis, depending on the location, risk factor profile and socio-demographic characteristics of the population studied.[6, 7] Transient bacteraemia, which occurs in the setting of poor oral hygiene and periodontal diseases, dental procedures, or in the course of normal daily activities (e.g. tooth brushing), is thought to be a precursor to the development of some cases of infective endocarditis.[8]

For over 50 years, oral antibiotic prophylaxis (AP) was given to patients at risk of infective endocarditis undergoing dental procedures. Between 2007 and 2009, however, the European Society for Cardiology (ESC), American Heart Association/American College of Cardiology (AHA/ACC) and the National Institute for Health and Care Excellence (NICE) recommended restriction of AP to varying degrees.[9, 10, 11] In Europe and the USA there was relative AP restriction to those at highest risk (e.g. patients with previous infective endocarditis, congenital heart disease and rheumatic heart disease, and selected heart transplant recipients) undergoing high-risk dental procedures. In the UK, NICE advised against use of prophylaxis entirely (total AP restriction) in 2008 but softened this stance in July 2016 to state that antibiotics should not *routinely* be recommended as prophylaxis for dental procedures.[12]

The rationale for relative or total AP restriction was threefold. First, as medicine shifted towards evidence-based practice there was (and remains) no randomised controlled trial assessing the efficacy of AP for prevention of infective endocarditis. Second, the relative importance of dental procedures as a cause of infective endocarditis remained in doubt, compared with other portals of entry or low grade

recurrent bacteraemia occurring in the course of daily life.[8, 13] Third, in moderate risk (and high risk in England) groups, the overall hazards of antibiotic use (particularly anaphylaxis and the development of antibiotic resistance) were felt to weigh against use of AP. The NICE guideline committee also deemed that AP was not cost effective as a result of lack of efficacy and the perceived risks of anaphylaxis.

The primary object of this study was to provide a systematic review and synthesis of evidence that directly or indirectly informs clinical use of AP for at-risk patients undergoing dental procedures. The evidence base comprises three types of study: first, trials examining the effect of AP on the incidence of bacteraemia following dental procedures; second, observational studies assessing the efficacy of AP for prevention of infective endocarditis; and finally, time trend studies which examine the effect of changing national or international AP guidelines on the population incidence of infective endocarditis.

Methods

Eligibility and search strategy:

We searched the following databases from inception until 25 February 2016 to identify studies of the efficacy of AP for the prevention of bacteraemia or infective endocarditis in patients undergoing dental procedures: Medline & Medline In-Process (OvidSP) [1946-present], Embase (OvidSP) [1974 to 2016 February 08], Cochrane Central Register of Controlled Trials (Cochrane Library, Wiley) [Issue 1 of 12, January 2016], Cochrane Database of Systematic Reviews (Cochrane Library, Wiley) [Issue 2 of 12, February 2016], Database of Abstracts of Reviews of Effects (Cochrane Library, Wiley) [Issue 2 of 4, April 2015], Science Citation Index Expanded & Conference Proceedings Citation Index- Science (Web of Science Core Collection) [1945-present], Clinicaltrials.gov (http://clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/Default.aspx). Search terms used included subject headings and title/abstract keywords for bacterial endocarditis, antibiotics and prophylaxis (see search strategy in Appendix 1). We also searched the reference lists of all included articles. The following categories of study were excluded: studies conducted prior to 1960, studies of AP in patients undergoing cardiac surgery or implantation of cardiac electronic devices, topical therapies, and comparative antibiotic trials with no placebo/control arm.

Data abstraction:

We assessed methodological quality of studies using the Cochrane Risk of Bias tool[14] (for trials) or a checklist adapted from the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria (for observational studies).[15] Two reviewers (TJC and JLH) independently adjudicated the eligibility of studies, assessed the methodology of included studies, and performed data extraction. Disagreement was resolved through consensus.

We extracted data on the study design: for case control studies we extracted baseline characteristics on the cases and the controls; for time trend studies we extracted study population characteristics, the study time period, relevant guideline changes and effects on incidence of IE per 100,000 population. The primary outcome of interest was the incidence of infective endocarditis, incidence of (any) bacteraemia, or for time trend studies, population-adjusted incidence of infective endocarditis. Where total incidence of bacteraemia was not reported, the time point at which the

highest incidence of bacteraemia was observed in the placebo group was used for comparison.

Data analysis:

We derived summary tables to report methodological quality and main results of the included studies according to study design. For pooled effects we used a fixed-effects model to generate Forest plots and used odds ratios as the summary measure. We assessed heterogeneity using I-square values, with 25%, 50% and 75% representing mild, moderate and substantial heterogeneity, respectively.[16] Forest plots and data summary graphs were compiled using RevMan (Cochrane, UK) and SPSS (SPSS Inc., Chicago, IL, USA), respectively.

Results

The electronic search identified 3830 articles, after removal of case reports, editorials, animal studies and duplicates (Figure 1). After screening of the title and/or abstract of these, 178 articles were deemed eligible for full text assessment. In total, 36 studies were deemed suitable for inclusion (see Supplementary Table 1 for excluded studies), comprising 10 time-trend studies, 5 observational studies (4 case-control studies and 1 retrospective cohort study) and 21 trials. All identified trials used bacteraemia as a surrogate endpoint for infective endocarditis. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart for study inclusion is shown in Figure 1.

Time trend population studies

We identified 10 studies assessing the effect of changing national and international guidelines concerning the use of AP on the population incidence of infective endocarditis. These included 9 studies of relative AP restriction (from the USA and Europe) and 1 study examining the effect of total AP restriction (from the UK) (Table 1). Changes in the guidelines between 2007 and 2009 by the ESC, ACC/AHA and NICE greatly reduced the use of antibiotic prophylaxis. Annual incidence was reported in two studies[17, 18] and obtained from the authors for two studies.[19, 20] Figure 2 shows the incidence of infective endocarditis per 100,000 population before and after changes in ACC/AHA and NICE guidelines. While only 1 study identified a significant rise in the incidence trend of infective endocarditis, it is important to note that this change was observed in the only population with total AP restriction.

Observational studies

We identified 5 observational studies for inclusion, including 4 case-control studies and 1 retrospective cohort study (Table 2). Data extracted included characteristics of cases and controls (or the two cohorts which were compared[21]), exposures and interventions (i.e. invasive procedures, use of AP), and, where possible, the numbers of patients specifically undergoing dental procedures (Table 2). All studies were assessed to be at high risk of intrinsic methodological bias (Supplementary Table 3). Meta-analysis was conducted on 3 studies with available data concerning the numbers of cardiac patients exposed to dental procedures, use of AP, and infective

endocarditis outcome. Overall, the odds ratio for use of AP in patients with infective endocarditis was 0.59 (95% confidence interval 0.27-1.30, p = 0.14, I^2=48%), suggesting no statistically significant difference in exposure to AP between cases (patients with infective endocarditis) and controls. In Van Der Meer *et al*, cases and controls were analysed up to 30 days post-procedure and subgroups combined (first time and recurrent infective endocarditis; definite and possible indications for AP). If patients without a definite AP indication were excluded, this study provided an overall OR of 0.63 (95% CI 0.17-2.36) for AP, modifying the overall meta-analysis to an OR of 0.47 (95% CI 0.21-1.06, p = 0.07).

Bacteraemia trials

We included 21 studies investigating the effect of AP on the incidence of bacteraemia (as a surrogate for infective endocarditis) following a dental procedure. All studies reported the incidence of bacteraemia in a placebo group compared to an AP intervention group after a dental procedure. Some studies tested multiple antibiotic regimens (detailed in Supplementary Table 3), and some compared additional endpoints such as the duration or magnitude of bacteraemia, a breakdown of specific organisms grown, or antibiotic sensitivity patterns. A forest plot summarising a total of 35 antibiotic arms against control or placebo is shown in Figure 4. AP was associated with a risk ratio of 0.53 (95% CI 0.49-0.57, p < 0.01, I^2 = 90%) for bacteraemia in patients following dental procedures.

Table 1 – Time trend studies examining effect of antibiotic prophylaxis guideline change on the incidence of infective endocarditis

First author, year	PMID	Paper/abstract	Region, Country	Population	Diagnosis	Study time period	Guideline change Level of AP restriction	Increased incidence post-guideline change	Increase in rate of change of incidence post guideline	Guideline time point identified by change point analysis?
Bates 2016[22]	27418041	Paper	USA	Children ≤ 18 yrs identified from Pediatric Health Information System Database (29 hospitals)	All cases – acute and subacute bacterial IE	2003 - 2014	AHA/ACC April 2007 Relative restriction	No	No	NA
Bikdeli 2013[23]	23994421	Paper	USA	Adults ≥ 65 yrs	All cases - principal or secondary discharge dx of IE	1999-2010	AHA/ACC April 2007 Relative restriction	No	NA	NA
Dayer 2015[19] & Thornhill 2011[24]*	25467569	Paper	England, UK	All	All cases - primary dx acute or subacute IE	January 1 2000 - March 31 2013	NICE March 2008 Total restriction	Yes	Yes	Yes
DeSimone 2015[20] & De Simone 2012[25]*	26141329	Paper	Olmsted County, Minnesota, USA	Adults ≥ 18 yrs	VGS IE	January 1 1999 to December 31 2013	AHA/ACC April 2007 Relative restriction	No	NA	NA
Duval 2012[26]	22624837	Paper	3 regions of France (Greater Paris, Lorraine, and Rhône-Alpes)	Adults ≥ 20 yrs	All cases of IE and subgroups by causative organism	3 survey years - 1991, 1999, 2008	French guideline restrictions 2002 Relative restriction	No	NA	NA

Keller 2016[27]	27816113	Paper	Germany	All patients hospitalizaed with acute or subacute IE	IE due to Streptococcus and Staphylococcus (reported separately)	2005 - 2014	ESC October 2009 Relative restriction	Yes	Yes	No
Mackie 2016[28]	26868840	Paper	Canada (except Quebec and the Northern Territories)	All patients hospitalized with acute or subacute IE as main diagnosis	All hospitalizations with primary dx of IE	April 2002 - March 2013	AHA/ACC April 2007 Relative restriction	Total IE increase, decrease in VGS	Yes	No
Pant 2015[17]	25975469	Paper	USA	Patients in Nationwide Inpatient Sample with ICD codes for IE	All cases of IE and subgroups by causative organism	2000 - 2011	AHA/ACC April 2007 Relative restriction	Yes	Yes	Not performed
Salam 2014[29]	NA	Abstract	Qatar	All patients hospitalized with IE in State of Qatar	All cases	2002 - 2012	AHA/ACC April 2007 Relative restriction	No	NA	NA
van den Brink 2016[18]	Pending	Paper	Netherlands	All patients identified from the national healthcare insurance database	All cases of IE	2005 - 2011	ESC October 2009 Relative restriction	Yes, significant increase in VGS	Yes	NA

* Earlier publications from same research group using same methodology. Study with longer follow-up used for analysis

Table 2 – Observational studies of antibiotic prophylaxis and infective endocarditis

Study	Study design	Cases	Controls	Exposures and/or outcomes analysed	Outcomes for patients undergoing dental interventions	Included in meta-analysis?
Horstkotte 1987[21]	Retrospective cohort study	Group 1: 229 patients with prosthetic heart valves, in whom 287 diagnostic/therapeutic procedures were performed using a prophylactic antibiotic regime	Group 2: 304 patients with prosthetic heart valves, who had undergone "one of the procedures we regard as requiring endocarditis prophylaxis, without having received any antibiotic regime"	Incidence of PVE	Subgroup analysis of patients undergoing dental procedures: 2 cases of PVE from 117 patients undergoing dental procedures without AP. 0 cases (total number of patients undergoing dental procedures is not reported) in those with AP	No – as no denominator provided for total number of dental procedures in the group which received AP
Imperiale 1990[30]	Case control	Patients with a first episode of NVE within 12 weeks of a dental procedure	Patients matched for age, high-risk lesion on echo and frequency of dental visit	Use of antibiotics pre and after procedure	AP used in 1/8 cases, 15/24 controls	Yes
Lacassin 1995[31]	Case control	Adults with definite, probable or possible IE. PVE < 1 year from implantation excluded	Subjects without IE recruited from wards/echocardiography during same period as cases. Matched 1:1 for sex, age, group of underlying cardiac condition	All invasive procedures (not limited to dental) in 3 month period prior to IE, and use of AP	Subgroup analysis of patients undergoing dental procedures with cardiac disease: AP used in 6/26 cases, 6/22 controls	Yes – only patients undergoing dental procedures
Strom 1998[32]	Case control	Persons with community-acquired IE not associated with IV drug use (39 prosthetic valve) 104/273 cases had cardiac disease	Community residents, matched by age, sex, and neighbourhood of residence – i.e. not matched by cardiac risk factors 17/283 had cardiac disease	Survey on risk factors including recent dental treatment, use of AP	Only the patients with cardiac risk factors are relevant Study does not state what proportion of this subgroup received AP	No – details not provided for number of controls with cardiac disease given antibiotic prophylaxis – without this cannot be compared to the cases
Van der Meer 1992[33]	Case control	Patients with NVE and cardiac risk factors and <180 days post procedure (medical or dental) requiring prophylaxis	Cardiac outpatients matched for age and procedures	Survey of recent dental procedures and use of AP Caveat is that not all interventions have 'definite' indication for AP	30-day rate of IE analysed for cases Equivalent time period used for controls follow-up (Table 3) AP used in 5/25 cases, 8/42 controls	Yes, although not possible to separate out the number of patients who underwent dental procedures (cf. other medical procedures) although these account for <10% of both cases and controls

Abbreviations: AP – antibiotic prophylaxis, IE – infective endocarditis, NVE – native valve endocarditis, PVE – prosthetic valve endocarditis

Discussion

In this study we have systematically reviewed the evidence base for the use of AP for prevention of infective endocarditis. This comprises a) population time trend analyses of the effect of changing national and international guidelines on the incidence of infective endocarditis b) focused observational studies, including 4 case control studies and a retrospective cohort, and c) trials of antibiotics after dental procedures, using bacteraemia as a surrogate endpoint for the development of infective endocarditis. No randomised controlled trial (RCT) of AP has been undertaken.

This is the first study to systematically appraise the total evidence base for AP across a range of study designs. We have conducted a comprehensive search and extensively reviewed studies that either directly or indirectly address the question of AP efficacy. All studies have been quality assessed, with risk of bias assessed in a systematic manner. However, our study has some limitations. Our conclusions are limited by the poor methodological quality of included studies (and their heterogeneity) and the lack of randomized trials. Furthermore, we have excluded studies prior to 1960 (in order to maintain relevance to current antimicrobial practice) and have not reviewed the data on use of AP to prevent infective endocarditis in animal models, where some evidence suggests that single dose amoxicillin prophylaxis is effective in preventing streptococcal infective endocarditis.

In total, we identified 10 studies assessing the effect of national and international guideline change on the incidence of infective endocarditis. In all countries where AP is still recommended, there has been no significant change in the overall rate of increase of IE, although in several it is claimed that there has been an increase in the number of streptococcal cases. However, IE rates have increased overall in the only study of total AP cessation from the UK.[19] Although this study was unable to ascertain whether this increase was driven by a rising incidence of streptococcal infective endocarditis, a further study is underway to identify the microbiological aetiology of these additional cases. These studies are intrinsically at high risk of methodological bias (as determined by the STROBE criteria) due to their observational study design and cannot fully account for confounding variables. Studies relying solely on discharge coding may not adequately account for re-admissions or re-coding of historical diagnoses. Pant *et al* included secondary diagnoses of infective endocarditis in their analysis, leading to higher estimates than other studies.[17] Several smaller population studies with validated diagnoses have

provided lower estimates for the incidence of infective endocarditis of fewer than 5 cases per 100,000 per year.[7, 34, 35] Finally, even the larger time trend studies may remain underpowered to detect a significant change in infective endocarditis incidence given the limited duration of follow-up. In particular, detection of any small change in incidence in studies of relative AP restriction requires a large population or prolonged duration of follow-up.

We identified 5 observational studies assessing the efficacy of AP. These were retrospective, of poor methodological quality, varying design (4 case control, 1 retrospective cohort) and small sample size. Accordingly, they are at high risk of methodological bias and conclusions should be drawn with caution. With this major caveat, our meta-analysis of 3 observational studies did not show a statistically significant difference in exposure to AP in cases (patients with infective endocarditis after dental procedures) compared to controls. There was a trend towards a protective effect of AP, however, and the lack of statistical significance may reflect the small sample sizes in the primary studies. Furthermore, most of the patients in these studies did not have replacement valves or other high-risk pathology so would not have been considered for AP even according to US or European guidelines. Two studies (Duval; Horstkotte) not included in our meta-analysis examined the protective effect of AP in patients with replacement valves. Both suggested a protective effect from AP. In the study by Horskotte *et al*, 229 patients with replacement heart valves were followed after 287 diagnostic interventions (including some dental) requiring AP.[21] A group of 304 patients who had undergone invasive procedures without AP was used for comparison. Six cases of infective endocarditis occurred in the group with no AP, compared to 0 in the AP group. In a population study by Duval *et al*, approximately 14 times more IE occurred after unprotected than protected dental procedures in people with replacement valves.[36] The study by Horstkotte *et al* was excluded because the number of dental procedures was not stated and the study by Duval *et al* was excluded due to use of extrapolated rather than absolute numbers.

We identified 21 trials assessing the efficacy of AP in reducing the incidence of bacteraemia after dental procedures. Overall, AP is effective at reducing the incidence of bacteraemia. Other surrogate measures addressed in some studies include the nature of isolated bacteria, the duration of bacteraemia, and its magnitude. However, the relationship between bacteraemia and infective endocarditis is not straightforward. In particular, the relative importance of bacteraemia following dental extraction remains debated, and low level bacteraemia

occurs commonly in association with daily activities such as tooth brushing, especially in the setting of periodontal disease.[37] As such, its validity as a surrogate endpoint for infective endocarditis is uncertain.

An RCT of AP has been debated for several decades but is unlikely to be performed for several reasons. Using infective endocarditis as the primary outcome, such a trial would require several hundred thousand participants with a prolonged duration of recruitment and follow-up. In addition, there may be a lack of equipoise in an RCT, given that the standard of care for high-risk individuals (based on ESC and ACC/AHA guidelines) is to give AP. The size, scale and cost of a government-sponsored trial has been deemed unacceptable to national funding bodies in both the UK and USA.[38]

There is general acceptance that the majority of cases of infective endocarditis caused by oral bacterial species are likely to result from frequent bacteraemia arising from routine daily activities, but this does not exclude the possibility that some cases result from infrequent invasive dental procedures.[13] The focus of clinical research on IE prevention has therefore shifted in recent years from surrogate bacteraemia studies to those examining the role played by inflammation and ulceration of gingival tissues. A large multicentre case control study assessing the associations between poor oral hygiene, dental disease and infective endocarditis is currently underway and may provide the necessary data to permanently shift the focus away from AP as the best strategy to prevent IE.

As the debate continues, infective endocarditis is changing. Oral streptococci – the target of AP – account for a falling proportion of cases in developed world series.[7] In the absence of high quality evidence and with significant barriers to an RCT, uncertainty is likely to prevail. For cardiologists and dental practitioners faced with high-risk individuals, AP remains a low risk, inexpensive approach that may have benefit.[39, 40] We have previously described a framework for discussion of the risk:benefit balance for high-risk patient groups based on current ESC guidelines.[41] Despite the low quality and limited evidence base, these guidelines (and their counterpart from the ACC/AHA) advising AP for patients at highest risk provide a pragmatic and justified approach.

Figure Legends

Figure 1. PRISMA flow chart

Figure 2. Annual incidence of infective endocarditis reported in time-trend analyses. The data for annual incidence or prevalence was reported in three studies[17, 18, 27] and obtained from the authors for two studies.[19, 20] The incidence of viridans streptococcal infective endocarditis in DeSimone *et al* was 0 in 2009 and 2011. The incidence values for Pant *et al* [17] are higher than other studies due to the inclusion of infective endocarditis as both a primary and secondary diagnosis (included solely as a primary diagnosis in the other studies).

Figure 3. Meta-analysis of case-control studies testing the association between antibiotic prophylaxis (AP) and infective endocarditis after dental procedures. In these studies, cases are patients with infective endocarditis and controls are matched patients at risk (Table 2). The number of 'events' is the use of AP in each group as a proportion of the total number of procedures. Overall, the odds ratio of AP comparing patients with infective endocarditis to those without is 0.59 (95% confidence interval 0.27-1.30, p = 0.14), suggesting no statistically significant difference in AP exposure between cases and controls. Abbreviations: AP antibiotic prophylaxis; IE infective endocarditis.

Figure 4. Meta-analysis of trials of antibiotic prophylaxis for prevention of bacteraemia after dental procedures. Where an individual study tested multiple antibiotic regimes, these are represented as (a), (b) etc. and compared against the control/placebo arm. Details of the dental procedure and antibiotic regimen are shown in Supplementary Table 5. Overall, use of AP was associated with a risk ratio for bacteraemia of 0.53 (95% CI 0.49-0.57, $p < 0.01$, $I^2 = 90\%$). Abbreviations: AP antibiotic prophylaxis

Competing interests

M.J.D. was a non-voting member of the NICE panel that reviewed guidance concerning the use of antibiotic prophylaxis to prevent infective endocarditis in 2015.

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Figure 1 – PRISMA flow chart

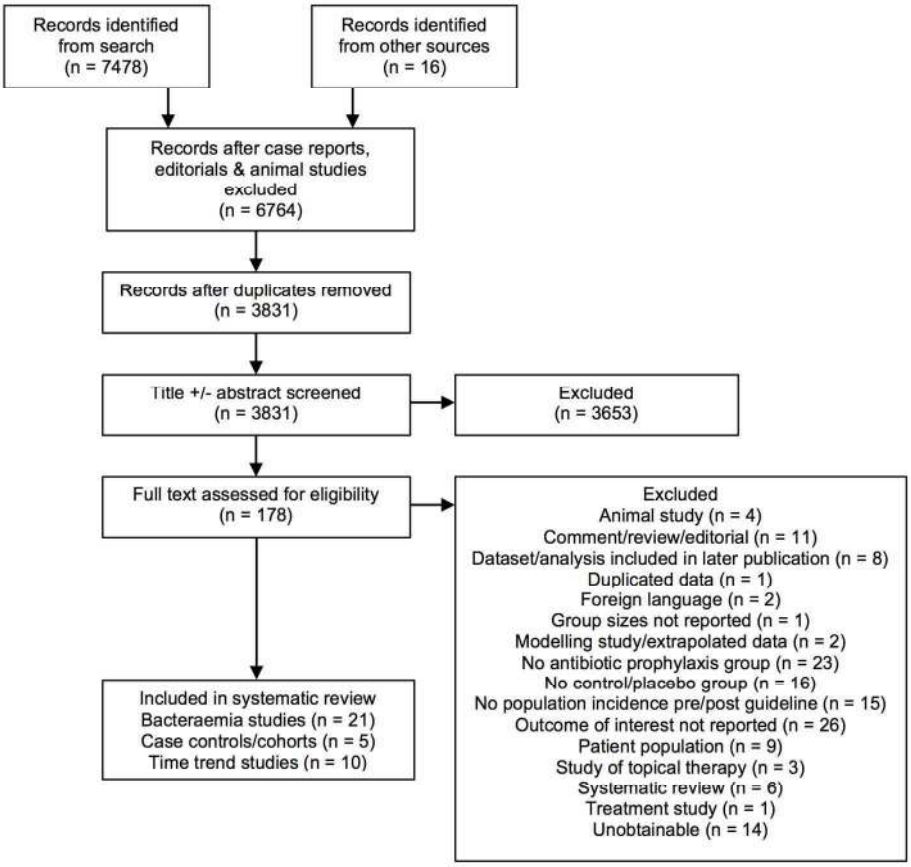


Figure 1. PRISMA flow chart
Figure 1
155x154mm (300 x 300 DPI)

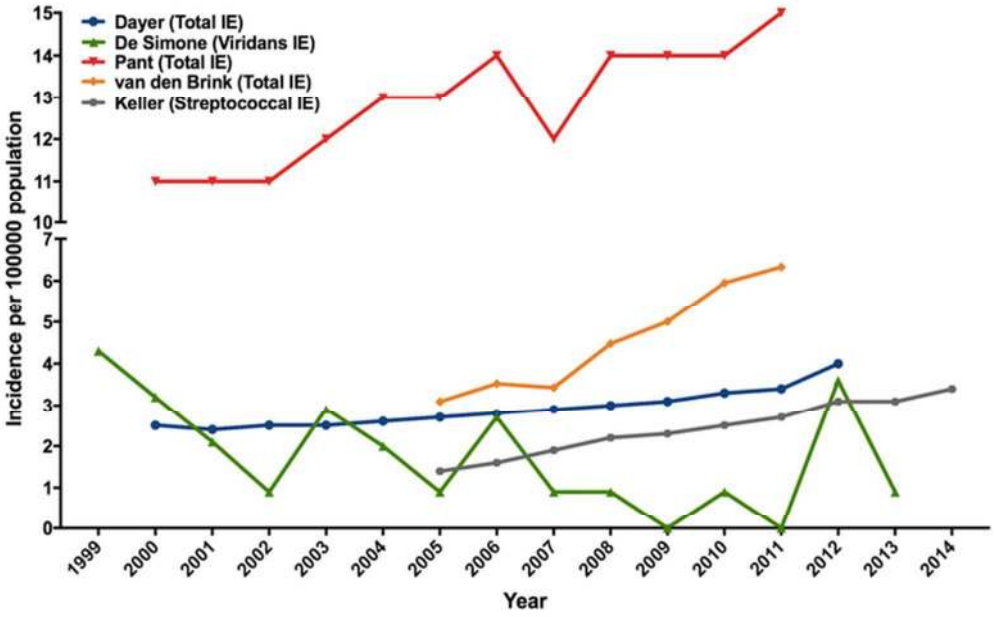


Figure 2. Annual incidence of infective endocarditis reported in time-trend analyses. The data for annual incidence or prevalence was reported in three studies[17, 18, 27] and obtained from the authors for two studies.[19, 20] The incidence of viridans streptococal infective endocarditis in DeSimone et al was 0 in 2009 and 2011. The incidence values for Pant et al [17] are higher than other studies due to the inclusion of infective endocarditis as both a primary and secondary diagnosis (included solely as a primary diagnosis in the other studies).

Figure 2
31x19mm (600 x 600 DPI)

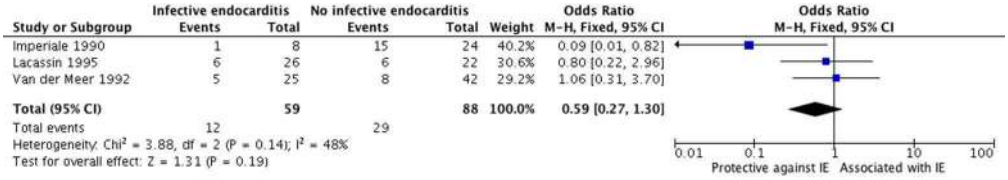


Figure 3. Meta-analysis of case-control studies testing the association between antibiotic prophylaxis (AP) and infective endocarditis after dental procedures. In these studies, cases are patients with infective endocarditis and controls are matched patients at risk (Table 2). The number of 'events' is the use of AP in each group as a proportion of the total number of procedures. Overall, the odds ratio of AP comparing patients with infective endocarditis to those without is 0.59 (95% confidence interval 0.27-1.30, p = 0.14), suggesting no statistically significant difference in AP exposure between cases and controls. Abbreviations: AP antibiotic prophylaxis; IE infective endocarditis.

344x62mm (72 x 72 DPI)

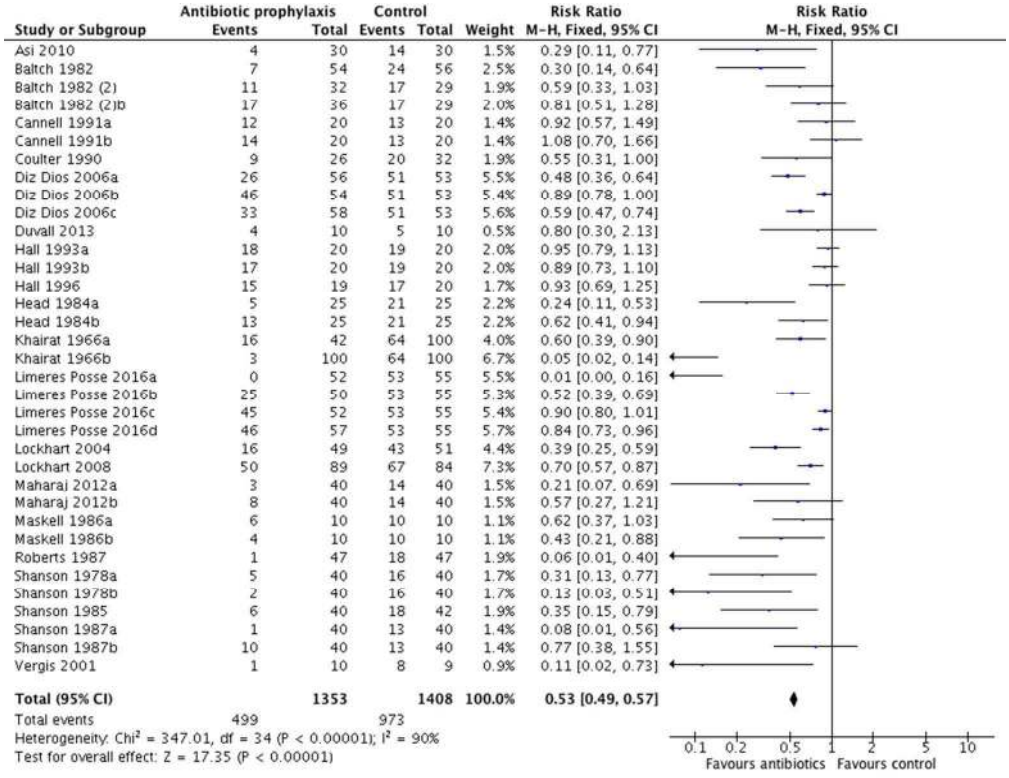


Figure 4. Meta-analysis of trials of antibiotic prophylaxis for prevention of bacteraemia after dental procedures. Where an individual study tested multiple antibiotic regimes, these are represented as (a), (b) etc. and compared against the control/placebo arm. Details of the dental procedure and antibiotic regimen are shown in Supplementary Table 5. Overall, use of AP was associated with a risk ratio for bacteraemia of 0.53 (95% CI 0.49-0.57, p < 0.01, I2 = 90%). Abbreviations: AP antibiotic prophylaxis

312x242mm (72 x 72 DPI)

SUPPLEMENTARY DATA

Supplementary Appendix 1: Search strategy

MEDLINE

# ▲	Searches
1	exp Endocarditis, Bacterial/ or Endocarditis/
2	((bacter* or infective or inflammatory) adj5 endocarditis).ti,ab.
3	((infect* or inflam*) adj5 endocardium).ti,ab.
4	endocarditis.ti.
5	1 or 2 or 3 or 4
6	exp Anti-Bacterial Agents/
7	(antibiotic? or anti-biotic? or antimicrobial? or anti-microbial? or antibacterial? or anti-bacterial? or anti-infective).ti,ab.
8	(penicillin or amoxicillin or ampicillin or cefazolin or ceftriaxone or cephalexin or clindamycin or azithromycin or clarithromycin or vancomycin).ti,ab.
9	6 or 7 or 8
10	(prophyla* or prevent* or premedicat* or pre-medicat*).ti,ab.
11	9 and 10
12	Antibiotic Prophylaxis/
13	11 or 12
14	5 and 13
15	exp Endocarditis, Bacterial/pc [Prevention & Control]
16	9 and 15
17	(endocarditis and prophyla*).ti.
18	14 or 16 or 17
19	exp animals/ not humans.sh.
20	18 not 19

EMBASE

# ▲	Searches
1	exp endocarditis/
2	((bacter* or infective or inflammatory) adj5 endocarditis).ti,ab.
3	((infect* or inflam*) adj5 endocardium).ti,ab.
4	endocarditis.ti.
5	1 or 2 or 3 or 4
6	exp *antibiotic agent/
7	(antibiotic? or anti-biotic? or antimicrobial? or anti-microbial? or antibacterial? or anti-bacterial? or anti-infective).ti,ab.
8	(penicillin or amoxicillin or ampicillin or cefazolin or ceftriaxone or cephalexin or clindamycin or azithromycin or clarithromycin or vancomycin).ti,ab.
9	6 or 7 or 8
10	(prophyla* or prevent* or premedicat* or pre-medicat*).ti,ab.
11	9 and 10
12	Antibiotic Prophylaxis/
13	11 or 12
14	5 and 13
15	(endocarditis and prophyla*).ti.
16	14 or 15
17	(exp animals/ or nonhuman/) not human/

18	16 not 17

COCHRANE

ID	Search
#1	endocarditis:ti,ab,kw (Word variations have been searched)
#2	((bacter* or infective or inflammatory) near endocarditis):ti,ab,kw (Word variations have been searched)
#3	abe or sabe:ti,ab,kw (Word variations have been searched)
#4	#1 or #2 or #3
#5	MeSH descriptor: [Anti-Bacterial Agents] explode all trees
#6	(antibiotic? or anti-biotic? or antimicrobial? or anti-microbial? or antibacterial? or anti-bacterial? or anti-infective):ti,ab,kw (Word variations have been searched)
#7	penicillin or amoxicillin or ampicillin or cefazolin or ceftriaxone or cephalexin or clindamycin or azithromycin or clarithromycin or vancomycin:ti,ab,kw (Word variations have been searched)
#8	#5 or #6 or #7
#9	prophyla* or prevent* or premedicat* or pre-medicat*:ti,ab,kw (Word variations have been searched)
#10	#8 and #9
#11	MeSH descriptor: [Antibiotic Prophylaxis] explode all trees
#12	#10 or #11
#13	#4 and #12
#14	MeSH descriptor: [Endocarditis, Bacterial] explode all trees and with qualifier(s): [Prevention & control - PC]
#15	endocarditis and prophyla*:ti (Word variations have been searched)
#16	#13 or #14 or #15

WOK

Set	Results	Save search history and/or create an alertOpen a saved search history
1	29,469	TOPIC: (endocarditis) OR TOPIC: (((infect* or inflam*) NEAR/5 endocardium)) OR TOPIC: (ABE OR SABE)
2	459,418	TS=(antibiotic* or anti-biotic* or antimicrobial* or anti-microbial* or antibacterial* or anti-bacterial* or anti-infective) OR TS=(penicillin or amoxicillin or ampicillin or cefazolin or ceftriaxone or cephalexin or clindamycin or azithromycin or clarithromycin or vancomycin)
3	1,167,210	TOPIC: (prophyla* or prevent* or premedicat* or pre-medicat*)
4	1,506	#3 AND #2 AND #1
5	606	TITLE: (endocarditis AND prophyla*)
6	1,785	#5 OR #4

Supplementary Table 1: Excluded studies

First author	Publication year	PMID/PMCID	Reason excluded
Agha	2005	15951458	Outcome of interest not reported
Aitken	1995	7599015	No control/placebo group
Alexander	2013	Abstract	No population incidence pre/post guideline reported
Al-Karaawi	2001	11119466	Outcome of interest not reported
Al-Omari	2014	24624933	Treatment of infective endocarditis study
Aoki	1996	NA	No abx prophylaxis intervention group
Baddour	2013	NA	Comment/editorial/review
Bain	1985	NA	Comment/editorial/review
Baltch	1988	3365078	No control/placebo group
Bates	2015	Abstract	No population incidence pre/post guideline reported
Bikdeli	2012	Abstract	Dataset/analysis included in later publication
Bolukbasi	2012	22157668	No abx prophylaxis intervention group
Bor	2013	23527296	No population incidence pre/post guideline reported
Bor	1984	6711576	Modelling study/extrapolated data
Brennan	2007	17197406	Dataset/analysis included in later publication
Bublak	2014	25608390	Comment/editorial/review
Bunnell	2011	NA	No control/placebo group
Carretta	1988	3167905	Unobtainable
Casas	1999	10231302	Unobtainable
Cannon	1987	3610906	Outcome of interest not reported
Cecchi	2009	18404005	No control/placebo group
Chen	2015	26512586	Outcome of interest not reported
Cherry	2007	17309589	Study of topical antibiotic/antiseptic
Clark	1969	5192402	Patient population
Connor	1967	5234633	Unobtainable
Cosgrove	2011	Abstract	No population incidence pre/post guideline reported
Couturier	2000	NA	Comment/editorial/review
Crasta	2009	19426179	No abx prophylaxis intervention group
Curran	1976	1075923	Unobtainable
Daly	1997	9153833	No abx prophylaxis intervention group
Daly	2001	11288795	No abx prophylaxis intervention group
Dankert	1982	NA	No abx prophylaxis intervention group
Dankert	1985	NA	Animal study
Darhous	1993	9588119	Unobtainable
Dayer	2010	Abstract	Dataset/analysis included in later publication
Dayer	2014	Abstract	Dataset/analysis included in later publication
Dayer	2011	Abstract	Dataset/analysis included in later publication
DeSimone	2015	26386808	No population incidence pre/post guideline reported
De Aguir	2012	22522720	No abx prophylaxis intervention group
De Leo	1974	4519445	No abx prophylaxis intervention group
Delahaye	2011	Abstract	Dataset/analysis included in later publication
Dell'Atti	2013	Abstract	Outcome of interest not reported
Diz	2013	Abstract	Group sizes not reported
Doshi	2007	Abstract	No population incidence pre/post guideline reported
Durak	1982	6632128	Outcome of interest not reported
Durak	1975	NA	Comment/editorial/review
Duval	2006	16705565	Modelling study/extrapolated data
Edwards	2015	Abstract	No population incidence pre/post guideline reported
Ellervall	2010	20134479	Systematic review
Erichsen	2016	27339641	No population incidence pre/post guideline reported
Esposito	2013	18646101	Systematic review
Feinstein	1961	13698654	Comment/editorial/review
Francioli	1985	3925031	Animal study
Friedlander	2010	20189771	Comment/editorial/review

Garlando	1988	3292185	Patient population
Glenny	2013	241108511	Systematic review
Goker	1992	1308784	Unobtainable
Grattan	2013	26319967	No abx prophylaxis intervention group
Grimard	1987	3680973	Unobtainable
Grimard	1986	NA	No abx prophylaxis intervention group
Guntheroth	1984	6486031	Outcome of interest not reported
Guze	1983	6418063	Animal study
Hakata	2014	NA	No abx prophylaxis intervention group
Harris	1999	10604613	Patient population
Hartzell	2005	15832100	No abx prophylaxis intervention group
Harvey	1961	13712066	Outcome of interest not reported
Hess	1977	NA	Foreign language
Hess	1981	Abstract	No control/placebo group
Hess	1983	6549771	No control/placebo group
Hess	1983	6550789	No control/placebo group
Ho	2015	NA	No population incidence pre/post guideline reported
Kaplan	1971	NA	Comment/editorial/review
Kaplan	1983	6889082	Comment/editorial/review
Kaplan	1983	NA	Unobtainable
Kaneko	1995	8869455	No control/placebo group
Katoh	1992	1300669	No control/placebo group
Kernodle	1993	8494364	Animal study
Kinane	2005	15966875	No abx prophylaxis intervention group
Klug	2007	17724263	Patient population
Kumana	1986	3099944	Outcome of interest not reported
Lador	2012	41122	No control/placebo group
Lee	2007	17761735	Outcome of interest not reported
Lee	2009	NA	Outcome of interest not reported
Lockhart	2009	2770162	No abx prophylaxis intervention group
Longman	1991	1990136	Outcome of interest not reported
Lucas	2000	10769852	Outcome of interest not reported
Oakley	1982	NA	No control/placebo group
Macgregor	1987	NA	Unobtainable
Magelli	1987	NA	Unobtainable
Maharaj	2012	3734757	No abx prophylaxis intervention group
Martin	1964	14244278	Unobtainable
Mazocchi	2007	17954332	No abx prophylaxis intervention group
Messini	1999	10412852	No abx prophylaxis intervention group
Monaco	2009	19531419	Outcome of interest not reported
Mougeot	2015	25758845	Dataset/analysis included in later publication
Murillo	1978	NA	Outcome of interest not reported
Murillo	1979	463947	Outcome of interest not reported
Murphy	2006	16968327	No abx prophylaxis intervention group
Murugiah	2013a	Abstract	No population incidence pre/post guideline reported
Murugiah	2013b	Abstract	No population incidence pre/post guideline reported
Niederau	1994	7988813	Patient population
Nelson	1965	NA	Patient population
Niwa	2005	1768964	Outcome of interest not reported
Oliver	2004	15106220	Systematic review
Pant	2015b	26338002	Comment/editorial/review
Pasquali	2011	Abstract	No population incidence pre/post guideline reported
Pasquali	2012	22607869	No population incidence pre/post guideline reported
Pasquantonio	2012	23058035	Outcome of interest not reported
Peterson	1976	1253389	No abx prophylaxis intervention group
Pineiro	2010	20701619	Study of topical antibiotic/antiseptic
Piper	2012	Abstract	Outcome of interest not reported
Rahn	1995	NA	Unobtainable

Rechmann	1989	2639069	Study of topical antibiotic/antiseptic
Rieder	1980	7423172	Patient population
Roberts	1997	8960488	No abx prophylaxis intervention group
Roberts	2002	12572738	No control/placebo group
Roberts	2000	10689771	No abx prophylaxis intervention group
Rogers	2008	18513601	No population incidence pre/post guideline reported
Sasaki	1994	NA	No control/placebo group
Sasaki	1998	NA	No control/placebo group
Sasaki	2001	NA	Foreign language
Santinga	1976	1067349	Outcome of interest not reported
Santinga	1984	NA	No control/placebo group
Sefton	1990	2196261	Duplicate data (Cannell et al)
Schirger	1964	14146015	No control/placebo group
Schlein	1991	2028936	No abx prophylaxis intervention group
Schwartz	2007	17904722	Systematic review
Shanson	1983	6130318	Outcome of interest not reported
Shanson	1984	6334070	Outcome of interest not reported
Sheenchen	1994	8310405	Patient population
Smith	1989	2732123	Outcome of interest not reported
Tempelhof	2012	NA	Systematic review
Thompson	1979	NA	Outcome of interest not reported
Thornhill	2011	21540258	Dataset/analysis included in later publication
Thornhill	2015	25925595	Outcome of interest not reported
Tozer	1966	4159601	Outcome of interest not reported
Tuback	2002	NA	Comment/editorial/review
Tzuckert	1978	285049	Unobtainable
Wong	2011	NA	No population incidence pre/post guideline reported
Yoshimura	1985	2939227	Unobtainable
Yurtman	2010	NA	Patient population
Zhang	2013	23137266	No abx prophylaxis intervention group

Supplementary Table 2: Risk of bias summary – time trend studies

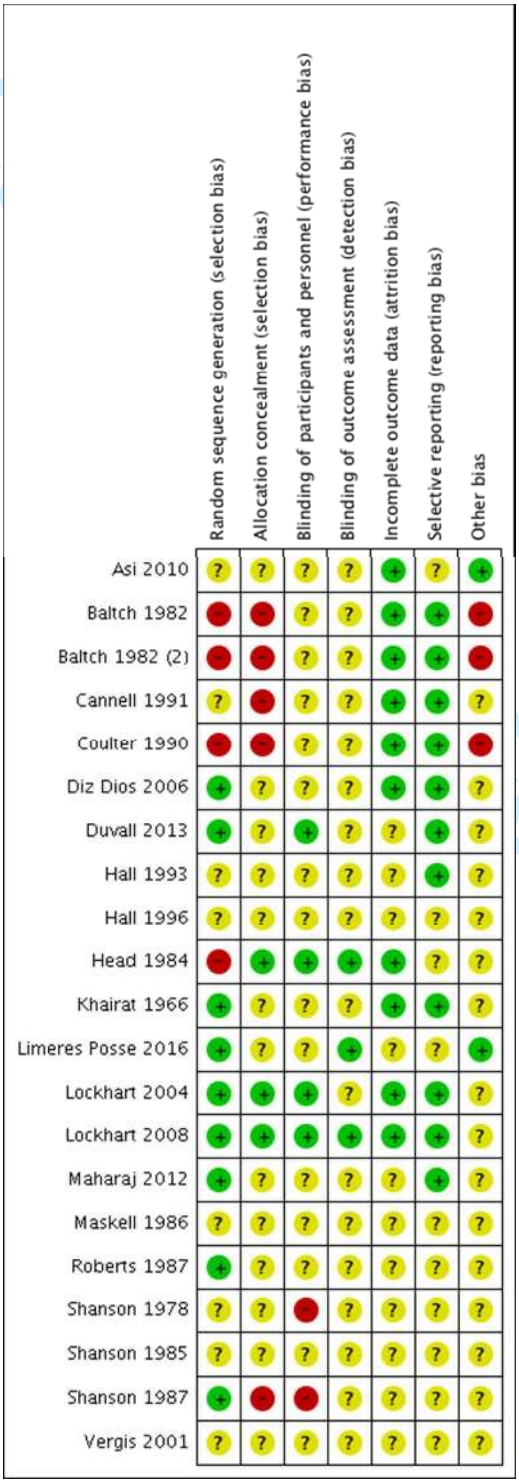
	Bates et al 2016[1]	Bikdeli et al 2013[2]	Dayer et al 2015[3]	DeSimone et al 2015[4]	Duval et al 2012[5]	Mackie et al 2016[6]	Pant et al 2015[7]	Salam et al 2014[8]	van den Brink et al 2016[9]
Definition of study group and IE diagnosis	Clearly defined. Quote: 'children ≤18 years of age hospitalised with infective endocarditis – defined as having an ICD-9 diagnosis code for "acute and subacute bacterial endocarditis"'	Clearly defined. Quote: 'All inpatient admissions of fee-for-service beneficiaries age >65yrs from 1999 to 2010'. 'Patients with a principal or secondary ICD-9-CM discharge diagnosis of endocarditis were included'	Clearly defined. Quote: 'We identified all patients with a primary discharge diagnosis of acute or subacute infectious endocarditis (ICD-10 code 133.0) including those who died in hospital'	Clearly defined. Quote: 'All Olmsted County residents aged >18yrs with definite or possible IE caused by VGS as defined by the modified Duke criteria between January 1, 1999 and December 31, 2013 were identified'	Clearly defined. Quote: The modified von Reyn classification being the only available classification for all 3 surveys was chosen to describe the changes over the 3 periods'	Clearly defined. Quote: 'All hospitalisations with 'acute or subacute endocarditis (ICD-9 421.0-421.9 or ICD-10 133.0-133.9) in the main diagnosis filed were included'	Clearly defined. Quote: 'We used the ICD clinical modification code to identify patients discharged with acute and subacute bacterial endocarditis between 2000 and 2011'	Not defined. Abstract only.	Clearly defined. Quote: 'This insurance database has a code uniquely for IE'
Characteristics of each group described	Yes. Age, gender, presence of congenital heart disease and in hospital mortality.	Yes. Age, gender, race, CV risk factors, past medical history	No group demographics or characteristics provided	Age- and sex-adjusted incidence	Yes: Age, sex, past medical history	Yes: Age, sex, cardiac predisposing factors, other predisposing factors	No group demographics or characteristics provided	No group demographics or characteristics provided	Yes. Age, gender, pre-existing valve disease, prosthetic valves, mortality, blood cultures, valve involved, organism
Interval of sampling	6-monthly	Yearly	Monthly	Yearly	1991, 1999 & 2008	Yearly	Yearly	4-yearly	Yearly
Data source	Quote: 'The Pediatric Health Information System Database was utilised'	Quote: 'Using the Centers for Medicare & Medicaid Services Medicare inpatient Standard Analytic Files'	Quote: 'Data for the prescription of antibiotic prophylaxis were obtained from the NHS Business Services Authority'. 'Incidence data for IE & associated mortality were obtained from national episode statistics'	Quote: 'The Endocarditis Registry of the Division of Infectious Diseases at Mayo Clinic and the Rochester Epidemiology Project (REP) database were our primary resources for case ascertainment and data collection'	Quote: 'Population-based survey methods'	Quote: 'The Canadian Institute for Health Information Discharge Abstract Database … data included from all Canadian provinces except Quebec and the Northern territories between April 1, 2002 and March 31, 2013'	Quote: The healthcare cost and utilisation project NIS database'	Not defined	Quote: 'Data were extracted from the Dutch Healthcare Authority'
Is the group representative of the population of interest?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes
Correlated change in incidence with change in antibiotic prophylaxis over time?	No	No	Yes	No	No	No	No	No	No
Overall risk of bias	High	High	High	High	High	High	High	High	High

Supplementary Table 3: Risk of bias summary – observational studies

	Horstkotte et al 1987[10]	Imperiale et al 1990[11]	Lacassin et al 1995[12]	Strom et al 1998	Van der Meer et al 1992[13]
Definition of cases	Catchment area and time period not specified. Cases defined as '229 patients in whom 287 diagnostic and therapeutic procedures were performed using a prophylactic antibiotic regime correctly administered.	Catchment area and time period specified. Clearly defined inclusion and exclusion criteria. Presence of infective endocarditis determined using the modified Von Reyn criteria.	Catchment area and time period specified. Clearly defined inclusion and exclusion criteria. Quote: 'Definite and probably IE was defined according to Von Reyn's criteria revised with the following modifications to include echocardiographic and macroscopic findings for definite and probably cases. Definite endocarditis was defined on macroscopy or microbiological findings on operation or necropsy; probably endocarditis was defined as (1) persistently positive blood cultures with underlying heart disease plus echocardiographic vegetation or with vascular phenomena plus echocardiographic vegetation or with vascular phenomena plus echocardiographic vegetation or (2) negative or intermittently positive blood cultures with fever, underlying heart disease, vascular phenomena, and echocardiographic vegetation'.	Catchment area and time period specified. Inclusion and exclusion criteria clearly defined. Infective endocarditis not determined using diagnostic criteria. Quote: 'These experts used their own global clinical judgement to classify potential cases as definite, probably or possible cases'.	Catchment area and time period specified. Clearly defined inclusion and exclusion criteria. Presence of infective endocarditis was determined by the Von Reyn criteria.
Definition of controls	Catchment area and time period not specified. 'The second patient group consisted of 304 out of 1898 patients questioned in our outpatient clinic, who gave reliable information that they had undergone one of the procedures we regard as requiring endocarditis prophylaxis, without having received any antibiotic regime'.	Time period specified and catchment area specified and same as cases. Inclusion clearly defined. Exclusion criteria clearly defined and same as cases.	Defined, but different population as cases. Quote: 'Controls were subjects without infective endocarditis who satisfied the same exclusion criteria as the cases. There were all recruited randomly from wards either during a consultation for echo or during hospitalisation in the same period of observations as cases'. 'Each case was matched to one control as regards sex, age and group of underlying cardiac conditions'.	Catchment area and time period not specified. Inclusion poorly defined. Exclusion criteria for controls not defined. Recruited using a modification of the Waksberg random-digit dialling method	Catchment area specified, differing from cases. Time period not specified. Inclusion and exclusion criteria clearly described
Characteristics of each group described	No	Yes: Age, gender, cardiac lesion, history or rheumatic fever, murmur duration, frequency of dental visits, dental clearing at zero time visit, use of diuretics, use of digitalis, penicillin allergy	Yes: Age, sex, valve disease, duration of previous cardiac disease, known cardiac disease	Only age	Yes: Age, procedures, interval between procedure and onset of symptoms
Groups recruited at common stage, in the same manner	Not specified	Cases and controls were recruited during the same time period and from the same catchment area. Both cases and controls were recruited in the same manner, in the form of a letter.	Cases and controls were recruited during the same time period, but catchment area and manner of recruitment not specified	Catchment area and time period for recruitment of controls not specified. Method of recruitment not specified.	Cases and controls were recruited from different catchment areas. Time period of recruitment of controls not specified. Manner of recruitment differed between cases and controls: cases were selective consecutively and interviewed in person; controls were selected randomly, sent a letter and then a telephone call
Sampling strategy	Not specified	Cases: preliminary selected by review of medical and dental records, and completion of telephone interview. Controls: all patients who underwent echocardiographic evaluation during the period covered by the study.	Not specified	Catchment area and time period for recruitment of controls not specified. Sampling strategy varied: controls were randomly recruited from the community; controls were recruited from all in patients with a putative diagnosis of endocarditis.	Cases: Quote 'All patients who were consecutively admitted to hospital in the Netherlands and who were suspected of having bacterial endocarditis'. Comment: defined catchment area over a defined period of time. Controls: sampling strategy not specified.

Is the group representative of the population of interest	In part, but also included procedures other than dental, such as urological and gynaecological	Yes	Yes – only dental subgroup analysed	Yes	Overall yes, although < 10% of procedures were non-dental
Duration of follow-up	No follow-up	No-follow up	No follow-up	No follow-up	No follow-up
Outcome assessment: Objective or independently adjudicated?	Outcome: Prosthetic valve endocarditis. Method or criteria for diagnosis of endocarditis is not described.	Telephone interview, use of a standard structured questionnaire not described. Specific purpose of research was not revealed to the interview subjects. Use of independent adjudicator not described.	Cases and controls were interviewed using the same questionnaire. Use of an independent adjudicator, or blinding of the participants to the study purpose is not described	Structured telephone interview where cases and controls completed the same structured questionnaire. Use of an independent adjudicator or blinding of the participants to the study purpose is not described	Telephone interview where cases and controls completed the same structured questionnaire. Use of an independent adjudicator, or blinding of the participants to the study purpose is not described
Overall risk of bias	High	High	High	High	High

Supplementary Table 4 – Risk of bias summary – bacteraemia trials



Supplementary Table 4. Risk of bias assessment for trials of antibiotic prophylaxis. All trials were assessed using the Cochrane risk of bias tool. Symbols: + low risk of bias, − high risk of bias, ? unclear risk of bias

Supplementary Table 5: Data extraction – bacteraemia trials

First author, year	PMID	Study design	Paper/abstract	Country of origin	Population (children, adults, mixed)	Intervention	Antibiotic prophylaxis regime (drug, route, dose, duration, timing) - arm 1	Antibiotic prophylaxis regime (drug, route, dose, duration) - arm 2	Antibiotic prophylaxis regime (drug, route, dose, duration) - arm 3	Antibiotic prophylaxis regime (drug, route, dose, duration) - arm 4	Comparison arm	Study method	Total no of patients - abx prophylaxis arm 1	Total number of patients - abx prophylaxis arm 2	Total number of patients - abx prophylaxis arm 3	Total number of patients - abx prophylaxis arm 4	Total number of patients – control/placebo arm	Incidence of any bacteraemia in post procedure cultures - prophylaxis group 1	Incidence of any bacteraemia in post procedure cultures - prophylaxis group 2	Incidence of any bacteraemia in post procedure cultures - prophylaxis group 3	Incidence of any bacteraemia in post procedure cultures - prophylaxis group 4	Incidence of any bacteraemia in post procedure cultures - placebo group	Secondary outcome: level/duration bacteraemia	Secondary outcome: incidence of strep bacteraemia
Asi, 2010[14]	20922074	TNR	Paper	India	Adults (aged 35-45 years)	Periodontal flap procedure (under LA)	Amoxicillin 500mg PO, 2h pre-procedure	NA	NA	NA	Each patient served as own control - separate quadrants	Blood cultures taken during procedure	30	NA	NA	NA	30	4/30 (13.3%)	NA	NA	NA	14/30 (46.6%)	Not reported	Control group: 4/30 (13.3%). Abx group: 1/30 (3.3%)
Baltch, 1982[15]	7148652	TNR	Paper	USA	Adults (age not specified): 28 with known cardiac abnormality (prophylaxis group); 28 without cardiac abnormality (control group)	Dental cleaning	Penicillin G 2million units IV, over 30-40mins pre-procedure, continued for 72h	NA	NA	NA	Control group	Blood cultures taken pre- and 5 and 30 mins post-procedure	28	NA	NA	NA	28	3/28 (10.7%) at 5 minutes; 4/26 (15.4%) at 30 minutes	NA	NA	NA	17/28 (60.7%) at 5 minutes; 7/28 (25%) at 30 minutes	Not reported	Control group: 4/28 (14.3%) at 5 mins, 1/28 (3.6%) at 30 mins. Abx group: 1/28 (3.6%) at 5 mins, 1/26 (3.9%) at 30 mins

Baltch, 1982b[16]	7044125	TNR	Paper	USA	Adults (range 19 – 83) undergoing dental extraction, 33/128 with known valvular heart disease	Dental extraction (LA)	Aqueous penicillin G 2 million units IV 30 minutes before the procedure and every 4 hours for 72 hours thereafter	Penicillin V orally 0.5-1g 30-45 minutes prior to the procedure	NA	NA	Control group (29 under local anaesthesia used to match antibiotic groups)	Blood cultures pre- and 5 and 30 mins post-procedure	33	36	NA	NA	29	11/32 (34.4%) at 5 minutes; 4/33 (12.1%) at 30 minutes	17/36 (47.2%) at 5 minutes; 5/36 (13.9%) at 30 minutes	NA	NA	17/29 (58.6%) at 5 minutes; 8/29 (26.7%) at 30 minutes	Number of isolates per positive blood culture at 5 minutes: IV penicillin 1.6, PO penicillin 2.5, control group 4.1	Proportion with streptococcal bacteraemia at 5 mins: IV penicillin 1/32 (3.1%), PO penicillin 1/36 (2.8%), control group 17/30 (56.7%)
Cannell, 1991[17]	1832916	RCT	Paper	UK	Adults (aged 18-65 years)	Dental extraction (anaesthetic not specified)	Erythromycin 1.5g PO, 1-1.5h pre-procedure	Josamycin base 1.5g, 1-1.5h pre-procedure	NA	NA	Placebo group	Blood cultures taken, timing not specified	20	20	NA	NA	20	12/20 (60%)	14/20 (70%)	NA	NA	13/20 (65%)	Not reported	Not reported
Coulter, 1990[18]		TNR	Paper	UK	Children (aged 2-13 years) 26 with known cardiac abnormality (prophylaxis group); 32 with no cardiac abnormality (control group)	Dental extraction (under GA)	Penicillin IM (dose and timing not specified)	Amoxicillin PO (dose and timing not specified)	Amoxicillin IV (dose and timing not specified)	Erythromycin IV (dose and timing not specified)	Control group	Blood cultures taken 1-2 minutes post-extraction	8	8	6	4	32	Overall 9/26 (35%)	NA	NA	NA	20/32 (63%)	Not reported	Number of patients with streptococcal bacteraemia in each group: 3/26 with AP; 12/32 without AP
Diz Dios, 2006[19]		RCT	Paper	Spain	Adults (aged >/=18 years) with learning difficulties	Dental extraction (under GA)	Amoxicillin 2g PO, 1-2h pre-procedure	Clindamycin 600mg PO, 1-2h pre-procedure	Moxifloxacin 400mg PO, 1-2h pre-procedure	NA	Control group	Blood cultures taken at 0s, 30s, 15min and 1h post-extraction	56	202	58	NA	53	46.4% (n=26) at 30s, 10.7% at 15mins, 3.7% at 1h	85.1% (n=46) at 30s, 70.4% at 15mins, 22.2% at 1h	56.9% at 30s (n=33), 24.1% at 15mins, 7.1% at 1h	NA	96.2% (n=51) at 30s, 64.2% at 15mins, 20% at 1h	Not reported	% of cultures +ve for streptococci: Control group: 63.1%. Amox group: 44.4%. Clindamycin group: 58.5%. Moxifloxacin: 67.7%
Duvall, 2013[20]	23453612	RCT	Paper	USA	Adults (aged 18-29 years)	Dental extraction (under LA)	Amoxicillin 2g PO, 1h pre-procedure	Chlorhexidine rinse. 1h pre-procedure	NA	NA	Placebo group	Blood cultures taken before and 1.5 minutes after 2nd extraction, 1.5 mins after 4th extraction, then at 10 mins after 4th extraction	10	10	NA	NA	10	4/10 (40%)	6/10 (60%)	NA	NA	5/10 (50%)	Magnitude of bacteraemia (SD): placebo group 3.61+/-7.09 CFU/ml; amoxicillin 0.63+/-1.33 cfu/ml; chlorhex 2.76+/-4.28 cfu/ml	Number of alpha/hemolytic/VGS isolates: placebo 5, chlorhexidine 2, amoxicillin 1

Hall, 1993[21]	8399865	RCT	Paper	Sweden	Adults (aged 23-74 years)	Dental extraction (under LA)	Penicillin V 1g PO x2, 1h pre-procedure	Amoxicillin 750mg PO x4, 1h pre-procedure	NA	NA	Placebo group	Blood cultures taken during procedure and 10 minutes post-procedure	20	20	NA	NA	20	Overall 90% (n=18). 90% during procedure, 70% at 10 mins	Overall 85% (n=17). 85% during procedure, 60% at 10 mins	NA	NA	Overall 95% (n=19). 90% during surgery, 80% at 10 mins	Median cfu per ml reported: During procedure Pen V 0.66, Amox 1.08, Placebo 0.84; 10mins post-procedure: Pen V 0.36, Amox 0.24, Placebo 0.36	VGS isolated during procedure: Pen V 70%, Amox 55%, Placebo 70%; VGS 10mins post-procedure: Pen V 25%, Amox 30%, Placebo 40%
Hall, 1996[22]	8894572	RCT	Paper	Sweden	Adults (aged 21-66 years)	Dental extraction (anaesthetic not specified)	Cefaclor 1g PO, 1h pre-procedure	NA	NA	NA	Placebo group	Blood cultures taken pre-, during and 10 minutes post-procedure	19	NA	NA	NA	20	79% (n=15) during procedure, 53% at 10 mins	NA	NA	NA	85% (n=17) during, 47% at 10 mins	See bacteraemia at 10 minutes outcome	Control group: 50% during procedure, 30% at 10 mins post-procedure. Cefaclor group: 79% during procedure, 26% at 10 mins post-procedure
Head, 1984[23]	6435046	RCT	Paper	Canada	Adults (aged 16-60 years)	Dental extraction (under LA)	Penicillin V 2g PO, 1h pre-procedure	Metronidazole 2g PO, 1h pre procedure	NA	NA	Placebo group	Blood cultures taken 1 minute post-extraction	25	25	NA	NA	25	20%	52%	NA	NA	84%	Pour plates' were all negative - bacteraemias< 1 microorganism per ml of blood	Reported - need to check
Khairat, 1966[24]	5928605	RCT	Paper	Canada	Not specified	Dental extraction (under LA)	Erythromycin PO, varying dose from 250mg-1000mg at varying time 90-240mins pre-procedure	Tetracycline 275mg IV, 3 mins pre-procedure	NA	NA	Control group	Blood cultures taken, timing not specified	42	100	NA	NA	100	16/42 (38%)	3/100 (3%)	NA	NA	64/100 (64%)		Control group: 44 (44%); Pyrrolidino group: 2 (2%)
Limeres Posse, 2016[25]	27029851	RCT	Paper	Spain	Adults (aged >=18 years)	Dental extraction (under GA)	Amoxicillin/clavulanate 1000/200mg IV, after induction	Amoxicillin 2g PO, 1-2h before induction	Clindamycin 600mg PO, 1-2h before induction	Azithromycin 500mg PO, 1-2h before induction	Control group - unmedicated	Blood cultures pre-procedure, 30s post-extraction, and 15 and 60 mins post-procedure	52	50	52	57	55	0/52 (0%)	25/50 (50%)	45/52 (87%)	46/57 (81%)	53/55 (96%)	Results also reported at 15 mins and 1h	Percentage of positive cultures that were VGS: Control-50%; Amoxicillin/Clavulanate-0%; Amoxicillin-31%; Clindamycin 56%; Azithromycin 53%

Lockhart, 2004[26]	15173031	RCT	Paper	USA	Children (mean age 3.5 years)	Dental extraction (under GA)	Amoxicillin 50mg/kg PO, 1h pre-procedure	NA	NA	NA	Placebo group	Blood cultures taken pre-, during and 15, 30 and 45 mins post-procedure	49	NA	NA	NA	51	16/49 (33%)	NA	NA	NA	43/51 (84%)	Duration reported: at 15 minutes 12% vs 1%, at 30 mins 9% vs 0%, at 45 mins 5% vs 0% - all prophylaxis vs placebo	Numbers of positive cultures for VGS. Control group: 45% (n=57). Amoxicillin group: 33% (n=8)
Lockhart, 2008[27]	18541739	RCT	Paper	USA	Not specified, (mean age 40 years)	Dental extraction (under LA)	Amoxicillin (dose, route and timing not specified)	Tooth brushing	NA	NA	Placebo group	Blood cultures taken pre-, during, and 20, 40 and 60 mins post-procedure	90	89	NA	NA	89	56%	32%	NA	NA	80%	Duration is reported. All analysed samples were below the detection threshold of 104 CFU per millilitre of blood	Numbers of positive cultures for VGS. Control group: 106/151 (70%). Amoxicillin group: 23/47 (49%)
Maharaj, 2012[28]	23108516	RCT	Paper	South Africa	Adults (aged 18-66 years), without underlying valve disease or prosthetic valve	Dental extraction (anaesthetic not specified)	Amoxicillin 3g PO, 1h pre-procedure	Clindamycin 600mg PO, 1h pre-procedure	Chlorhexidine rinse, 1h pre-procedure	NA	Control group	Blood cultures taken, timing not specified	40	40	40	NA	40	3/40 (7.5%)	8/40 (20%)	16/40 (40%)	NA	14 (35%)	Not reported	Number of patients with positive VGS cultures: control group 5; chlorhexidine 5; amoxicillin 0; clindamycin 0
Maskell, 1986[29]	2941404	TNR	Paper	UK	Not specified	Dental extraction (anaesthetic not specified)	Teicoplanin 200mg IM, 1h pre-procedure	Amoxicillin 3g PO, 1h pre-procedure	NA	NA	Control group	Blood cultures taken during procedure	10	10	NA	NA	10	6/10 (60%)	4/10 (40%)	NA	NA	10 /10 (100%)	NA	Control group 9/10 (90% of patients had oral streptococci isolated; 5/10 in teicoplanin group; 3/10 in amoxicillin group
Roberts, 1987[30]	NA	Randomised trial	Paper	UK	Children < 16 years	Dental extraction	Amoxicillin 50mg/kg PO, 2h pre-procedure	NA	NA	NA	Control group	Blood cultures pre procedure, post intubation and 2 minutes post extraction	47	NA	NA	NA	47	1/47 (2.13%)	NA	NA	NA	18/47 (38.3%)	NA	Control group – 14/47 patients positive cultures for strep (VGS, non-haemolytic or anaerobic strep) Amoxicillin group – 0/47 positive culture due to strep

Shanson, 1978[31]	99423	RCT	Paper	UK	Adults (age not specified)	Dental extraction (anaesthetic not specified)	Penicillin V 2g PO, 1h pre-procedure	Amoxicillin 2g PO, 1h pre-procedure	NA	NA	Control group - unmedicated	Blood cultures taken 2 mins post-extraction	40	40	NA	NA	40	5/40 (12%)	2/40 (5%)	NA	NA	16/40 (40%)		
Shanson, 1985[32]	3882657	TNR	Paper	UK	Adults (aged 18-71)	Dental extraction (LA)	Erythromycin stearate PO, 1.5g given 1h pre-procedure	NA	NA	NA	Placebo group	Blood cultures 1-2 minutes following extraction	40	NA	NA	NA	42	6/40 (15%)*	NA	NA	NA	18/42 (43%)*	Serial dilutions reported	See primary outcome for this study (only streptococcal bacteraemia reported)
Shanson, 1987[33]	2957348	RCT	Paper	UK	Adults (aged 18-60 years), without underlying valve disease or prosthetic valve	Dental extraction (under GA)	Teicoplanin 400mg IV, 5-10mins before extraction	Amoxicillin 1g IM, 20-30mins before GA	NA		Control group - unmedicated	Blood cultures and antibiotic assay (treatment arms only) 1.5-2mins post-extraction. Antibiotic assay (treatment arms only) at 4h	40	40	NA	NA	40	2.50%	25%	NA	NA	32.50%	Not reported	VGS incidence. Control group: 13/40. Teicoplanin group: 1/40
Vergis, 2001[34]	11174592	RCT	Paper	USA	Adults (aged 21-79 years), without underlying valve disease or prosthetic valve	Dental extraction (anaesthetic not specified)	2 x 60ml mouthwash applications containing 3g amoxicillin suspension per application, retained for 1-2 mins each (2 hours and 1 hour before extraction)	3g amoxicillin PO (1 hour before extraction)	NA	NA	Control group - unmedicated	Blood cultures taken post-extraction (for 1 extraction, after extraction; for 2 extractions, after 2nd tooth extracted; for 3 or more extractions, after 3rd or 4th tooth extracted)	10	10	NA	NA	9	6/10 (60%)	1/10 (10%)	NA	NA	8/9 (89%)		

Abbreviations: LA – local anaesthetic, GA – general anaesthetic, IM intramuscular, IV intravenous, NA – not applicable, PO per oral, RCT – randomized controlled trial, TNR – trial, non-randomised
*only viridans streptococcal bacteraemia reported

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	5
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Suppl
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8-9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8-9

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	14, 15, Suppl
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Suppl
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	14, 15, Figures
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figures
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Suppl
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	NA

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