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Antibiotic Prophylaxis and Infective Endocarditis Incidence Following Invasive Dental Procedures
A Systematic Review and Meta-Analysis

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IMPORTANCE The association between antibiotic prophylaxis and infective endocarditis after invasive dental procedures is still unclear. Indications for antibiotic prophylaxis were restricted by guidelines beginning in 2007.

OBJECTIVE To systematically review and analyze existing evidence on the association between antibiotic prophylaxis and infective endocarditis following invasive dental procedures.

DATA SOURCES PubMed, Cochrane-CENTRAL, Scopus, Web of Science, Proquest, Embase, Dentistry and Oral Sciences Source, and ClinicalTrials.gov were systematically searched from inception to May 2023.

STUDY SELECTION Studies on the association between antibiotic prophylaxis and infective endocarditis following invasive dental procedures or time-trend analyses of infective endocarditis incidence before and after current antibiotic prophylaxis guidelines were included.

DATA EXTRACTION AND SYNTHESIS Study quality was evaluated using structured tools. Data were extracted by independent observers. A pooled relative risk (RR) of developing infective endocarditis following invasive dental procedures in individuals who were receiving antibiotic prophylaxis vs those who were not was computed by random-effects meta-analysis.

MAIN OUTCOMES AND MEASURES The outcome of interest was the incidence of infective endocarditis following invasive dental procedures in relation to antibiotic prophylaxis.

RESULTS Of 11 217 records identified, 30 were included (1 152 345 infective endocarditis cases). Of them, 8 (including 12 substudies) were either case-control/crossover or cohort studies or self-controlled case series, while 22 were time-trend studies; all were of good quality. Eight of the 12 substudies with case-control/crossover, cohort, or self-controlled case series designs performed a formal statistical analysis; 5 supported a protective role of antibiotic prophylaxis, especially among individuals at high risk, while 3 did not. By meta-analysis, antibiotic prophylaxis was associated with a significantly lower risk of infective endocarditis after invasive dental procedures in individuals at high risk (pooled RR, 0.41; 95% CI, 0.29-0.57; P for heterogeneity = .51; I^2, 0%). Nineteen of the 22 time-trend studies performed a formal pre-post statistical analysis; 9 found no significant changes in infective endocarditis incidence, 7 demonstrated a significant increase for the overall population or subpopulations (individuals at high and moderate risk, streptococcus-infective endocarditis, and viridans group streptococci–infective endocarditis), whereas 3 found a significant decrease for the overall population and among oral streptococcus-infective endocarditis.

CONCLUSIONS AND RELEVANCE While results from time-trend studies were inconsistent, data from case-control/crossover, cohort, and self-controlled case series studies showed that use of antibiotic prophylaxis is associated with reduced risk of infective endocarditis following invasive dental procedures in individuals at high risk, while no association was proven for those at low/unknown risk, thereby supporting current American Heart Association and European Society of Cardiology recommendations. Currently, there is insufficient data to support any benefit of antibiotic prophylaxis in individuals at moderate risk.

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Supplemental content

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Infective endocarditis is a rare but life-threatening condition.[1,2] The estimated global crude incidence ranges from 1.5 to 11.6 cases per 100 000 person-years,[3] but recent studies suggest the incidence is rising.[4-10] Incidence rates are higher in individuals with underlying cardiac conditions such as prosthetic heart valves, congenital heart disease, or noncardiac conditions, such as presence of central venous catheters, hemodialysis for kidney failure, and intravenous drug use.[1] Despite optimal treatment, infective endocarditis is associated with high morbidity and an estimated mortality rate at 1 year of 30% to 40%.[1,2,11-13] Therefore, the identification of effective prevention strategies is crucial.

For several decades, the evidence surrounding antibiotic prophylaxis for infective endocarditis prevention has undergone substantial evolution, prompting a reassessment of traditional approaches. In 1955, the American Heart Association (AHA) issued the first statement on prevention of infective endocarditis: antibiotic prophylaxis was recommended for "all subjects with rheumatic or congenital heart disease undergoing dental extractions and other dental manipulations which disturb the gums, the removal of tonsils and adenoids, the delivery of pregnant women, and operations on the gastrointestinal or urinary tracts."[14] In the ensuing 50 years, antibiotic prophylaxis was recommended to a wide range of individuals, with controversies regarding individual and procedure selections, choice of antibiotics, and overall risk-benefit ratio.[15,16] Between 2007 and 2009, the AHA, the European Society of Cardiology (ESC), and the National Institute for Health and Care Excellence (NICE) recommended restrictions on antibiotic prophylaxis to different degrees. The AHA and ESC recommended antibiotic prophylaxis to be considered only in individuals at the highest risk (ie, those with a previous history of infective endocarditis, prosthetic heart valves or prosthetic material used in cardiac valve repair, unrepaired cyanotic congenital heart disease, congenital heart disease with prosthetic materials or devices placed in the previous 6 months or with residual defects and those undergoing surgical or interventional procedures) who undergo an invasive dental procedure, defined as procedures that involve manipulation of the gingival tissue, periapical region of teeth, or perforation of the oral mucosa.[17,18] Conversely, antibiotic prophylaxis was no longer recommended for individuals at moderate risk, such as those with acquired valvular heart disease, hypertrophic cardiomyopathy, and most other congenital heart diseases. This message was later reinforced in updated statements.[19,20] In 2008, NICE advised against antibiotic prophylaxis use,[21] although in 2016 this message was revised with a softer statement suggesting antibiotic prophylaxis not be routinely recommended.[22]

The long-standing dispute over the effectiveness of antibiotic prophylaxis to prevent infective endocarditis following invasive dental procedures persists due to the scarcity of robust data and absence of randomized clinical trials. In this setting, a comprehensive analysis of existing evidence is valuable. Herein, we reviewed and meta-analyzed the existing evidence to evaluate the association of antibiotic prophylaxis and the incidence of infective endocarditis following invasive dental procedures. In particular, we explored if antibiotic prophylaxis is able to influence the association between invasive dental procedures and infective endocarditis (case-control/crossover or cohort studies and self-controlled case series) and if changes in the antibiotic prophylaxis guidelines were associated with infective endocarditis incidence over time (time-trend studies). Particular attention was given to stratified analyses by individual risk profile.

Key Points

Question Is antibiotic prophylaxis associated with decreased risk of infective endocarditis after invasive dental procedures?

Findings This systematic review and meta-analysis including data on 1 152 345 cases of infective endocarditis found that antibiotic prophylaxis was associated with a reduced risk of infective endocarditis following invasive dental procedures in individuals at high risk but not in those at moderate or low/unknown risk.

Meaning These findings support the use of antibiotic prophylaxis for individuals at high risk undergoing invasive dental procedures, supporting current American Heart Association and European Society of Cardiology guidelines.

Methods

Data collection and reporting followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE)[23] and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines.[24] The study was conducted within the initiative World Workshop on Oral Medicine VIII (https://wworalmed.org) and registered in the PROSPERO (CRD4202017398).

Data Sources and Search Strategy

A systematic search of PubMed, Cochrane-CENTRAL, Scopus, Web of Science, Proquest, Embase, Dentistry and Oral Sciences Source, and ClinicalTrials.gov was conducted from inception to May 17-19, 2023. The search strategy was developed with the help of a dental librarian (L.G.) using both keywords and controlled vocabulary terms around the topics of *infective endocarditis*, *antibiotic prophylaxis*, *guideline*, and *dental procedure* (eMethods 1 in Supplement 1). References of selected articles were screened by hand to identify additional articles. Covidence software (Veritas Health Innovation) was used to support the review process.

Study Selection

Studies were screened by 2 independent investigators (K.F., M.B., M.G., H.H., L.M., and V.E.) at the title and abstract level. The same reviewers independently performed the full-text review. Reasons for exclusion were systematically recorded. Disagreements were discussed with senior investigators (G.L. and P.D.D.) until consensus was reached.

Studies were selected if they included data on infective endocarditis incidence and either (1) data on the association between antibiotic prophylaxis and infective endocarditis following invasive dental procedures or (2) a time-trend analysis of infective endocarditis incidence around the time of

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antibiotic prophylaxis guidelines implementation. The main outcome of interest was the infective endocarditis incidence following invasive dental procedures in relation to antibiotic prophylaxis. Clinical trials, observational prospective or retrospective cohort studies, case-crossover studies, case-control studies, self-controlled case series, or longitudinal ecological time-trend studies were all candidates for inclusion. Reviews, case reports, case series (n ≤ 10 to eliminate positive outcome bias), letters, editorials, animal studies, and conference abstracts were excluded. Criteria for exclusion are listed in eFigure 1 in Supplement 1.

Quality Assessment

Quality of selected studies was independently assessed by 2 investigators (K.F. and M.B.) and reviewed by 2 senior investigators (F.T. and F.S.). The following quality assessment tools were adapted following a consensus process involving all authors: (1) the Effective Practice and Organization of Care criteria developed by the Cochrane Collaboration for time-trend studies and (2) the National Heart Lung and Blood Institutes Quality Assessment Tool for Observational Cohort Studies for cohort/self-controlled case series and the National Heart Lung and Blood Institutes Quality Assessment Tool for Case-Control Studies for case-control/crossover studies[25,26] (eMethods 2-4 in Supplement 1).

Data Extraction and Visualization

Data extraction was performed independently by 2 investigators (M.B., M.G., H.H., K.F., G.L, F.S., and F.T.). Disagreements were discussed with senior investigators (G.L., P.D.D., and V.E.) until consensus was reached. Data were collected and summarized in structured tables approved by all investigators. Subanalyses based on pathogen or risk profile were also extracted. Records with overlapping data were flagged.

From case-control, case-crossover, and cohort studies, we extracted results of the 2 possible types of assessment for the association between antibiotic prophylaxis and infective endocarditis incidence. Direct assessment indicates a single comparison between individuals who underwent invasive dental procedures and received antibiotic prophylaxis vs those who did not receive antibiotic prophylaxis before invasive dental procedures; indirect assessment indicates a 2-fold comparison between individuals who did or did not receive antibiotic prophylaxis before invasive dental procedures both vs those who did not undergo invasive dental procedures. Results from the indirect assessment were plotted using a forest plot. For time-trend studies, we extracted any measure of infective endocarditis incidence changes (eg, incidence rate ratios, differences in slope, differences in annual percentage change) before and after antibiotic prophylaxis guidelines.

Statistical Analysis

For the direct assessment, we performed a random-effects meta-analysis of relative risk (RR) estimates (RR, odds ratio [OR], or incidence rate ratio [IRR]) of developing infective endocarditis in individuals at high risk who underwent invasive dental procedures and received antibiotic prophylaxis vs those who did not receive antibiotic prophylaxis before invasive dental procedures, by using the Der Simonian and Laird method.[27] Heterogeneity among studies was assessed using the χ^2 test and inconsistency was quantified using the I^2 statistic.[28] All statistical analyses were performed using Stata version 18 (Stata Corp).

Results

Study Selection and Characteristics

A total of 11 217 records were identified. Following removal of duplicates (n = 7331), 3886 titles and abstracts were screened. Of the 123 full-text articles retrieved, 30 were included, for a total of 1 152 345 infective endocarditis cases (eFigure 1 in Supplement 1).[4-13,29-48] All studies were observational: 8 were either case-control/crossover or cohort studies or self-controlled case series (4 included 2 separate substudies with different designs, for a total of 12 substudies) and 22 were time-trend studies. Twenty-seven (90%) were multicenter studies (23 based on national databases) and 3 (10%) were single-center studies. Twelve studies (40%) collected data from the US, 13 (43%) from Europe (United Kingdom, France, Germany, the Netherlands, and Sweden), 3 (10%) from Taiwan, and 2 (7%) from Canada.

Role of Antibiotic Prophylaxis in the Association Between Invasive Dental Procedures and Infective Endocarditis: Results From Case-Control/Crossover or Cohort Studies and Self-Controlled Case Series

Seven of 12 substudies (58%) with designs among case-control/crossover or cohort studies and self-controlled case series found a significant association between invasive dental procedures and infective endocarditis (2 in the overall population,[31,35] 3 among individuals at high risk,[32,36] and 2 among individuals at moderate and low/unknown risk[32,36]) (**Table 1**; eTable 1 in Supplement 1). Regarding the role of antibiotic prophylaxis in this association (8 substudies with available data), 3 of the 4 substudies that provided a direct assessment found a significantly lower risk of infective endocarditis in individuals at high risk who underwent invasive dental procedures and received antibiotic prophylaxis compared to those who underwent invasive dental procedures without antibiotic prophylaxis (**Figure**)[32,36]; by random-effects meta-analysis, the pooled RR for developing infective endocarditis after invasive dental procedures when receiving vs not receiving antibiotic prophyhlaxis among individuals at high risk was 0.41 (95% CI, 0.29-0.57; *P* for heterogeneity = .51 by χ^2 test; I^2 statistic = 0%) (Figure). None of the pooled studies contained overlapping data. One of the 4 substudies showed a significant inverse association between use of antibiotic prophylaxis before invasive dental procedures and infective endocarditis for individuals at moderate risk,[32] while no substudies found a significant association in individuals at low/unknown risk. Regarding the indirect assessment, 3 of 6 substudies found a significantly higher risk of infective endocarditis in individuals who underwent invasive dental procedures without antibiotic prophylaxis compared to those who did not undergo invasive dental procedures (1 for the overall population[31] and 2 in individuals at high risk only[32,36]); such

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Table 1. Study Characteristics and Findings on Associations Between Invasive Dental Procedures (IDPs) and Infective Endocarditis (IE) and the Role of Antibiotic Prophylaxis (AP)

Source	Setting	Guideline	Study design	Study period	Description of study population	Association between IDPs and IE	Role of AP in the association between IDPs and IE
Chen et al,[29] 2015[a]	National data, Taiwan	Taiwan guidelines	Case-crossover study	1999-2012	713 Individuals with IE (mean [SD] age, 58 [20] y)	No significant association between IDPs and IE (eTable 1 in Supplement 1).	After adjusting for AP, no difference in odds of IE between case and matched control periods (eTable 1 in Supplement 1).
Sun et al,[30] 2017	National data, Taiwan	Taiwan guidelines	Nested case-control study	1997-2010	237 Individuals with IE (median [IQR] age, 1.2 [0.6-3.0] y) and 4725 control individuals (similar age due to matching)	No analysis for overall IDP.	No significant association between use of AP before IDPs and IE (IDPs without AP: OR of IE, 0.35; 95% CI, 0.11-1.27 vs no IDPs; IDPs with AP: OR of IE, 1.31; 95% CI, 0.64-2.66 vs no IDPs) (indirect assessment).
Chen et al,[31] 2018[a]	National data, Taiwan	Taiwan guidelines	Case-crossover study	2005-2011	9120 Individuals with IE (age ≥20 y)	No significant association between IDPs and IE (eTable 1 in Supplement 1).	NR
			Self-controlled case series	2004-2013	8181 Individuals with IE (age ≥20 y)	Significant increase in IE incidence in the 1-4 wk after IDPs vs control period (IRR of IE, 1.14; 95% CI, 1.02-1.26) but not in IE occurring 5-16 wk after IDPs.	Significant increase in IE incidence in the 1-4 wk after IDPs without AP (IRR of IE, 1.16; 95% CI, 1.03-1.31 vs no IDPs) but not for IE occurring 5-16 wk after. No significant increase in IE incidence after IDPs with AP for all the timeframes (1-4 wk IRR of IE, 1.07; 95% CI, 0.88-1.30 vs no IDPs) (indirect assessment).
Thornhill et al,[32] 2022	National data, USA	AHA guidelines 2007	Cohort study	2000-2015	3774 Individuals with IE; total study population of 7 951 972 (age ≥18 y)	No significant association between IDPs and IE (OR of developing IE in the 4 wk following IDPs in individuals at high risk[c] vs no IDPs, 1.17; 95% CI, 0.74-1.92). Significant direct association between dental extraction and IE (OR for individuals at high risk,[c] 9.22; 95% CI, 5.54-15.88; moderate risk,[c] 3.25; 95% CI, 1.61-6.46; and low risk, 2.41; 95% CI, 1.44-3.95). Significant direct association between oral surgery and IE (OR for those at high risk,[c] 20.18; 95% CI, 11.22-36.74; low risk, 3.74; 95% CI, 1.79-7.15).	Significant inverse association between use of AP before IDPs and IE in individuals at high risk[c] (OR of IE, 0.38; 95% CI, 0.22-0.62 vs no AP) (direct assessment). No significant association in individuals at moderate risk.[c]
			Case-crossover study	2000-2015	3774 Individuals with IE (age ≥18 y)	Significant direct association between IDPs and IE in individuals at high risk[c] (OR of IE, 2.00; 95% CI, 1.59-2.52 vs control period). No association between IDPs and IE in individuals at moderate[c] or low/unknown risk.	Significant inverse association between use of AP before IDPs and IE in individuals at high risk[c] (OR of IE, 0.49; 95% CI, 0.29-0.85 vs no AP) (direct assessement). Risk of IE after IDPs without AP vs no IDPs in individuals at high risk[c]: OR of IE, 2.44; 95% CI, 1.87-3.18. Risk of IE after IDPs with AP vs no IDPs in individuals at high risk[c]: OR of IE, 1.20; 95% CI, 0.74-1.93 (indirect assessment). Significant inverse association between use of AP before IDPs and IE in individuals at moderate risk[c]: OR of IE, 0.34; 95% CI, 0.14-0.88 vs no AP (direct assessment).
Tubiana et al,[33] 2017	National data, France	ESC guidelines 2015	Cohort study	2009-2014	267 Individuals with IE; total study population of 138 876 individuals (median [IQR] age, 74 [63-80] y)	Study included only individuals at high risk[c] (prosthetic valves). No significant association between IDPs and IE (IRR of developing IE in the 3 mo following IDPs, 1.25; 95% CI, 0.82-1.82 vs no IDPs).	Study included only individuals at high risk[c] (prosthetic valves). After stratifying for AP, no difference in risk of IE after IDPs (IDPs without AP: IRR of IE, 1.57; 95% CI, 0.90-2.53 vs no IDPs; IDPs with AP: IRR of IE, 0.83; 95% CI, 0.33-1.69 vs no IDPs) (indirect assessment).
			Case-crossover study	2009-2014	648 Individuals with IE (median [IQR] age, 77 [68-82] y)	Study included only individuals at high risk[c] (oral streptococcal IE on prosthetic valves). Significant direct association between IDPs and IE (OR of IE, 1.66; 95% CI, 1.05-2.63 vs control period).	Study included only individuals at high risk[c] (oral streptococcal IE on prosthetic valves). After stratifying for AP, results were similar but no longer significant (IDPs without AP: OR of IE, 1.62; 95% CI, 0.81-3.27 vs no IDPs; IDPs with AP: OR of IE, 1.69; 95% CI, 0.93-3.06 vs no IDPs) (indirect assessment).

(continued)

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Table 1. Study Characteristics and Findings on Associations Between Invasive Dental Procedures (IDPs) and Infective Endocarditis (IE) and the Role of Antibiotic Prophylaxis (AP) (continued)

Source	Setting	Guideline	Study design	Study period	Description of study population	Association between IDPs and IE	Role of AP in the association between IDPs and IE
Thornhill et al,[34] 2022[b]	National data, England	NICE guidelines 2008	Case-crossover study	2010-2016	17 732 Individuals with IE (mean [SD] age, 61 [21] y); 4296 of these individuals with linked dental data (mean [SD] age, 62 [19] y)	Significant inverse association between IDPs in the 3 mo before IE and IE in individuals at high risk[c] (IRR of IE for the control period, 1.36; 95% CI, 1.16-1.59 vs case period).	Individuals with IE not receiving AP for IDPs: 7205/7340 (98.16%); individuals with IE receiving AP for IDPs: 135/7340 (1.84%). Total IDPs without AP: 3 675 440/3 744 280 (98.16%); total IDPs with AP: 68 840/3 744 280 (1.84%).
Thornhill et al,[35] 2023[b]	National data, England	NICE guidelines 2008	Case-crossover study	2010-2016	14 731 Individuals with IE (mean [SD] age, 62 [20] y)	Significant direct association between dental extraction and IE (OR of developing IE in the 3 mo following IDPs, 2.14; 95% CI, 1.22-3.76) vs control period). Increased risk of other surgical scaling or gingival procedures as well (not statistically significant).	Assumed that no AP was administered, given NICE guidelines 2008. In individuals at high risk,[c] estimated 50 additional IE cases/100 000 dental extractions (95% CI, 9-120). In individuals at moderate risk,[c] estimated 4 additional IE cases/100 000 dental extractions (95% CI, 1-9).
Thornhill et al,[36] 2023	National data, US	AHA guidelines 2007	Cohort study	2000-2015	2647 Individuals with IE; total study population of 1 678 190 (age ≥18 y)	Significant direct association between IDPs and IE (OR of developing IE in the 30 d following IDPs vs no IDPs in individuals at high risk,[c] 6.58; 95% CI, 2.76-20.33; low/unknown risk, 2.06; 95% CI, 1.07-4.33; and moderate risk,[c] 4.09; 95% CI, 1.18-11.99).	Significant inverse association between AP before IDPs and IE in individuals at high risk[c] (OR of developing IE, 0.20; 95% CI, 0.06-0.53 vs no AP) (direct assessment). No significant association in individuals at moderate[c] or low/unknown risk.
			Case-crossover study	2000-2015	2647 Individuals with IE (age ≥18 y)	Significant direct association between IDPs and IE in individuals at high risk[c] (OR of IE, 2.91; 95% CI, 2.15-3.95 vs control period). No association between IDPs and IE in individuals at moderate[c] or low/unknown risk.	No significant association between AP before IDPs and IE in individuals at high risk[c] (OR of IE, 0.50; 95% CI, 0.17-1.49 vs no AP) (direct assessment). Risk of IE after IDPs without AP in individuals at high risk[c]: OR of IE, 3.14; 95% CI, 2.28-4.32 vs no IDPs. Risk of IE after IDPs with AP in individuals at high risk[c]: OR of IE, 1.57; 95% CI, 0.55-4.44 vs no IDPs (indirect assessment). No significant association in individuals at moderate[c] or low/unknown risk.

Abbreviations: AHA, American Heart Association; ESC, European Society of Cardiology; IRR, incidence rate ratio; NICE, National Institute for Health and Care Excellence; NR, not reported; OR, odds ratio; RR, relative risk.

[a] Chen et al,[31] 2018, partially overlaps with Chen et al,[29] 2015.

[b] Thornhill et al,[35] 2023, overlaps with Thornhill et al,[34] 2022.

[c] Individuals at high risk were defined as those with cardiac conditions that included previous IE, prosthetic cardiac valve replacement or prosthetic material used in cardiac valve repair, and certain forms of congenital heart disease (ie, unrepaired cyanotic congenital heart disease, congenital heart disease and prosthetic materials or devices placed in the previous 6 months or with residual defects, or those undergoing surgical or interventional procedures). Individuals at moderate risk were defined as those with cardiac conditions that included acquired valvular heart disease, hypertrophic cardiomyopathy, and most other congenital heart diseases. Additional details are reported in eTable 1 in Supplement 1.

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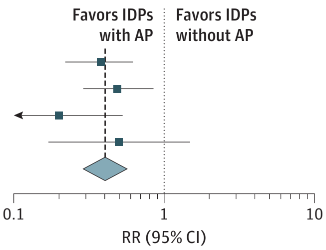
Figure. Risk of Infective Endocarditis After Invasive Dental Procedures (IDPs) in Individuals at High Risk Who Received Antibiotic Prophylaxis (AP) vs Those Who Did Not

Source	Analysis	RR (95% CI)	Weight, %
Thornhill et al,[32] 2022	Cohort	0.38 (0.22-0.62)	41.98
Thornhill et al,[32] 2022	Case-crossover	0.49 (0.29-0.85)	38.97
Thornhill et al,[36] 2023	Cohort	0.20 (0.06-0.53)	9.49
Thornhill et al,[36] 2023	Case-crossover	0.50 (0.17-1.49)	9.56
Overall: $I^2 = 0.0\%$; $P = .51$		0.41 (0.29-0.57)	100



Relative risks (RRs) and 95% CIs are shown for each study using black blue squares and bars, respectively. The diamond represents the pooled RR and 95% CI.

substudies did not find significantly higher risks for those who underwent invasive dental procedures receiving antibiotic prophylaxis compared to those who did not undergo invasive dental procedures (eFigure 2 in Supplement 1).

Association Between Antibiotic Prophylaxis Guidelines Change and the Incidence of Infective Endocarditis: Results From Time-Trend Studies

Twenty-two time-trend studies were included in the systematic review (**Table 2**; eTable 2 in Supplement 1). In time-trend analyses, interrupted time series of infective endocarditis incidence were collected at multiple time points before and after antibiotic prophylaxis guideline changes (ie, intervention). The effect of the intervention was generally evaluated by changes in the level and slope of the postintervention time series, compared to a counterfactual trend estimated based on the preintervention data. The most frequent statistical approaches were segmented regression, which assumes the change has occurred at the guideline change time point, and change-point analysis, which assumes that changes, if any, might have occurred at any point over time (eTable 2 in Supplement 1). Ten studies found a significant change in trends of hospitalization for infective endocarditis after guideline changes (7 with a significant increase and 3 with a significant decrease), 9 studies did not detect significant changes, and 3 did not perform any formal statistical pre-post comparison. Among the 7 studies that found a significant increase in infective endocarditis rate, 4 were conducted in North America around the change in AHA guidelines and found a significant increase in specific subpopulations (individuals at high and moderate risk only,[8,40] streptococcus-infective endocarditis,[39] or viridans group streptococcus [VGS]-infective endocarditis[7]), while 3 were conducted in Europe around the NICE[47] or ESC guideline changes[5,44] and found a significant increase in the overall population (Table 2; eTable 2 in Supplement 1). Of note, 2 of these studies contained overlapping data.[7,39] Conversely, 3 studies found a significant decrease in infective endocarditis trends: 2 were conducted in the US around the AHA guideline change[11,13] and found a significant decrease in the overall population, while 1 was conducted in Europe around the release of new French national guidelines[46] and found a significant decrease in oral streptococcus-infective endocarditis only (Table 2; eTable 2 in Supplement 1). No significant change in trends of infective endocarditis incidence was demonstrated in individuals at low/unknown risk.

Quality Assessment

Study quality is detailed in eFigure 3 and eTable 3 in Supplement 1. Case-control, case-crossover, and cohort studies and self-controlled case series were overall of good quality, with 9 of 12 studies (75%) with at most 2 items not met. The lowest scoring criteria were the sample size justification that was fulfilled in 1 study (8%), followed by the blinding of the assessors to either the case/control status (case-control/crossover studies) or the exposure status (cohort studies/self-controlled case series), which was fulfilled by 2 studies (17%). Control for confounding with adjustment or stratification and subanalysis was assessed in 9 studies (75%). Time-trend studies were overall of good quality, with 16 of 22 studies (73%) having 0, 1, or 2 items at high risk of bias. The lowest scoring criteria were the performance of time-trend analyses by subgroups (9 [41%]), and the parallel evaluation of actual implementation of the intervention (12 [54%]). A statistically appropriate time-trend analysis was carried out in 17 studies (77%), 18 (82%) had clearly defined time points, and 19 (86%) had a sufficiently large time interval before and after intervention.

Discussion

This systematic review and meta-analysis explored the role of antibiotic prophylaxis on the incidence of infective endocarditis following invasive dental procedures bringing together data from 30 studies and 8 countries, for a total of 1 152 345 infective endocarditis cases. Among the 12 case-control, case-crossover, cohort, or self-controlled case series substudies, 8 formally evaluated the role of antibiotic prophylaxis on infective endocarditis after invasive dental procedures: 5 supported a protective role of antibiotic prophylaxis, especially among individuals at high risk (cohort and case-crossover studies[32,36] and a self-controlled case series[31]), while 3 did not (nested case-control[30] and cohort and case-crossover studies[33]). By meta-analysis, we found that individuals at high risk who received antibiotic prophylaxis before invasive dental procedures were 59% (95% CI, 43-71) less likely to develop infective endocarditis compared to those who did not receive antibiotic prophylaxis, thereby supporting current AHA and ESC recommendations. This association was not proven for individuals at moderate or low/unknown risk. In parallel, we found that results from time-trend studies were inconsistent.

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Table 2. Study Characteristics and Findings for Time-Trend Studies Assessing the Association Between Antibiotic Prophylaxis (AP) Guideline Change and Infective Endocarditis (IE) Incidence

Source	Setting	Guideline	Study period	Description of study population	Reported IE measure before and after guidelines: Before	After	Association between AP guideline change and incidence of IE and reported measure of change
Bates et al,[6] 2017[c]	Multicenter, US	AHA guidelines 2007	2003-2014	841 Individuals with IE (median [IQR] age, 13 [9-15] y)	Mean IR, 4.6/10 000 child/6 mo	Mean IR, 4.6/10 000 child/6 mo	Study included only oral streptococcus IE. No significant change in trends of IE before and after guidelines: difference in slope NR ($P = .895$). CHD: NS.
Bikdeli et al,[11] 2013	National data, USA	AHA guidelines 2007	1999-2010	262 658 Individuals with IE (mean [SD] age: 1999-2000, 79.4 [8.0] y; 2009-2010, 79.2 [8.8] y)	IR 1999: 72.0/100 000/y; IR 2005: 83.5/100 000/y; IR 2007: 81.4/100 000/y	IR 2008: 79.2/100 000/y; IR 2009: 74.9/100 000/y; IR 2010: 70.6/100 000/y	Significant decrease in trends of IE after vs before guidelines: 2008 vs 2007 IRR, 0.97; 95% CI, 0.94-0.99; 2009 vs 2007 IRR, 0.91; 95% CI, 0.89-0.93; 2010 vs 2007 IRR, 0.86; 95% CI, 0.84-0.88.
DeSimone et al,[12] 2015[a]	National data, US	AHA guidelines 2007	2000-2011	Projected nationwide estimates: from 17 110 (2003) to 13 334 (2010) individuals with IE (age NR)	NR	NR	Study included VGS-IE only. No significant change in trends of IE before and after guidelines (P value NR).
DeSimone et al,[41] 2021[a]	National data, US	AHA guidelines 2007	1970-2018	269 Individuals with IE (median [IQR] age, 67 [52-78] y)	IR 2000-2009: female, 5.4 (95% CI, 3.7-7.8)/100 000/y; male, 7.8 (95% CI, 5.5-10.7)/100 000/y	IR 2010-2018: female, 5.7 (95% CI, 3.9-8.0)/100 000/y; male, 13.3 (95% CI, 10.2-16.9)/100 000/y	No overall analysis. No significant increase in trends of VGS-IE incidence before and after guidelines: difference NS ($P = .482$).
Pant et al,[39] 2015[a]	National data, US	AHA guidelines 2007	2000-2011	457 052 Individuals with IE (age NR)	IR 2000: 11/100 000/y; IR 2006: 14/100 000/y	IR 2008: 14/100 000/y; IR 2011: 15/100 000/y	No significant change in trends of IE before and after guidelines: difference in slope, 0.06; 95% CI, −0.36 to 0.49; $P = .74$. Streptococcus IE: significant increase ($P = .002$). Staphylococcus IE: NS. Valve replacement for IE: NS.
Pasquali et al,[38] 2012[c]	Multicenter, US	AHA guidelines 2007	2003-2010	1157 Individuals with IE (median [IQR] age, 2.9 y [2.5 mo-12.4 y])	Annual change in IE cases per 1000 hospital admissions, −5.9; 95% CI, −9.9 to −1.8	Annual change in IE cases per 1000 hospital admissions, −11.5; 95% CI, −15.7 to −7.1	No significant change in trends of IE before and after guidelines: annual change difference, −5.9%; 95% CI, −13.3 to 2.2; $P = .15$. Oral streptococcus IE: NS. IE in CHD: NS.
Rogers et al,[37] 2008	Single center, US	AHA guidelines 2007	2001-2008	396 Individuals with IE (age NR)	39-50 IE incident cases/mo	42 IE incident cases/mo	No substantial change in IE incidence before and after guidelines.
Sakai-Bizmark et al,[7] 2017[a]	National data, US	AHA guidelines 2007	2001-2012	3748 Individuals with IE (median [IQR] age, 8.4 [1.6-13.6] y)	IR 2001: 3.48/1 000 000/y; IR 2006: 5.26/1 000 000/y	IR 2008: 4.06/1 000 000/y; IR 2012: 4.14/1 000 000/y	No significant change in trends of IE before and after guidelines: difference in slope, −0.02; 95% CI, −0.23 to 0.20; $P = .89$. VGS-IE ≥10 y: significant increase ($P < .01$); VGS-IE <10 y: NS.
Thornhill et al,[40] 2018	National data, US	AHA guidelines 2007	2003-2015	20 340 Individuals with IE (age >18 y)	IR for individuals at high risk,[e] 11.04 IE cases/100 000/mo; moderate risk,[e] 1.9 IE cases/100 000/mo; low/unknown risk, NR	IR for individuals at high risk,[e] 30.6 IE cases/100 000/mo; moderate risk,[d,e] 3.4 IE cases/100 000/mo; low/unknown risk, NR	Significant increase in trends of IE after compared to before guidelines among individuals at high risk[e] (177% estimated increase; 95% CI, 66 to 361) and moderate risk[e] (75% estimated increase; 95% CI, 3 to 300). No significant change in trends of IE before and after guidelines among individuals at low/unknown risk (12% estimated increase; 95% CI, −29 to 76).
Toyoda et al,[13] 2017	Multicenter, US	AHA guidelines 2007	1998-2013	75 829 Individuals with IE (mean [SD] age, 62.3 [18.9] y)	NR	NR	Significant decrease in trends of IE before and after guidelines: difference in slope, −0.07; 95% CI, −0.11 to −0.02; $P = .004$. Oral streptococcus IE: significant decrease ($P = .002$). Staphylococcus IE: NS.
Garg et al,[8] 2019	Multicenter, Canada	AHA guidelines 2007	2002-2014	7551 Individuals with IE (6684 study participants) (median [IQR] age, 63 [48-75] y)	2002-2006: 395448 IE incident cases/y	2008-2014: 447-813 IE incident cases/y	No significant change in trends of IE before and after guidelines (P value NR). Significant increase in trends of IE after 2010 in individuals at high and moderate risk.[e]
Mackie et al,[42] 2016	National data, Canada	AHA guidelines 2007	2002-2013	9431 Individuals with IE (median [IQR] age, 55 [38-71] y)	Monthly change in IE cases per 10 000 000 general population, 0.05; 95% CI, 0.005-0.009	Monthly change in IE cases per 10 000 000 general population, 0.07; 95% CI, NR	No significant change in trends of IE before and after guidelines: difference in slope NR ($P = .521$).

(continued)

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Table 2. Study Characteristics and Findings for Time-Trend Studies Assessing the Association Between Antibiotic Prophylaxis (AP) Guideline Change and Infective Endocarditis (IE) Incidence (continued)

Source	Setting	Guideline	Study period	Description of study population	Reported IE measure before and after guidelines		Association between AP guideline change and incidence of IE and reported measure of change
					Before	After	
Duval et al,[46] 2012	Multicenter, France	France guidelines 2002	1991-1999	993 Individuals with IE (mean [SD] age: 1991, 58 [17] y; 1999, 60 [16] y; 2008, 62 [16] y)	IR 1991: 35.2 IE cases/1 000 000/y; IR 1999: 33.5 IE cases/1 000 000/y	IR 2008: 32.1 IE cases/1 000 000/y	No significant differences in IE incidence rates among the 3 time points (2 before and 1 after guidelines; $P = .980$). Oral streptococcus IE: NS. Staphylococcus IE: NS. Previously known native heart disease: NS. Oral streptococcus IE in previously known native heart disease: significant decrease ($P = .03$). Staphylococcus IE in previously known native heart disease: NS.
Knirsch et al,[43] 2020	Single center, Switzerland	AHA guidelines 2007	1995-2017	25 Individuals with IE (median [IQR] age, 7 [0.1-19] y)	IR 1995-2005: 0.195/1000 CHD pediatric patients/y	IR 2006-2017: 0.399/1000 CHD pediatric patients/y	Study included patients with CHD only. No change in IE incidence after compared to before guidelines ($P = .072$).
Dayer et al,[47] 2015[b]	National data, England	NICE guidelines 2008	2000-2013	19 804 Individuals with IE (mean [SD] age: 2000-2007, 59 [20] y; 2008-2013, 59 [21] y)	NR	NR	Significant increase in trends of IE incidence before and after guidelines: difference in slope, 0.11; 95% CI, 0.05-0.16; $P < .0001$. Individuals at high risk[e]: significant increase in trends of IE incidence ($P = .025$). Individuals at moderate[e] or low risk: significant increase in trends of IE incidence ($P = .0002$).
Quan et al,[9] 2020[b]	National data, England	NICE guidelines 2008	1998-2017	35 752 Individuals with IE (age NR)	IR 1998: 22.2-41.3 /1 000 000/y depending on *ICD-10* code-based criteria	IR 2017: 42.0-67.7/ 1 000 000/y depending on *ICD-10* code-based criteria	No apparent change in trends of IE before and after guidelines based on multiple models and *ICD-10* criteria (different change-points identified by different models).
Shah et al,[48] 2020	National data, Scotland	NICE guidelines 2008	1990-2014	7638 Individuals with IE (7513 participants) (mean [SD] age, 65 [17] y)	IR 1990: 5.3/100 000/y; IR 2007: 7.6/100 000/y	IR 2009: 7.8/100 000/y; IR 2014: 8/100 000/y	No significant increase in incidence of IE before vs after guideline: RR of change, 1.06; 95% CI, 0.94-1.20.
Keller et al,[4] 2017	National data, Germany	ESC guidelines 2009	2005-2014	94 364 Individuals with IE (age NR)	2005-2008: 8283 IE incident cases/y	2010-2014: 10 455 IE incident cases/y	Relative increase in the annual IE incidence (26%) after compared to before guidelines
Weber et al,[44] 2022	Multicenter, Germany	ESC guidelines 2009	1994-2018	4917 Individuals with IE (median [IQR] age, 65 [54-73] y)	NR	NR	Significant increase in trends of IE involving the mitral valve before and after guidelines ($P = .035$). No significant changes in trends of IE before and after guidelines for aortic, pulmonary, and tricuspid valve. Streptococcus IE: significant increase ($P = .002$). Staphylococcus IE: NS. Enterococcus IE: NS. Other pathogens: NS.
van den Brink et al,[5] 2017	National data, the Netherlands	ESC guidelines 2009	2005-2011	5213 Individuals with IE (mean [range] age, 67.5 [22-97] y)	IR 2005: 30.2 IE/1 000 000/y	IR 2011: 62.9 IE/1 000 000/y	Significant increase in IE incidence after compared to before guidelines: IRR, 1.33; 95% CI, 1.21-1.46; $P < .001$ in 2009.
Krul et al,[45] 2015	Single center, the Netherlands	The Netherlands guidelines 2008	2008-2013	89 Individuals with IE (median [IQR] age, 68 [59-75] y)	NR	NR	Increase in the annual IE incidence, especially after guidelines between 2011 and 2013.
Vähäsarja et al,[10] 2020	National data, Sweden	Sweden guidelines 2012	2008-2017	4649 Individuals with IE (mean [range] age, 65 [17-100] y)	Monthly change in IE cases per 10 000 000 general population, 0.344; 95% CI, 0.187-0.502	Monthly change in IE cases per 10 000 000 general population, 0.266; 95% CI, 0.115-0.416	No significant change in trends of IE before and after guidelines: change in slope, −0.007; 95% CI, −0.085 to 0.082. VGS-IE: NS. *Staphylococcus aureus* IE: NS.

Abbreviations: AHA, American Heart Association; CHD, congenital heart disease; ESC, European Society of Cardiology; *ICD-10*, *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*; IR, incidence rate; IRR, incidence rate ratio; NICE, National Institute for Health and Care Excellence; NR, not reported; NS, not significant; RR, relative risk; VGS, viridans group streptococcus.

[a] DeSimone et al,[12] 2015, Sakai-Bizmark et al,[7] 2017, and DeSimone et al,[41] 2021, overlap with Pant et al,[39] 2015 (National Inpatient Sample database).

[b] Quan et al,[9] 2020, overlaps with Dayer et al,[47] 2015 (National Hospital Episode Statistics database).

[c] Bates et al,[6] 2017, overlaps with Pasquali et al,[38] 2012 (Pediatric Health Information System database).

[d] DeSimone et al,[12] 2015, also included an analysis derived from the hospital internal database and the Rochester Epidemiology Project database, which was excluded due to duplicate data with DeSimone et al,[41] 2021.

[e] Individuals at high risk were defined as those with cardiac conditions that included previous IE, prosthetic cardiac valve replacement or prosthetic material used in cardiac valve repair, and certain forms of CHD (unrepaired cyanotic CHD or individuals with CHD undergoing surgical or interventional procedures). Individuals at moderate risk were defined as those with cardiac conditions that included acquired valvular heart disease, hypertrophic cardiomyopathy, and most other CHDs. Additional details are reported in eTable 2 in Supplement 1.

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While roughly one-third showed a significant increase in infective endocarditis incidence after antibiotic prophylaxis restriction, two-thirds showed no change or a significant decrease in incidence. None of the studies demonstrated a significant change in infective endocarditis incidence in individuals at low/unknown risk.

The absence of randomized clinical trials addressing the association between antibiotic prophylaxis and the incidence of infective endocarditis remains a critical limitation for the establishment of definitive causal relationships. However, major challenges and restraints exist in performing a randomized clinical trial. First, the rare incidence of infective endocarditis engenders a large sample size requirement, extended trial duration, and high resource demands, thereby impacting trial feasibility. Moreover, ethical concerns exist around withholding antibiotic prophylaxis measures from at-risk populations.[22] In this setting, the synthesis of evidence from observational studies assumes particular importance. A meta-analysis of observational studies published in 2017[49] found that antibiotic prophylaxis decreased the risk for bacteremia (pooled RR, 0.53; 95% CI, 0.49-0.57) but not the risk for infective endocarditis (pooled OR, 0.59; 95% CI, 0.27-1.30), likely due to limited statistical power. Another meta-analysis of 4 studies[50] revealed a 0% pooled incidence of infective endocarditis after invasive dental procedures among individuals at high risk receiving antibiotic prophylaxis (0/413 participants) concluding that antibiotic prophylaxis was likely to reduce infective endocarditis incidence. These meta-analyses[49,50] were limited by either small sample sizes of the included studies, evaluation of the overall population without stratifying for individual risk profile,[49] or lack of a comparison group not exposed to antibiotic prophylaxis.[50] Our meta-analysis brings together the most recent data—including 2 large case-crossover/cohort studies[32,36]—allowing for control group comparison and group stratification, providing stronger, although still limited, evidence to support the role of antibiotic prophylaxis in preventing infective endocarditis after invasive dental procedures in individuals at high risk.

Results from time-trend studies remain controversial. While 9 of the included studies showed no significant changes in trends of infective endocarditis incidence after guidelines recommending antibiotic prophylaxis restriction, 7 showed a significant increase and 3 a significant decrease. Reasons for inconsistency of these results are numerous. The infrequent occurrence of infective endocarditis necessitates large populations to generate adequate statistical power. Studies assessing prescription data are scant, and most studies assume guideline adherence. However, a recent systematic review[51] including studies across 20 countries showed that only approximately 25% of dentists were compliant. Changes in the epidemiology of infective endocarditis pathogens may have influenced results: around one-third of infective endocarditis cases may be attributed to oral streptococci, which are most commonly implicated in infective endocarditis following invasive dental procedures, while the prevalence of staphylococcus-infective endocarditis is rising.[1,52] Furthermore, the epidemiology of pathogens also differs by country.[1,52] Variation exists in duration of the defined exposure period, length of follow-up, and infective-endocarditis diagnostic criteria. While age and sex were often considered as confounders, comorbidities, immunosuppression, and exposure to other invasive procedures or presence of intravascular devices were not assessed. Further, we cannot exclude that any changes in infective endocarditis incidence over time might have been driven by other factors that changed concurrently. Overall, time-trend studies exhibit important limitations in effectively defining the role of antibiotic prophylaxis in determining the incidence of infective endocarditis.

Although 1 case-crossover study identified a small but significant effect of antibiotic prophylaxis in reducing infective endocarditis incidence following invasive dental procedures in individuals at moderate risk,[32] this was not confirmed in 3 other case-crossover[36] and cohort studies.[32,36] Similarly, results from time-trend studies regarding individuals at moderate risk were inconsistent. While studies continue to investigate and confirm the increased risk of infective endocarditis for some individuals in lower-risk categories, such as those with cardiac implantable electronic devices and hypertrophic cardiomyopathy, compared to the general population,[53,54] there is currently insufficient evidence to suggest that antibiotic prophylaxis is effective in reducing infective endocarditis incidence in these individuals. Further studies are needed to clarify this topic.

Limitations

This study has limitations. Evidence was derived from different study designs with a different potential to answer the study question, from the more informative direct assessments to the least informative time-trend studies. Meta-analysis was limited to direct assessment and included only 4 studies. Meta-analysis was not feasible for indirect assessments due to the lack of an overarching statistical measure comparing the 2 study-specific RRs, nor for time-trend studies, given the variety of statistical measures used. The included studies are observational and are therefore affected by intrinsic biases. The definition of infective endocarditis varied across studies, ranging from clinical criteria to *International Classification of Diseases* codes. *International Classification of Diseases* codes are affected by poor granularity, and coding variability exists across countries. Data on guideline adherence were limited, and assumptions were made on antibiotic prophylaxis prescription, administration, and regimen. Additionally, external factors such as individuals' increased longevity, greater individual complexity and comorbidities, increased number of prosthetic valves and cardiac implantable electronic device placements, and improvements in infective endocarditis diagnosis—which may at least in part explain an increase in infective endocarditis incidence—were not accounted for by most studies.

Conclusions

The findings from this study add valuable evidence in defining the role of antibiotic prophylaxis in preventing infective endocarditis following invasive dental procedures. While consistent conclusions from time-trend studies are difficult to extrapolate due to their intrinsic limitations and heterogeneity, data from case-control, case-crossover, and cohort studies and

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self-controlled case series provided clearer evidence of an association between antibiotic prophylaxis and reduced infective endocarditis incidence following invasive dental procedures in individuals at high risk, while no association was proven for individuals at low/unknown risk, thereby supporting the current AHA and ESC recommendations. There are currently insufficient data to support the use of antibiotic prophylaxis in individuals at moderate risk. Overall, further studies with a rigorous scientific approach are needed. These may include pragmatic clinical trials, which, despite their acknowledged limitations, could leverage national health system data to achieve the necessary statistical power with reasonable feasibility.

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