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Antibiotic prophylaxis and the incidence of infective endocarditis following invasive dental procedures: A systematic review and meta-analysis

Francesca Sperotto*, MD, PhD, Katherine France*, DMD, MBE, Margherita Gobbo, DMD, MSc, Mohammed Bindakhil, DDS, MS, Kununya Pimolbutr, DDS, MSc, PhD, Haly Holmes, BDS, MSc, MChD, Luis Monteiro, DDS, MSc, PhD, Laurel Graham, MLS, ML, Catherine HL Hong, BDS, MS, Thomas P Sollecito, DMD, Giovanni Lodi, PhD, Peter B Lockhart, DDS, Martin Thornhill, MBBS, BDS, PhD, Pedro Diz Dios, MD, DDS, PhD, Federica Turati[#], PhD, Valeria Edefonti[#], PhD

*equally contributed as first authors

[#]equally contributed as last authors

Affiliations

Francesca Sperotto – Department of Cardiology, Boston Children's Hospital, and Department of Pediatrics, Harvard Medical School, Boston, USA; francesca.sperotto@childrens.harvard.edu
Katherine France – Department of Oral Medicine, University of Pennsylvania, Philadelphia, USA; kfrance@upenn.edu
Margherita Gobbo – Unit of Oral and Maxillofacial Surgery, Ca' Foncello Hospital, Treviso, Italy; margherita.gobbo@aulss2.veneto.it
Mohammed Bindakhil – Division of Oral Medicine, Department of Oral Biology and Diagnostic Sciences, Augusta University, Augusta, USA; bindakhil@alumni.upenn.edu
Kununya Pimolbutr – Department of Oral Medicine and Periodontology, Mahidol University, Bangkok, Thailand; kununya.pim@mahidol.edu
Haly Holmes – Department of Oral Medicine and Periodontology, University of the Western Cape, Cape Town, South Africa; hholmes@uwc.ac.za
Luis Monteiro – University Institute of Health Sciences (CESPU), Porto, Portugal; luis.monteiro@iucs.cespu.pt
Laurel Graham – Dental Medicine Library, University of Pennsylvania, Philadelphia, USA; laurelg@upenn.edu
Catherine HL Hong – Faculty of Dentistry, National University of Singapore, Singapore; denchhl@nus.edu.sg
Thomas P Sollecito – Department of Oral Medicine, University of Pennsylvania, Philadelphia, USA; tps@upenn.edu
Giovanni Lodi – Dipartimento di Scienze Biomediche, Chirurgiche e Odontoiatriche, Università degli Studi di Milano, Milan, Italy; giovanni.lodi@unimi.it
Peter B Lockhart – Department of Otolaryngology, Wake Forest University School of Medicine, Atrium Health, Charlotte, USA; peter.lockhart@atriumhealth.org

Martin Thornhill – Department of Oral & Maxillofacial Medicine, Surgery and Pathology, University of Sheffield School of Clinical Dentistry, Sheffield, UK; m.thornhill@sheffield.ac.uk
Pedro Diz Dios – Medical-Surgical Dentistry Research Group (OMEQUI), Health Research Institute of Santiago de Compostela (IDIS), School of Medicine and Dentistry, Santiago de Compostela University, Santiago de Compostela, Spain; pedro.diz@usc.es
Federica Turati – Branch of Medical Statistics, Biometry, and Epidemiology "G.A. Maccacaro", Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Milan, Italy; federica.turati@unimi.it
Valeria Edefonti – Branch of Medical Statistics, Biometry, and Epidemiology "G.A. Maccacaro", Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; valeria.edefonti@unimi.it

Corresponding authors:
Federica Turati, PhD, Branch of Medical Statistics, Biometry, and Epidemiology "G.A. Maccacaro", Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Milan, Italy; federica.turati@unimi.it
Katherine France, DMD, MBE, Department of Oral Medicine, University of Pennsylvania, Philadelphia, USA; kfrance@upenn.edu

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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 demonstrated that antibiotic prophylaxis is associated with reduced risk of infective endocarditis following invasive dental procedures in high-risk subjects. This association was not proven for subjects with moderate risk, nor for those with low/unknown risk.

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

Tweet: This #metaanalysis demonstrated that #antibioticprophylaxis is associated with reduced risk of #infectiveendocarditis following invasive #dentalprocedures in high-risk subjects, supporting current #AHA and #ESC guidelines.

Abstract

Importance: The association between antibiotic prophylaxis (AP) and infective endocarditis (IE) after invasive dental procedures (IDPs) is still unclear. Indications for AP were restricted by guidelines beginning in 2007.

Objective: To systematically review and analyse existing evidence on the association between AP and IE following IDPs.

Data Sources: We systematically searched PubMed, Cochrane-CENTRAL, Scopus, Web of Science, Proquest, Embase, Dentistry and Oral Sciences Source, and clinicaltrials.gov, from inception to May 2023.

Study selection: Studies on the association between AP and IE following IDPs or time-trend analyses of IE incidence pre- and post-current AP 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 IE following IDPs in patients receiving AP versus not was computed by random-effects meta-analysis.

Main Outcomes and Measures: The outcome of interest was the incidence of IE following IDPs, in relation to AP.

Results: Of 11,217 records identified, 30 were included (1,152,345 IE cases). Of them, 8 (including 12 sub-studies) were either case-control/crossover, cohort studies, or self-controlled case-series, while 22 were time-trend studies; all were of good quality. Eight of the 12 case-control/crossover, cohort or self-controlled case-series sub-studies performed a formal statistical analysis; 5 supported a protective role of AP, especially among high-risk subjects, while 3 did not. By meta-analysis, AP was associated with a significantly lower risk of IE after IDPs in high-risk subjects (pooled-RR=0.41, 95% confidence interval 0.29-0.57; p for heterogeneity=0.513; I^2=0%). Nineteen of the 22 time-trend studies performed a formal pre-post statistical analysis; 9 found no significant changes in IE incidence, 7 demonstrated a significant increase for the overall population or sub-populations (high- and moderate-risk subjects, *Streptococcus*-IE, and *viridans group streptococci*-IE), whereas 3 found a significant decrease for the overall population and among oral *Streptococcus*-IE.

Conclusions and Relevance: While results from time-trend studies are inconsistent, data from case-control/crossover, cohort, and self-controlled studies showed that use of AP is associated with reduced risk of IE following IDPs in high-risk subjects, while no association was proven for low/unknown-risk subjects, thereby supporting current American

Heart Association and European Society of Cardiology recommendations. Currently, there is insufficient data to support any benefit of AP in subjects at moderate risk.

Keywords: Infective endocarditis; Antibiotic prophylaxis; Invasive dental procedures; Evidence-based policy development; Guidelines; Systematic review; Meta-analysis.

Introduction

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

For several decades, the evidence surrounding antibiotic prophylaxis (AP) for IE 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 IE[14]: AP was recommended for *all subjects with rheumatic or CHD 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, AP was recommended to a wide range of subjects, with controversies regarding subject 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 restriction to AP to different degrees. The AHA and ESC recommended AP to be considered only in subjects at the highest risk (i.e. those with a previous history of IE, prosthetic heart valves or prosthetic material used in cardiac valve repair, unrepaired cyanotic CHD, CHD subjects with prosthetic materials/devices placed in the previous six months or with residual defects and those undergoing surgical or interventional procedures) who undergo an invasive dental procedure (IDP), defined as procedure that involve manipulation of the gingival tissue, periapical region of teeth or perforation of the oral mucosa[17,18]. Conversely, AP was no longer recommended for subjects at moderate risk, i.e. subjects with acquired valvular heart disease, hypertrophic cardiomyopathy, and most of the other CHDs. This message was later reinforced in updated statements[19,20]. In parallel, in 2008, NICE advised against routine AP use[21], although in 2016 this message was revised with a softer statement suggesting AP not be *routinely* recommended[22].

The longstanding dispute over the effectiveness of AP to prevent IE following IDPs persists due to the scarcity of robust data and absence of randomised controlled trials (RCTs). In this setting, a comprehensive analysis of existing

evidence is valuable. Herein, we reviewed and meta-analysed the existing evidence to evaluate the association of AP and the incidence of IE following IDPs. In particular, we explored if AP is able to influence the association between IDP and IE (case-control/crossover, cohort studies, and self-controlled case-series) and if changes in the AP guidelines were associated with IE incidence over time (time-trend studies). Particular attention was given to stratified analyses by patient risk profile.

Methods

Data collection and reporting followed the guidelines for Systematic Review and Meta-Analysis of Observational Studies (MOOSE)[23] and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[24]. The study was conducted within the initiative World Workshop of Oral Medicine VIII (https://wworalmed.org) and registered in the National Institute for Health and Care Research (NIHR) International Prospective Register of Systematic Reviews (PROSPERO, CRD4202017398, https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=272740).

Data sources and search strategy

A systematic search of PubMed, Cochrane-CENTRAL, Scopus, Web of Science, Proquest, Embase, Dentistry and Oral Sciences Source (DOSS), 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**). References of selected articles were screened by hand to identify additional articles. Covidence software (Veritas Health Innovation, Melbourne, Australia) was used to support the review process.

Study selection

Studies were screened by two independent investigators (K.F., M.B., M.G., H.H., L.M., 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., P.D.D.) until consensus was reached.

Studies were selected if they included data on IE incidence and either: (1) data on the association between AP and IE following IDPs, or (2) a time-trend analysis of IE incidence around the time of AP guidelines implementation. The main outcome of interest was the IE incidence following IDPs, in relation to AP. 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 ($n \leq 10$ to eliminate positive outcome bias), letters, editorials, animal studies, and conference abstracts were excluded. Criteria for exclusion are listed in **eFigure 1**.

Quality assessment

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

Data extraction and visualization

Data extraction was performed independently by two investigators (M.B., M.G., H.H., K.F., G.L, F.S., F.T.). Disagreements were discussed with senior investigators (G.L., P.D.D., V.E.) until consensus was reached. Data were collected and summarized in structured tables, approved by all investigators. Sub-analyses 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 two possible types of assessment for the association between AP and IE incidence: (1) *direct assessment*: single comparison between subjects who underwent IDPs and received AP versus subjects who did not receive AP before IDPs, and (2) *indirect assessment*: the two-fold comparison between subjects who did or did not receive AP before IDPs, both versus subjects who did not undergo IDPs. Results from the indirect assessment were plotted using a forest plot. For time-trend studies, we

extracted any measure of IE incidence changes (e.g., incidence rate ratios, differences in slope, differences in annual percentage change) pre- and post-AP 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 IE in high-risk subjects who underwent IDPs and received AP versus subjects who did not receive AP before IDPs, 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 Statistical Software (version 18; Stata Corp., College Station, TX).

Results

Study selection and characteristics

A total of 11,217 records were identified. Following removal of duplicates (n=7,331), 3,886 titles and abstracts were screened. Of the 123 full-text articles retrieved, 30 were included, for a total of 1,152,345 IE cases (**eFigure 1**)[4-13,29–48]. All studies were observational: 8 were either case-control, case-crossover, cohort studies, or self-controlled case-series (4 included two separate sub-studies with different designs, for a total of 12 sub-studies) and 22 were time-trend studies. Twenty-seven (90%) were multi-centre (23 based on national databases) and 3 (10%) were single-centre studies. Twelve studies (40%) collected data from the United States, 13 (43%) from Europe (United Kingdom, France, Germany, The Netherlands, Sweden), three (10%) from Taiwan, and two (7%) from Canada.

Role of AP on the association between IDPs and IE: results from case-control/crossover, cohort studies, and self-controlled case-series

Seven of 12 sub-studies (58%) from case-control/crossover, cohort studies, and self-controlled case-series found a significant association between IDPs and IE (2 in the overall population[31,35], 3 among high-risk subjects[32,36], and 2 among moderate- and low/unknown-risk subjects[32,36]) (**Table 1 and eTable 1**). Regarding the role of AP on this association (8 sub-studies with available data), 3 out of the 4 sub-studies that provided a direct assessment found a

206 significantly lower risk of IE in high-risk subjects who underwent IDPs and received AP, compared to those who
207 underwent IDPs without AP (**Figure 1**)[32,36]; by random-effects meta-analysis, the pooled-RR for developing IE after
208 IDPs when receiving versus not receiving AP among high-risk subjects was 0.41 (95% confidence interval, CI 0.29-
209 0.57; p for heterogeneity=0.513 by χ^2 test; I^2 statistic=0%) (**Figure 1**). None of the pooled studies contained
210 overlapping data. Only one of the previous 4 sub-studies showed a significant inverse association between use of AP
211 before IDPs and IE for moderate-risk subjects[32], while no sub-studies found a significant association in low/unknown-
212 risk subjects. Regarding the indirect assessment, 3 out of 6 sub-studies found a significantly higher risk of IE in
213 subjects who underwent IDPs without AP, compared to subjects who did not undergo IDPs (one of them for the
214 overall population[31] and two in high-risk subjects only[32,36]); such sub-studies did not find significantly higher risks for
215 those who underwent IDPs receiving AP compared to those who did not undergo IDPs (**eFigure 2**).
216
217 *Association between AP guidelines change and the incidence of IE: results from time-trend studies*
218 Twenty-two time-trend studies were included in the systematic review (**Table 2 and eTable 2**). In time-trend
219 analyses, interrupted time series of IE incidence were collected at multiple time-points before and after AP guideline
220 changes (i.e. intervention). The effect of the intervention was generally evaluated by changes in the level and slope of
221 the post-intervention time series, compared to a counterfactual trend estimated based on the pre-intervention data. The
222 most frequent statistical approaches were segmented regression, which assumes the change has occurred at the
223 guideline change time-point, and change-point analysis, which assumes that changes, if any, might have occurred at
224 any point over time (details in **eTable 2)**. Ten studies found a significant change in trends of hospitalization for IE
225 after guideline changes (7 significant increase, 3 significant decrease), 9 studies did not detect significant changes, and
226 3 did not perform any formal statistical pre-post comparison. Among the 7 studies that found a significant increase in
227 IE rate, 4 were conducted in North America around the change in AHA guidelines and found a significant increase in
228 specific sub-populations (high- and moderate-risk subjects only[8,40], *Streptococcus* IE[39], or *viridans group*
229 *Streptococcus* [VGS]-IE[7]), while 3 were conducted in Europe around the NICE[47] or ESC guideline changes[5,44] and
230 found a significant increase in the overall population (**Table 2 and eTable 2**). Of note, two of these studies contained
231 overlapping data[7,39]. Conversely, 3 studies found a significant decrease in IE trends: 2 were conducted in the United

States around the AHA guideline change[11,13] and found a significant decrease in the overall population, while one was conducted in Europe around the release of new French national guidelines[46] and found a significant decrease in oral *Streptococcus* [OS]-IE only (**Table 2 and eTable 2**). No significant change in trends of IE incidence was demonstrated in low/unknown-risk subjects.

Quality assessment

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

Discussion

This systematic review and meta-analysis explored the role of AP on the incidence of IE following IDPs bringing together data from 30 studies and eight countries, for a total of 1,152,345 IE cases. Among the 12 case-control, case-crossover, cohort, or self-controlled case-series sub-studies, 8 formally evaluated a role of AP on IE after IDPs: 5 supported a protective role of AP, especially among high-risk subjects (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 high-risk subjects who received AP before IDPs were 59% (95% CI: 43-71%) less likely to develop IE compared to those who did not receive AP, thereby supporting current AHA and ESC recommendations.

This association was not proven for subjects with low/unknown risk nor for those with moderate risk. In parallel, we found that results from time-trend studies were inconsistent. While roughly one-third showed a significant increase in IE incidence after AP restriction, two-thirds showed no change or a significant decrease in incidence. None of the studies demonstrated a significant change in IE incidence in low/unknown-risk subjects.

The absence of RCTs addressing the association between AP and the incidence of IE remains a critical limitation for the establishment of definitive causal relationships. However, major challenges and restraints exist in performing an RCT. First, the rare incidence of IE engenders a large sample size requirement, extended trial duration and high resource demands, thereby impacting trial feasibility. Moreover, ethical concerns exist around withholding AP measures from at-risk populations[22]. In this setting, the synthesis of evidence from observational studies assumes particular significance. A meta-analysis of observational studies published in 2017 found that AP decreased the risk for bacteraemia (pooled-RR=0.53 [95% CI 0.49-0.57]), but not the risk for IE (pooled-OR=0.59 [95% CI 0.27-1.30]), likely due to limited statistical power[49]. Another meta-analysis of four studies revealed a 0% pooled-incidence of IE after IPDs among high-risk subjects receiving AP (0/413 subjects)[50] concluding that AP was likely to reduce IE incidence. These meta-analyses were limited by either small sample sizes of the included studies[49,50], evaluation of the overall population without stratifying for patient risk profile[49], or lack of a comparison group not exposed to AP[50]. Our meta-analysis brings together the most recent data – among which two large case-crossover/cohort studies[32,36] – allowing for control group comparison and group stratification, finally providing stronger – although still limited - evidence to support the role of AP in preventing IE after IDPs in high-risk patients.

Results from time-trend studies remain controversial. While 9 of the included studies showed no significant changes in trends of IE incidence after guidelines recommending AP restriction, 7 showed a significant increase, and 3 a significant decrease. Reasons for inconsistency of these results are numerous. The infrequent occurrence of IE 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 including studies across 20 countries showed that only approximately 25% of dentists were compliant[51]. Changes in the epidemiology of IE pathogens may have influenced results: around one third of IE cases may be attributed to oral *streptococci*, which are most commonly implicated in IE following IDPs, while the prevalence of *staphylococcus*-IE is rising[1,52]. Furthermore, pathogens'

epidemiology also differs by country[1,52]. Variation exists on duration of the defined exposure period, length of follow-up, and IE 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. Finally, we cannot exclude that any changes in IE incidence over time might have been driven by other factors that changed concurrently. Overall, time-trend studies exhibit significant limitations in effectively defining the role of AP in determining the incidence of IE.

Although one case-crossover study identified a small but significant effect of AP in reducing IE incidence following IDPs in subject 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 moderate-risk subjects are inconsistent. While recent studies continue to investigate and confirm the increased risk of IE for some of the lower-risk categories of subjects – e.g. those with cardiac implantable electronic devices (CIEDs) and hypertrophic cardiomyopathy - compared to the general population[53,54], there is currently insufficient evidence to suggest that AP is effective in reducing IE incidence in these subjects. 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 four studies. Meta-analysis was not feasible for indirect assessments due to the lack of an overarching statistical measure comparing the two study-specific RRs, nor for time-trend studies given the variety of statistical measures employed. The included studies are observational and are therefore affected by intrinsic biases. The definition of IE varied across studies, ranging from clinical criteria to International Classification of Diseases (ICD)-codes. ICD codes are affected by poor granularity, and coding variability exists across countries. Data on guideline adherence were limited and assumptions were made on AP prescription, administration, and regimen. Finally, external factors such as subjects' increased longevity, greater patient complexity and comorbidities, increased number of prosthetic valves and CIED placements, and improvements in IE diagnosis - which may, at least in part, explain an increase in IE incidence - were not accounted for by most studies.

Conclusions

Despite these limitations, we believe our data add valuable evidence in defining the role of AP in preventing IE following IDPs. While consistent conclusions from time-trend studies are difficult to extrapolate due to their intrinsic limitations and heterogeneity, data from case-control, case-crossover, cohort studies, and self-controlled case-series provide clearer evidence that AP is associated with reduced IE incidence following IDPs in high-risk subjects, while no association was proven for low/unknown-risk subjects, thereby supporting the current AHA and ESC recommendations. There are currently insufficient data to support the use of AP in subjects 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.

Acknowledgement Section

Contributors

FS, KF, FT, CHLH, TPS, GL, PBL, MT, PDD and VE contributed to the design and conceptualization of the study. FS, KF, FT, MG, MB, HH, LM, and VE contributed to data collection and verified the underlying data reported in the manuscript. FS, KF, FT, and VE contributed to data analysis or interpretation. VE led the World Workshop on Oral Medicine (WWOM) VIII group on infective endocarditis and had primary responsibility for the final content of the manuscript. All authors contributed to drafting the work or revising it critically for important intellectual content and approved the final version. All authors had full access to all the data, accept full responsibility of ensuring accuracy or integrity of any part of the work, approved the final version of the manuscript and agreed to submit it for publication.

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Non-author contributions

The WWOM VIII Steering Committee provided the conceptual framework and logistical support to produce the WWOM VIII Conference in May 2022 in Memphis, Tennessee, USA. In addition, the Steering Committee provided scientific and editorial critiques of this manuscript. The Steering Committee is listed below, in alphabetical order: Arwa M Farag (Saudi Arabia/USA), Timothy A Hodgson (UK), Catherine HL Hong (Singapore), Siri B Jensen (Denmark), Ross A Kerr (USA), Giovanni Lodi (Italy), Richeal N Riordain (Ireland), and Thomas P Sollecito (USA).

Access to Data and Data Analysis Statement

Valeria Edefonti had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Data sharing statement

Data are extracted from literature and are publicly available.

Conflict of interest disclosures

MT has research grant funding from the National Institutes for Health (USA), Delta Dental of Michigan Research and Data Institute's Research Committee, and Renaissance Health Service Corporation (USA). PBL was the liaison from the American Dental Association (ADA) to the American Heart Association (AHA) and served on the Guidelines Committees for the 2007 and 2021; he also has research grant funding from the National Institutes for Health, National Institute of Dental and Craniofacial Research (USA). None of these funding sources had any role in supporting the study design; in the collection, analysis, and interpretation of data; in the writing of the report, or in the decision to submit the paper for publication. All the other authors have no conflicts of interests to declare.

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495 **Figure Titles and Legends**

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497 **Figure 1. Forest plot and meta-analysis of relative risk measures comparing the risk of developing infective**
498 **endocarditis after invasive dental procedures in high-risk patients who received antibiotic prophylaxis versus**
499 **patients who did not (*direct assessment*).** Relative risks and 95% confidence intervals are showed for each study
500 using black squares and bars, respectively. The white diamond represents the pooled-relative risk and 95% confidence
501 intervals. AP: antibiotic prophylaxis; CI: confidence interval; IDP: invasive dental procedure; RR: relative risk.

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Table 1. Summary of study characteristics and main findings for case-control, case-crossover and cohort studies assessing the association between invasive dental procedures and infective endocarditis, as well as the role of antibiotic prophylaxis on this association.

Author, publication date, setting, country, study period, guidelines	Study design and study period	N of IE cases/ N of controls, N population at risk, Age	Association between IDPs and IE	Role of AP on the association between IDPs and IE
Chen et al., 2015[29] National data, Taiwan Taiwan guidelines **Partially overlapping data***	Case-crossover study 1999-2012	713 IE Mean age 58 years (SD 20)	**No significant association** between IDPs and IE (See eTable 1 for ORs for specific IDPs)	After adjusting for AP, **no difference in odds** of IE between case- and matched control-periods (See eTable 1 for ORs for specific IDPs)
Sun et al., 2017[30] National data, Taiwan Taiwan guidelines	Nested case-control study 1997-2010	237 IE Median age 1.2 years (IQR 0.6–3.0) Controls: 4,725 Similar age due to matching	No analysis for overall IDPs	**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 assessement]
Chen et al., 2018[31] National data, Taiwan Taiwan guidelines **Partially overlapping data***	Case-crossover study 2005-2011	9,120 IE Age ≥20 years	**No significant association** between IDPs and IE (See eTable 1 for the OR for the 12-weeks case-period)	NR
	Self-controlled case-series 2004-2013	8,181 IE Age ≥20 years	**Significant increase** in IE incidence in the **1-4 weeks after IDPs** (IRR of IE 1.14, 95% CI: 1.02-1.26, vs. control-period), but not for IE occurring 5-16 weeks after IDPs	**Significant increase** in IE incidence **in the 1-4 weeks 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 weeks after **No significant increase** in IE incidence **after IDPs with AP for all the timeframes** (1-4 weeks IRR of IE 1.07, 95% CI: 0.88-1.30, vs. no IDPs) [Indirect assessement]
Thornhill et al., 2022[32] National data, USA AHA guidelines 2007	Cohort study 2000-2015	3,774 IE/7,951,972 subjects Age ≥18 years	**No significant association** between IDPs and IE: OR to develop IE in the 4-weeks following IDPs in **high-risk**† subjects 1.17 (95% CI 0.74-1.92) vs. no IDPs **Significant direct association** between dental extraction and IE: - **high-risk**†: OR 9.22 (95% CI 5.54-15.88); - **moderate-risk**†: OR 3.25 (95% CI 1.61-6.46); - **low-risk**: OR 2.41 (95% CI 1.44-3.95) **Significant direct association** between oral surgery and IE: - **high-risk**†: OR 20.18 (95% CI 11.22-36.74); - **low-risk:** OR 3.74 (95% CI 1.79-7.15)	**Significant inverse association** between **use of AP** before IDPs and IE **in high-risk† subjects**: OR of IE 0.38 (95% CI 0.22-0.62) vs. no AP [Direct assessement] No significant association in moderate-risk† subjects
	Case-crossover study 2000-2015	3,774 IE Age ≥18 years	**Significant direct association** between IDPs and IE **in high-risk† subjects:** OR of IE 2.00 (95% CI: 1.59-2.52) vs. control-period No association between IDPs and IE in moderate-risk† or low/unknown-risk subjects	**Significant inverse association** between **use of AP** before IDPs and IE **in high-risk† subjects**: 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 **high-risk**† subjects: OR of IE 2.44 (95% CI: 1.87-3.18); Risk of IE after IDPs with AP vs. no IDPs in **high-risk**† subjects: OR of IE 1.20 (95% CI: 0.74-1.93) [Indirect assessement] **Significant inverse association** between use of AP before IDPs and IE in **moderate-risk** subjects†: OR of IE 0.34 (95% CI: 0.14-0.88) vs no AP [Direct assessement]
Tubiana et al., 2017[33] National data, France ESC guidelines 2015	Cohort study 2009-2014	267 IE/138,876 subjects Median age 74 years (IQR 63-80)	Study included only **high-risk**† subjects (prosthetic valves) **No significant association** between IDPs and IE: IRR to develop IE in the 3 months following IDPs 1.25 (95% CI: 0.82-1.82) vs. no IDPs	Study included only **high-risk**† subjects (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 assessement]

	Case-crossover 2009-2014	648 IE Median age 77 years (IQR 68-82)	Study included only **high-risk**† subjects (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 **high-risk**† subjects (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 assessement]
Thornhill et al., 2022[34] National data, England NICE guidelines 2008 **Overlapping data***	Case-crossover study 2010-2016	17,732 IE (4,296 with linked dental data) Mean age 61 years (SD 21) (62 years, SD 19, with linked dental data)	**Significant inverse association** between IDPs in the 3 months before IE and IE **in high-risk**† **subjects**: IRR of IE for the control-period 1.36 (95% CI: 1.16-1.59) vs. case-period	IE cases not receiving AP for IDPs: 7205/7340 (98.16%) IE cases receiving AP for IDPs: 135/7340 (1.84%) Total IDPs not receiving AP: 3,675,440/3,744,280 (98.16%) Total IDPs receiving AP: 68,840/3,744,280 (1.84%)
Thornhill et al., 2023[35] National data, England NICE guidelines 2008 **Overlapping data***	Case-crossover study 2010-2016	14,731 IE Mean age 62 years (SD 20)	**Significant direct association** between **dental extraction** and IE: OR to develop IE in the 3 months following IDPs 2.14 (95% CI: 1.22-3.76) vs. control-period Increased risk for other surgical scaling/gingival procedures as well, however not statistically significant	Assumed that no AP was administered given NICE guidelines 2008 In **high-risk**† subjects, estimated 50 (95% CI: 9-120) additional IE cases/100,000 dental extractions In **moderate-risk**† subjects, estimated 4 (95% CI: 1-9) additional IE cases/100,000 dental extractions
Thornhill et al., 2023[36] National data, USA AHA guidelines 2007	Cohort study 2000-2015	2,647 IE/1,678,190 subjects Age ≥18 years	**Significant direct association** between IDPs and IE: OR to develop IE in the 30 days following IDPs **- high-risk**†: 6.58 (95% CI: 2.76-20.33) vs. no IDPs; - **low/unknown-risk**: 2.06 (95% CI: 1.07-4.33) vs. no IDPs; - **moderate-risk**†: 4.09 (95% CI: 1.18-11.99) vs. no IDPs for oral surgery	**Significant inverse association** between **AP** before IDPs and IE **in high-risk**† **subjects**: OR to develop IE 0.20 (95% CI: 0.06-0.53) vs. no AP [Direct assessement] No significant association in moderate-risk† or low/unknown-risk subjects
	Case-crossover study 2000-2015	2,647 IE Age ≥18 years	**Significant direct association** between IDPs and IE **in high-risk**† **subjects**: OR of IE 2.91 (95% CI: 2.15-3.95) vs. control-period No association between IDPs and IE in moderate-risk† or low/unknown-risk subjects	**No significant association** between **AP** before IDPs and IE **in high-risk**† **subjects**: OR of IE 0.50 (95% CI: 0.17-1.49) vs. no AP [Direct assessement] Risk of IE after IDPs without AP **in high-risk**† **subjects**: OR of IE 3.14 (95% CI: 2.28-4.32) vs. no IDPs; Risk of IE after IDPs with AP **in high-risk**† **subjects**: OR of IE 1.57 (95% CI: 0.55-4.44) vs. no IDPs [Indirect assessement] No significant association in moderate-risk† or low/unknown-risk subjects

Additional details are reported in eTable 1.
* Chen et al., 2018[31] partially overlaps with Chen et al., 2015[29]; Thornhill et al., 2023[35] overlaps with Thornhill et al., 2022.[34]
† High-risk subjects were defined as subjects 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 (CHD) (i.e. unrepaired cyanotic CHD, CHD subjects with prosthetic materials/devices placed in the previous 6 months or with residual defects or those undergoing surgical or interventional procedures). Moderate-risk subjects were defined as subjects with cardiac conditions that included acquired valvular heart disease, hypertrophic cardiomyopathy, and most of the other CHDs.

Abbreviations: AHA: American Heart Association; AP: antibiotic prophylaxis; CI: confidence interval; ESC: European Society of Cardiology; IDP: invasive dental procedure; IE: infective endocarditis; IQR: interquartile range; IRR: incidence rate ratio; N: number; NICE: National Institute for Health and Care Excellence; NR: not reported; OR: odds ratio; RR: relative risk; SD: standard deviation.

518 519 **Table 2. Summary of study characteristics and main findings for time-trend studies assessing the association between AP guideline change and the incidence of infective endocarditis.**

Author, publication date, setting, country, study period, guidelines	N of IE cases, Age	Reported IE measure before and after guidelines		Association between AP guideline change and incidence of IE and reported measure of change (when available)
		Before	After	
Bates et al., 2017[6] Multicentre, USA 2003-2014 AHA guidelines 2007 **Overlapping data***	841 IE Median age 13 years (IQR 9-15)	Mean IR 4.6/10,000 child-6 months	Mean IR 4.6/10,000 child-6 months	Study included only oral *Streptococcus* IE **No significant change** in trends of IE before and after guidelines: difference in slope NR (p=0.895) CHD: NS
Bikdeli et al.,2013[11] National data, USA 1999-2010 AHA guidelines 2007	262,658 IE Mean age 79.4 years (SD 8.0) (1999-2000) – Mean age 79.2 years (SD 8.8) (2009-2010)	IR 1999: 72.0/100,000 per year 2005: 83.5/100,000 per year 2007: 81.4/100,000 per year	IR 2008: 79.2/100,000 per year 2009: 74.9/100,000 per year 2010: 70.6/100,000 per year	**Significant decrease** in trends of IE post- compared to pre-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)
De Simone et al., 2015[12] National data, USA 2000-2011 AHA guidelines 2007 **Overlapping data***	Projected nationwide estimates: from 17,110 (2003) to 13,334 (2010) 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., 2021[41] National data, USA 1970-2018 AHA guidelines 2007 **Overlapping data***	269 IE Median age 67 (IQR 52-78)	IR 2000-2009: Females 5.4 (95% CI: 3.7-7.8) /100,000 per year Males 7.8 (95% CI: 5.5-10.7) /100,000 per year	IR 2010-2018: Females 5.7 (95% CI: 3.9-8.0) /100,000 per year Males 13.3 (95% CI: 10.2-16.9) /100,000 per year	No overall analysis **No significant increase** in trends of VGS-IE incidence before and after guidelines: difference NS (p=0.482)
Pant et al., 2015[39] National data, USA 2000-2011 AHA guidelines 2007 **Overlapping data***	457,052 IE Age NR	IR 2000: 11/100,000 per year IR 2006: 14/100,000 per year	IR 2008: 14/100,000 per year IR 2011: 15/100,000 per year	**No significant change** in trends of IE before and after guidelines: difference in slope 0.06 (95% CI: -0.36, +0.49, p=0.74) *Streptococcus* IE: significant increase (p=0.002) *Staphylococcus* IE: NS Valve replacement for IE: NS
Pasquali et al., 2012[38] Multicentre, USA 2003-2010 AHA guidelines 2007 **Overlapping data***	1,157 IE Median age 2.9 years (IQR 2.5 months - 12.4 years)	Annual change in IE cases per 1,000 hospital admissions: -5.9 (95% CI: -9.9, -1.8)	Annual change in IE cases per 1,000 hospital admissions: -11.5 (95% CI: -15.7, -7.1)	**No significant change** in trends of IE before and after guidelines: annual change difference -5.9% (95% CI: -13.3%, +2.2%, p=0.150) Oral *Streptococcus* IE: NS IE in CHD: NS
Rogers et al., 2008[37] Single centre, USA 2001-2008 AHA guidelines 2007	396 IE Age NR	39 to 50 IE incident cases per month	42 IE incident cases per month	**No substantial change** in IE incidence before and after guidelines
Sakai-Bizmark et al., 2017[7] National data, USA 2001-2012 AHA guidelines 2007 **Overlapping data***	3,748 IE Median age 8.4 years (IQR 1.6–13.6)	IR 2001: 3.48/1,000,000 per year IR 2006: 5.26/1,000,000 per year	IR 2008: 4.06/1,000,000 per year IR 2012: 4.14/1,000,000 per year	**No significant change** in trends of IE before and after guidelines: difference in slope -0.02 (95% CI: -0.23, +0.20, p=0.89) VGS-IE ≥10 years: significant increase (p<0.01), VGS-IE <10 years NS
Thornhill et al., 2018[40] National data, USA 2003-2015 AHA guidelines 2007	20,340 IE Age >18 years	IR - **high-risk‡:** 11.04 IE cases/100,000 per month - **moderate-risk‡:** 1.9 IE cases/100,000 per month - low/unknown-risk: NR	IR - **high-risk‡:** 30.6 IE cases/100,000 per month - **moderate-risk‡:** 3.4 IE cases/100,000 per month - low/unknown-risk: NR	**Significant increase in trends** of IE post compared to pre-guidelines **among high-risk‡ subjects** (177% estimated increase, 95% CI: 66-361%) **and moderate-risk‡ subjects** (75% estimated increase, 95% CI: 3-300%) **No significant change** in trends of IE before and after guidelines **among low/unknown-risk subjects** (12% estimated increase, 95% CI: -29, +76%)
Toyoda et al., 2017[13] Multicentre, USA 1998-2013 AHA guidelines 2007	75,829 IE Mean age 62.3 years (SD 18.9)	NR	NR	**Significant decrease** in trends of IE before and after guidelines: difference in slope -0.07 (95% CI: -0.11, -0.02, p=0.004) Oral *Streptococcus* IE: significant decrease (p=0.002) *Staphylococcus* IE: NS
Garg et al., 2019[8] Multicentre, Canada 2002-2014 AHA guidelines 2007	7,551 IE (6684 subjects) Median age 63 years (IQR 48-75)	2002-2006: 395 - 448 IE incident cases per year	2008-2014: 447 - 813 IE incident cases per year	**No significant change** in trends of IE before and after guidelines (p value NR) Significant increase in trends of IE after 2010 in both **high-** and **moderate- risk‡** subjects

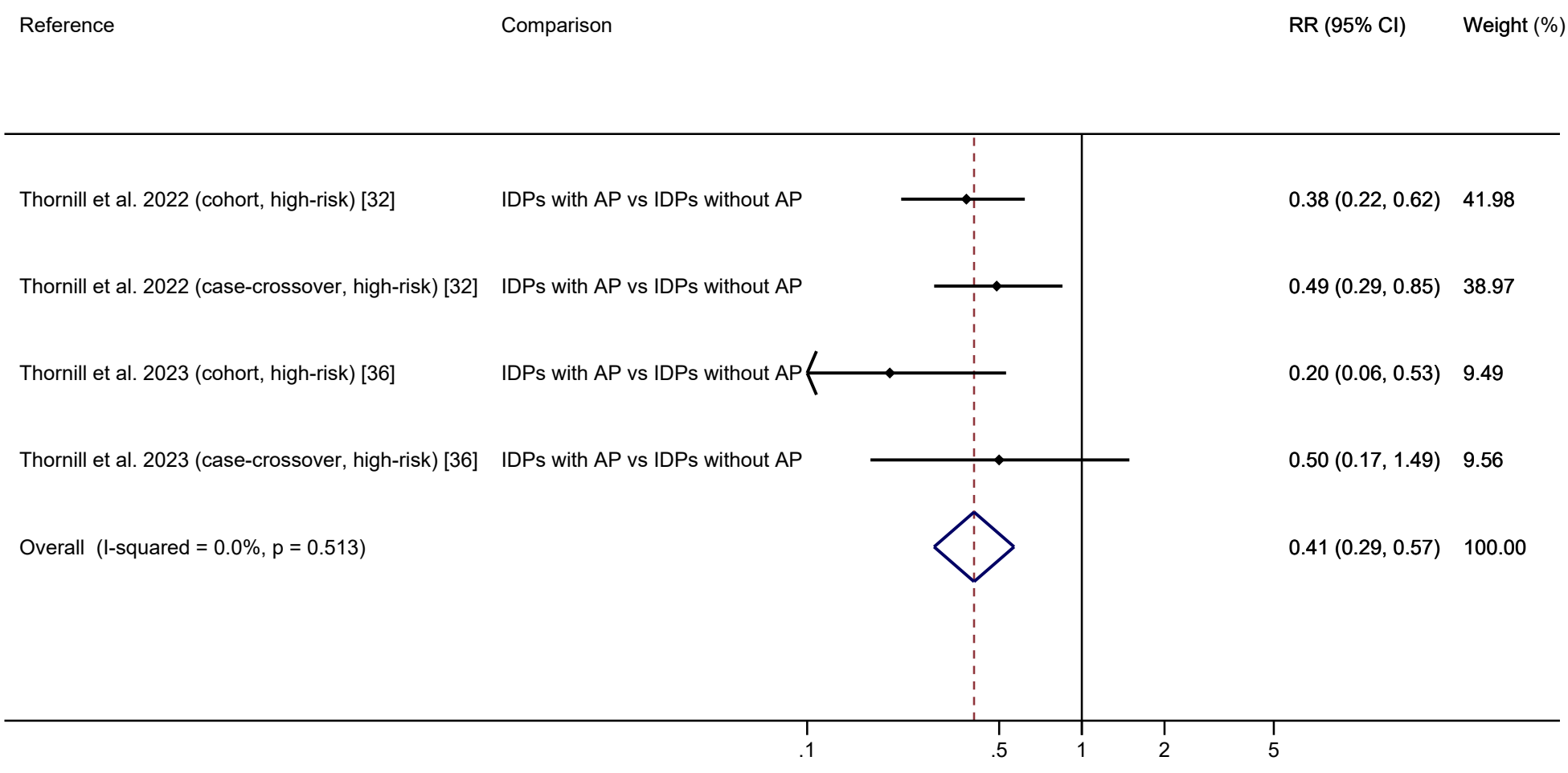
Mackie et al., 2016[42] National data, Canada 2002-2013 AHA guidelines 2007	9,431 IE Median age 55 years (IQR 38-71)	Monthly change in IE cases per 10,000,000 general population: 0.05 (95% CI: 0.005-0.009)	Monthly change in IE cases per 10,000,000 general population: 0.07 (95% CI: NR)	**No significant change** in trends of IE before and after guidelines: difference in slope NR (p=0.521)
Duval et al., 2012[46] Multicentre, France 1991-1999 France guidelines 2002	993 IE Mean age: 1991: 58 years (SD 17) 1999: 60 years (SD 16) 2008: 62 years (SD 16)	IR 1991: 35.2 IE cases/1,000,000 per year IR 1999: 33.5 IE cases/1,000,000 per year	IR 2008: 32.1 IE cases/1,000,000 per year	**No significant differences** in IE incidence rates among the three time points (two before and one after guidelines) (p=0.980) *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=0.03) *Staphylococcus* IE in previously known native heart disease: NS
Knirsch et al, 2020[43] Singlecentre, Switzerland 1995-2017 AHA guidelines 2007	25 IE Median age 7 years (IQR 0.1–19)	IR 1995–2005: 0.195/1,000 CHD pediatric subjects per year	IR 2006–2017: 0.399/1,000 CHD pediatric subjects per year	Study included CHD subjects only **No change** in IE incidence post- compared to pre-guidelines (p=0.072)
Dayer et al., 2015[47] National data, England 2000-2013 NICE guidelines 2008 **Overlapping data***	19,804 IE Mean age: 2000-2007: 59 years (SD 20) 2008-2013: 59 years (SD 21)	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<0.0001) **High-risk‡:** significant increase in trends of IE incidence (p=0.025) **Moderate-‡ or low-risk**: significant increase in trends of IE incidence (p=0.0002)
Quan et al., 2020[9] National data, England 1998-2017 NICE guidelines 2008 **Overlapping data***	35,752 IE Age NR	IR 1998: 22.2 - 41.3 /1,000,000 per year depending on ICD-10 code-based criteria	IR 2017: 42.0 - 67.7/1,000,000 per year 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 codes criteria (different change-points identified by different models)
Shah et al., 2020[48] National data, Scotland 1990-2014 NICE guidelines 2008	7,638 IE (7513 subjects) Mean age: 65 years (SD 17)	IR 1990: 5.3/100,000 per year IR 2007: 7.6/100,000 per year	IR 2009: 7.8/100,000 per year IR 2014: 8.1100,000 per year	**No significant increase** in incidence of IE pre- and post-guideline: RR of change 1.06 (95% CI: 0.94-1.20)
Keller et al., 2017[4] National data, Germany 2005-2014 ESC guidelines 2009	94,364 IE Age NR	2005-2008: 8,283 IE incident cases per year	2010-2014: 10,455 IE incident cases per year	**Relative increase in the annual IE incidence** (26%) post- compared to pre-guidelines
Weber et al., 2022[44] Multicentre, Germany 1994-2018 ESC guidelines 2009	4,917 IE Median age 65 years (IQR 54-73)	NR	NR	**Significant increase in trends** of IE involving the mitral valve before and after guidelines (p=0.035) **No significant changes** in trends of IE before and after guidelines for aortic, pulmonary, and tricuspid valve *Streptococcus* IE: significant increase (p=0.002) *Staphylococcus* IE: NS *Enterococcus* IE: NS Other pathogens: NS
van den Brink et al., 2017[5] National data, The Netherlands 2005-2011 ESC guidelines 2009	5,213 IE Mean age 67.5 years (range 22-97)	IR 2005: 30.2 IE/1,000,000 per year	IR 2011: 62.9 IE/1,000,000 per year	**Significant increase in IE incidence** post- compared to pre- guidelines: IRR 1.33 (95% CI: 1.21-1.46, p<0.001) in 2009
Krul et al., 2015[45] Single centre, The Netherlands 2008-2013 The Netherlands guidelines 2008	89 IE Median age 68 years (IQR 59-75)	NR	NR	**Increase in the annual IE incidence**, especially post-guidelines between 2011 and 2013
Vähäsarja et al., 2020[10] National data, Sweden 2008-2017 Sweden guidelines 2012	4,649 IE Mean age 65 years (range 17-100)	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, +0.082) VGS-IE: NS *Staphylococcus aureus* IE: NS

Additional details are reported in eTable 2.

*DeSimone et al.,2015, Sakai-Bizmark et al.,2017, and DeSimone et al., 2021, overlap with Pant et al., 2015 (National Inpatient Sample database). Quan et al., 2020, overlaps with Dayer et al., 2015 (National Hospital Episode Statistics database). Bates et al., 2017, overlaps with Pasquali et al., 2012 (Pediatric Health Information System database).

† DeSimone et al., 2015, included also an analysis derived from the hospital internal database and the Rochester Epidemiology Project (REP) database, which was excluded due to duplicate data with DeSimone et al., 2021.
‡ High-risk subjects were defined as subjects 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 CHD subjects undergoing surgical or interventional procedures). Moderate-risk subjects were defined as subjects with cardiac conditions that included acquired valvular heart disease, hypertrophic cardiomyopathy, and most of the other CHDs.

Abbreviations: AHA: American Heart Association; AP: antibiotic prophylaxis; CHD: congenital heart disease; CI: confidence interval; ESC: European Society of Cardiology; IE: infective endocarditis; IQR: interquartile range. IR: incidence rate; IRR: incidence rate ratio; NICE: National Institute for Health and Care Excellence; NR: not reported; NS: not significant; RR: relative risk; SD: standard deviation; VGS: *viridans* group *Streptococcus*.


Reference
Comparison
RR (95% CI)
Weight (%)
Thornill et al. 2022 (cohort, high-risk) [32]
IDPs with AP vs IDPs without AP
0.38 (0.22, 0.62)
41.98
Thornill et al. 2022 (case-crossover, high-risk) [32]
IDPs with AP vs IDPs without AP
0.49 (0.29, 0.85)
38.97
Thornill et al. 2023 (cohort, high-risk) [36]
IDPs with AP vs IDPs without AP
0.20 (0.06, 0.53)
9.49
Thornill et al. 2023 (case-crossover, high-risk) [36]
IDPs with AP vs IDPs without AP
0.50 (0.17, 1.49)
9.56
Overall (I-squared = 0.0%, p = 0.513)
0.41 (0.29, 0.57)
100.00
.1
.5
1
2
5