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

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54
55 **Manuscript word count:** 3,092

56 **Key points**

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

59 **Findings:** This systematic review and meta-analysis including data on 1,152,345 cases of infective endocarditis
60 demonstrated that antibiotic prophylaxis is associated with reduced risk of infective endocarditis following invasive
61 dental procedures in high-risk subjects. This association was not proven for subjects with moderate risk, nor for those
62 with low/unknown risk.

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

65

66

67

68 **Tweet:** This #metaanalysis demonstrated that #antibioticprophylaxis is associated with reduced risk of
69 #infectiveendocarditis following invasive #dentalprocedures in high-risk subjects, supporting current #AHA and
70 #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

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

99

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

102 **Introduction**

103 Infective endocarditis (IE) is a rare but life-threatening condition^{1,2}. The estimated global crude incidence ranges from
104 1.5 to 11.6 cases/100,000 person-years³, but recent studies suggest the incidence is rising⁴⁻¹⁰. Incidence rates are
105 higher in subjects with underlying cardiac conditions such as prosthetic heart valves, congenital heart disease (CHD),
106 or non-cardiac conditions such as presence of central venous catheters, haemodialysis for renal failure, and
107 intravenous drug use¹. Despite optimal treatment, IE is associated with high morbidity and an estimated mortality rate
108 at one year of 30-40%^{1,2,11-13}. Therefore, the identification of effective prevention strategies is crucial.

109 For several decades, the evidence surrounding antibiotic prophylaxis (AP) for IE prevention has undergone substantial
110 evolution, prompting a reassessment of traditional approaches. In 1955, the American Heart Association (AHA) issued
111 the first statement on prevention of IE¹⁴: AP was recommended for *all subjects with rheumatic or CHD undergoing*
112 *dental extractions and other dental manipulations which disturb the gums, the removal of tonsils and adenoids, the*
113 *delivery of pregnant women, and operations on the gastrointestinal or urinary tracts*¹⁴. In the ensuing 50 years, AP
114 was recommended to a wide range of subjects, with controversies regarding subject and procedure selections, choice
115 of antibiotics, and overall risk-benefit ratio^{15,16}. Between 2007 and 2009, the AHA, the European Society of
116 Cardiology (ESC), and the National Institute for Health and Care Excellence (NICE) recommended restriction to AP
117 to different degrees. The AHA and ESC recommended AP to be considered only in subjects at the highest risk (i.e.
118 those with a previous history of IE, prosthetic heart valves or prosthetic material used in cardiac valve repair,
119 unrepaired cyanotic CHD, CHD subjects with prosthetic materials/devices placed in the previous six months or with
120 residual defects and those undergoing surgical or interventional procedures) who undergo an invasive dental
121 procedure (IDP), defined as procedure that involve manipulation of the gingival tissue, periapical region of teeth or
122 perforation of the oral mucosa^{17,18}. Conversely, AP was no longer recommended for subjects at moderate risk, i.e.
123 subjects with acquired valvular heart disease, hypertrophic cardiomyopathy, and most of the other CHDs. This
124 message was later reinforced in updated statements^{19,20}. In parallel, in 2008, NICE advised against routine AP use²¹,
125 although in 2016 this message was revised with a softer statement suggesting AP not be *routinely* recommended²².

126 The longstanding dispute over the effectiveness of AP to prevent IE following IDPs persists due to the scarcity of
127 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) guidelines²⁴. 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.

154 Studies were selected if they included data on IE incidence and either: (1) data on the association between AP and IE
155 following IDPs, or (2) a time-trend analysis of IE incidence around the time of AP guidelines implementation. The
156 main outcome of interest was the IE incidence following IDPs, in relation to AP. Clinical trials, observational
157 prospective or retrospective cohort studies, case-crossover studies, case-control studies, self-controlled case-series, or
158 longitudinal ecological time-trend studies were all candidates for inclusion. Reviews, case reports, case-series ($n \leq 10$ to
159 eliminate positive outcome bias), letters, editorials, animal studies, and conference abstracts were excluded. Criteria
160 for exclusion are listed in **eFigure 1**.

162 *Quality assessment*

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

170 *Data extraction and visualization*

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

175 From case-control, case-crossover and cohort studies, we extracted results of the two possible types of assessment for
176 the association between AP and IE incidence: (1) *direct assessment*: single comparison between subjects who
177 underwent IDPs and received AP versus subjects who did not receive AP before IDPs, and (2) *indirect assessment*: the
178 two-fold comparison between subjects who did or did not receive AP before IDPs, both versus subjects who did not
179 undergo IDPs. Results from the indirect assessment were plotted using a forest plot. For time-trend studies, we

180 extracted any measure of IE incidence changes (e.g., incidence rate ratios, differences in slope, differences in annual
181 percentage change) pre- and post-AP guidelines.

182 183 *Statistical analysis*

184 For the *direct assessment*, we performed a random-effects meta-analysis of relative risk (RR) estimates (RR, odds
185 ratio [OR], or incidence rate ratio [IRR]) of developing IE in high-risk subjects who underwent IDPs and received AP
186 versus subjects who did not receive AP before IDPs, by using the Der Simonian and Laird method²⁷. Heterogeneity
187 among studies was assessed using the χ^2 test and inconsistency was quantified using the I^2 statistic²⁸. All statistical
188 analyses were performed using Stata Statistical Software (version 18; Stata Corp., College Station, TX).

189 190 **Results**

191 *Study selection and characteristics*

192 A total of 11,217 records were identified. Following removal of duplicates (n=7,331), 3,886 titles and abstracts were
193 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}.

194 All studies were observational: 8 were either case-control, case-crossover, cohort studies, or self-controlled case-series
195 (4 included two separate sub-studies with different designs, for a total of 12 sub-studies) and 22 were time-trend
196 studies. Twenty-seven (90%) were multi-centre (23 based on national databases) and 3 (10%) were single-centre
197 studies. Twelve studies (40%) collected data from the United States, 13 (43%) from Europe (United Kingdom, France,
198 Germany, The Netherlands, Sweden), three (10%) from Taiwan, and two (7%) from Canada.

199 200 *Role of AP on the association between IDPs and IE: results from case-control/crossover, cohort studies, and self- 201 controlled case-series*

202 Seven of 12 sub-studies (58%) from case-control/crossover, cohort studies, and self-controlled case-series found a
203 significant association between IDPs and IE (2 in the overall population^{31,35}, 3 among high-risk subjects^{32,36}, and 2
204 among moderate- and low/unknown-risk subjects^{32,36}) (**Table 1 and eTable 1**). Regarding the role of AP on this
205 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 subjects³², 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 population³¹ 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**).

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* IE³⁹, or *viridans group*
 229 *Streptococcus* [VGS]-IE⁷), while 3 were conducted in Europe around the NICE⁴⁷ 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 guidelines⁴⁶ 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 series³¹), while 3 did not (nested case-control³⁰ and cohort and case-crossover studies³³). 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.

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

262 The absence of RCTs addressing the association between AP and the incidence of IE remains a critical limitation for
263 the establishment of definitive causal relationships. However, major challenges and restraints exist in performing an
264 RCT. First, the rare incidence of IE engenders a large sample size requirement, extended trial duration and high
265 resource demands, thereby impacting trial feasibility. Moreover, ethical concerns exist around withholding AP
266 measures from at-risk populations²². In this setting, the synthesis of evidence from observational studies assumes
267 particular significance. A meta-analysis of observational studies published in 2017 found that AP decreased the risk
268 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]),
269 likely due to limited statistical power⁴⁹. Another meta-analysis of four studies revealed a 0% pooled-incidence of IE
270 after IPDs among high-risk subjects receiving AP (0/413 subjects)⁵⁰ concluding that AP was likely to reduce IE
271 incidence. These meta-analyses were limited by either small sample sizes of the included studies^{49,50}, evaluation of the
272 overall population without stratifying for patient risk profile⁴⁹, or lack of a comparison group not exposed to AP⁵⁰. Our
273 meta-analysis brings together the most recent data – among which two large case-crossover/cohort studies^{32,36} –
274 allowing for control group comparison and group stratification, finally providing stronger – although still limited –
275 evidence to support the role of AP in preventing IE after IDPs in high-risk patients.

276 Results from time-trend studies remain controversial. While 9 of the included studies showed no significant changes in
277 trends of IE incidence after guidelines recommending AP restriction, 7 showed a significant increase, and 3 a
278 significant decrease. Reasons for inconsistency of these results are numerous. The infrequent occurrence of IE
279 necessitates large populations to generate adequate statistical power. Studies assessing prescription data are scant, and
280 most studies assume guideline adherence. However, a recent systematic review including studies across 20 countries
281 showed that only approximately 25% of dentists were compliant⁵¹. Changes in the epidemiology of IE pathogens may
282 have influenced results: around one third of IE cases may be attributed to oral *streptococci*, which are most commonly
283 implicated in IE following IDPs, while the prevalence of *staphylococcus*-IE is rising^{1,52}. Furthermore, pathogens'

284 epidemiology also differs by country^{1,52}. Variation exists on duration of the defined exposure period, length of follow-
285 up, and IE diagnostic criteria. While age and sex were often considered as confounders, comorbidities,
286 immunosuppression, and exposure to other invasive procedures or presence of intravascular devices were not
287 assessed. Finally, we cannot exclude that any changes in IE incidence over time might have been driven by other
288 factors that changed concurrently. Overall, time-trend studies exhibit significant limitations in effectively defining the
289 role of AP in determining the incidence of IE.

290 Although one case-crossover study identified a small but significant effect of AP in reducing IE incidence following
291 IDPs in subject at moderate risk³², this was not confirmed in 3 other case-crossover³⁶ and cohort studies^{32,36}. Similarly,
292 results from time-trend studies regarding moderate-risk subjects are inconsistent. While recent studies continue to
293 investigate and confirm the increased risk of IE for some of the lower-risk categories of subjects – e.g. those with
294 cardiac implantable electronic devices (CIEDs) and hypertrophic cardiomyopathy - compared to the general
295 population^{53,54}, there is currently insufficient evidence to suggest that AP is effective in reducing IE incidence in these
296 subjects. Further studies are needed to clarify this topic.

297 **Limitations**

298 This study has limitations. Evidence was derived from different study designs with a different potential to answer the
299 study question, from the more informative direct assessments to the least informative time-trend studies. Meta-
300 analysis was limited to direct assessment and included only four studies. Meta-analysis was not feasible for indirect
301 assessments due to the lack of an overarching statistical measure comparing the two study-specific RRs, nor for time-
302 trend studies given the variety of statistical measures employed. The included studies are observational and are
303 therefore affected by intrinsic biases. The definition of IE varied across studies, ranging from clinical criteria to
304 International Classification of Diseases (ICD)-codes. ICD codes are affected by poor granularity, and coding
305 variability exists across countries. Data on guideline adherence were limited and assumptions were made on AP
306 prescription, administration, and regimen. Finally, external factors such as subjects' increased longevity, greater
307 patient complexity and comorbidities, increased number of prosthetic valves and CIED placements, and improvements
308 in IE diagnosis - which may, at least in part, explain an increase in IE incidence - were not accounted for by most
309 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.

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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

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

348 **Data sharing statement**

349 Data are extracted from literature and are publicly available.

351 **Conflict of interest disclosures**

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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 assessment]
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 IDPs 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 assessment]
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 assessment] 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 assessment] 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 assessment] 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 assessment]
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 assessment]

	Case-crossover study 2009-2014	648 IE Median age 77 years (IQR 68-82)	Study included only high-risk† subjects (oral <i>streptococcal</i> 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 <i>streptococcal</i> 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]
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 assessment] 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 assessment] 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 assessment] No significant association in moderate-risk† or low/unknown-risk subjects

Additional details are reported in eTable 1.

* Chen et al., 2018³¹ partially overlaps with Chen et al., 2015²⁹; Thornhill et al., 2023³⁵ 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.

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 <i>Streptococcus</i> 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) <i>Streptococcus</i> IE: significant increase (p=0.002) <i>Staphylococcus</i> 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 <i>Streptococcus</i> 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 <i>Streptococcus</i> IE: significant decrease (p=0.002) <i>Staphylococcus</i> 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) <i>Oral Streptococcus</i> IE: NS <i>Staphylococcus</i> IE: NS Previously known native heart disease: NS <i>Oral Streptococcus</i> IE in previously known native heart disease: significant decrease (p=0.03) <i>Staphylococcus</i> 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: 8.1/100,000 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 <i>Streptococcus</i> IE: significant increase (p=0.002) <i>Staphylococcus</i> IE: NS <i>Enterococcus</i> 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 <i>Staphylococcus aureus</i> 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).

524 † 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
525 duplicate data with DeSimone et al., 2021.

526 ‡ 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,
527 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
528 conditions that included acquired valvular heart disease, hypertrophic cardiomyopathy, and most of the other CHDs.
529

530 Abbreviations: AHA: American Heart Association; AP: antibiotic prophylaxis; CHD: congenital heart disease; CI: confidence interval; ESC: European Society of Cardiology; IE:
531 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
532 significant; RR: relative risk; SD: standard deviation; VGS: *viridans* group *Streptococcus*.
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