Received: 10 February 2023 | Revised: 27 March 2023 | Accepted: 7 April 2023

DOI: 10.1111/odi.14585

ORAL DISEASES Leading in Oral, Maxillofacial, Head & Neck Medicine WILEY

ORIGINAL ARTICLE

Endocarditis, invasive dental procedures, and antibiotic prophylaxis efficacy in US Medicaid patients

Martin H. Thornhill[1,2] | Teresa B. Gibson[3] | Frank Yoon[3] | Mark J. Dayer[4,5] | Bernard D. Prendergast[6] | Peter B. Lockhart[2] | Patrick T. O'Gara[7] | Larry M. Baddour[8]

[1]Unit of Oral & Maxillofacial Medicine, Surgery and Pathology, School of Clinical Dentistry, University of Sheffield, Sheffield, UK

[2]Department Oral Medicine/Oral & Maxillofacial Surgery, Atrium Health – Carolinas Medical Center, Charlotte, North Carolina, USA

[3]IBM Watson Health, Ann Arbor, Michigan, USA

[4]Department of Cardiology, Somerset Foundation Trust, Taunton, UK

[5]Faculty of Health, University of Plymouth, Plymouth, UK

[6]Department of Cardiology, St Thomas' Hospital and Cleveland Clinic, London, UK

[7]Cardiovascular Medicine Division, Brigham and Women's Hospital, and Harvard Medical School, Boston, Massachusetts, USA

[8]Division of Infectious Diseases, Departments of Medicine and Cardiovascular Medicine, Mayo Clinic College of Medicine, Rochester, Minnesota, USA

Correspondence
Martin H. Thornhill, Unit of Oral & Maxillofacial Medicine, Surgery and Pathology, School of Clinical Dentistry, University of Sheffield, School of Clinical Dentistry, Claremont Crescent, Sheffield S10 2TA, UK.
Email: m.thornhill@sheffield.ac.uk

Funding information
Delta Dental of Michigan Research Committee, Grant/Award Number: N/A; Renaissance Health Service Corporation, Grant/Award Number: N/A

Abstract

Objective: Antibiotic prophylaxis is recommended before invasive dental procedures to prevent endocarditis in those at high risk, but supporting data are sparse. We therefore investigated any association between invasive dental procedures and endocarditis, and any antibiotic prophylaxis effect on endocarditis incidence.

Subjects and Methods: Cohort and case-crossover studies were performed on 1,678,190 Medicaid patients with linked medical, dental, and prescription data.

Results: The cohort study identified increased endocarditis incidence within 30 days of invasive dental procedures in those at high risk, particularly after extractions (OR 14.17, 95% CI 5.40–52.11, $p < 0.0001$) or oral surgery (OR 29.98, 95% CI 9.62–119.34, $p < 0.0001$). Furthermore, antibiotic prophylaxis significantly reduced endocarditis incidence following invasive dental procedures (OR 0.20, 95% CI 0.06–0.53, $p < 0.0001$). Case-crossover analysis confirmed the association between invasive dental procedures and endocarditis in those at high risk, particularly following extractions (OR 3.74, 95% CI 2.65–5.27, $p < 0.005$) and oral surgery (OR 10.66, 95% CI 5.18–21.92, $p < 0.0001$). The number of invasive procedures, extractions, or surgical procedures needing antibiotic prophylaxis to prevent one endocarditis case was 244, 143 and 71, respectively.

Conclusions: Invasive dental procedures (particularly extractions and oral surgery) were significantly associated with endocarditis in high-risk individuals, but AP significantly reduced endocarditis incidence following these procedures, thereby supporting current guideline recommendations.

KEYWORDS
antibiotic prophylaxis, dental procedures, guidelines, health disparities, infective endocarditis, Medicaid, prevention

1 | INTRODUCTION

Infective endocarditis (IE) is life-threatening infection of the heart, particularly the heart valves, with 30%–40% first-year mortality (Bikdeli et al., 2013; DeSimone et al., 2015; Jensen et al., 2022; Toyoda et al., 2017). Although uncommon, many individuals with predisposing cardiac conditions are at increased IE-risk (M.H. Thornhill, Jones, et al., 2018). A causal link to invasive dental procedures (IDPs) has long been proposed to account for the 30%–40% of cases caused by oral bacteria (Lacassin et al., 1995; Lewis & Grant, 1923; Mylonakis & Calderwood, 2001; Strom et al., 1998). This relationship led the American Heart Association (AHA) to recommend antibiotic prophylaxis (AP) to prevent IE in those undergoing IDPs in 1955 (Jones et al., 1955). Subsequently, AP became the worldwide standard of care for IE prevention despite a lack of data to support its efficacy (Cahill et al., 2017).

The lack of efficacy data accompanied by concerns about antibiotic resistance and risk of adverse drug reactions led to the 2007 AHA recommendation to restrict AP to those at highest IE-risk undergoing IDPs (W. Wilson et al., 2007). In 2009, the European Society of Cardiology (ESC) implemented similar guidance (Habib et al., 2009). In support of these recommendations, a recent study of patients in the United States with employer-provided commercial medical and dental insurance, or employer-provided Medicare-Supplemental insurance (also known as Medigap, i.e., commercial medical and dental insurance for those over 65 years of age that supplements the care provided by Medicare alone) (Centers for Medicare and Medicaid Services, 2020) demonstrated a significant association between IDPs (particularly extractions and oral surgery) and subsequent IE in those at high IE-risk. It also demonstrated an association between AP use and a reduced risk of IE (M. H. Thornhill et al., 2022). However, there is a need to confirm these findings, ideally in another US population without the benefit of employer-provided private health cover (Bolger & Kazi, 2022).

In the United States, Medicaid is a joint federal and state public health insurance program that provides free or low-cost basic health cover for one in five Americans who are unable to afford commercial health insurance and are ineligible for Medicare (a federal health insurance program for those aged 65 or over) (Centers for Medicare and Medicaid Services, n.d; Rudowitz et al., 2019) (Centers for Medicare and Medicaid Services; Rudowitz, Garfield, & Hinton, 2019). Individual states are responsible for the Medicaid cover provided, and the extent of cover varies widely from state to state. Although all states provide basic dental care for Medicaid recipients under age 21, states may choose whether or not to provide dental benefits to Medicaid recipients 21 or over. While most states provide at least emergency dental services for adults, less than half provide more comprehensive care and there are no minimum requirements for adult dental coverage (US Department of Health & Human Services, 2021).

We, therefore, sought to investigate any temporal association between IDPs and IE, and if there was any association between AP use and reduced IE incidence following IDPs, in US Medicaid patients from states where adults receive both basic dental and medical cover, using the same cohort and case-crossover methodology used in the earlier study of a population from the US with employer-provided Commercial/Medicare-Supplemental medical and dental insurance cover (M. H. Thornhill et al., 2022). We also aimed to identify any IE-related health disparities between the Medicaid population and those with employer-provided medical and dental insurance cover.

2 | METHODS

2.1 | Data source

The study adhered to STROBE guidelines for cohort studies (STROBE, n.d) and used the IBM® MarketScan® data platform to integrate de-identified patient-level US health data from multiple databases. The MarketScan multi-state Medicaid database was used for states that provide Medicaid cover for adults. In addition, the MarketScan employer-funded commercial health insurance and Medicare-Supplemental databases were linked with prescription benefits and dental data before examination using the MarketScan platform (see Appendix S1).(IBM Watson Health, 2019) The MarketScan databases are not subject to IRB-review in the United States since they are statistically de-identified (in compliance with the US 1996 Health Insurance Portability and Accountability Act, HIPAA) and meet HIPAA limited-use criteria.(US Department for Health and Human Services, 1996). All enrollees aged ≥18 years with >16 months linked data (January 2000–August 2015) were included. We only included data until August 2015, because in October 2015, the US transitioned from ICD-9 to ICD-10 diagnosis and procedure codes and ICD-10 codes do not always translate directly into corresponding ICD-9 codes. Changes to CPT (medical procedure codes) and CDT (dental procedure codes) after October 2015 caused further disruption that could also have affected the data used in this study. To avoid the major disruption caused by these changes and ensure data integrity and continuity, we confined our study to the period before these changes (see Appendix S1 for further details).

2.2 | IE admissions and risk stratification

Databases were interrogated using ICD-9 primary or secondary discharge diagnostic codes 421.0, 421.1 or 421.9 to identify all IE hospital admissions. Previously described methods were used to ensure single counting of continuous IE-episodes (M. H. Thornhill et al., 2011). New episodes were distinguished from re-admissions by excluding IE-admissions <6 months apart (Chu et al., 2005; M. H. Thornhill, Gibson, et al., 2018).

Using available records back to January 2000, ICD-9 or CPT diagnostic/procedural codes were used to identify individuals at high

or moderate IE-risk based on AHA definitions (Tables S1, S3, S4) (Dajani et al., 1997; W. Wilson et al., 2007; W. R. Wilson et al., 2021); remaining individuals were considered at low/unknown IE-risk.

2.3 | Invasive dental procedures

The American Dental Association (ADA) Common Dental Terminology (CDT) codes (American Dental Association (ADA), 2019) and ICD-9 procedural codes (Centers for Disease Control and Prevention (CDC), 2019) were used to classify procedures into: (i) invasive-dental procedures (IDPs)—procedures involving manipulation of gingival tissue or the periapical region of the teeth, or perforation of the oral mucosa, for example, dental extractions, oral surgical procedures, scaling, and endodontic procedures (where AHA guidelines recommend AP "should" be used) (W. Wilson et al., 2007; W. R. Wilson et al., 2021); (ii) intermediate-dental procedures—procedures that may require AP when gingival manipulation is required to complete the procedure, for example, most restorative dental procedures, but not otherwise, (iii) non-IDPs—procedures where AP is not recommended, for example, routine dental examination or radiographs, placement of removable prosthodontic or orthodontic appliances (Table 2 and Table S3) (W. Wilson et al., 2007; W. R. Wilson et al., 2021). The most invasive procedure was ascribed to each visit and, when a treatment involved multiple visits, each visit was evaluated separately for procedures performed and AP cover. IDPs were also subanalyzed using codes specific for dental extractions, oral surgery procedures, scaling and endodontics (Tables S2 and S5).

Prescription benefits data were used to determine whether AP was prescribed (or not) for each dental visit using previously validated methodology (M.H. Thornhill et al., 2020) (see also Appendix S1).

2.4 | Cohort study

The entire cohort of 1.68 million Medicaid patients with linked medical, dental, and prescription data was examined and compared with 7.95 million individuals with employer-provided Commercial/Medicare-Supplemental health cover with linked dental and prescription benefits data. Data from the Commercial/Medicare-Supplemental health coverage cohort were recently published and are used herein for comparison with the Medicaid cohort (M. H. Thornhill et al., 2022). Subjects were stratified according to IE-risk (high, moderate or low/unknown) and followed until study completion, expiry of linked data or death.

For each risk group, the IE-incidence was quantified in the 30-day exposure period following IDPs, that we identified by plotting IDP-incidence over the 16 months leading up to IE admission (see Case-Crossover methods below). This analysis was also repeated using a 4-month exposure period. IE incidence was compared among different IE risk groups, different types of dental procedure and procedures with or without AP cover. Crude incidence rates were adjusted for any differences in age, sex, and Charlson Comorbidity Index (CCI) between groups (Charlson et al., 1987).

2.4.1 | Statistical analysis (cohort study)

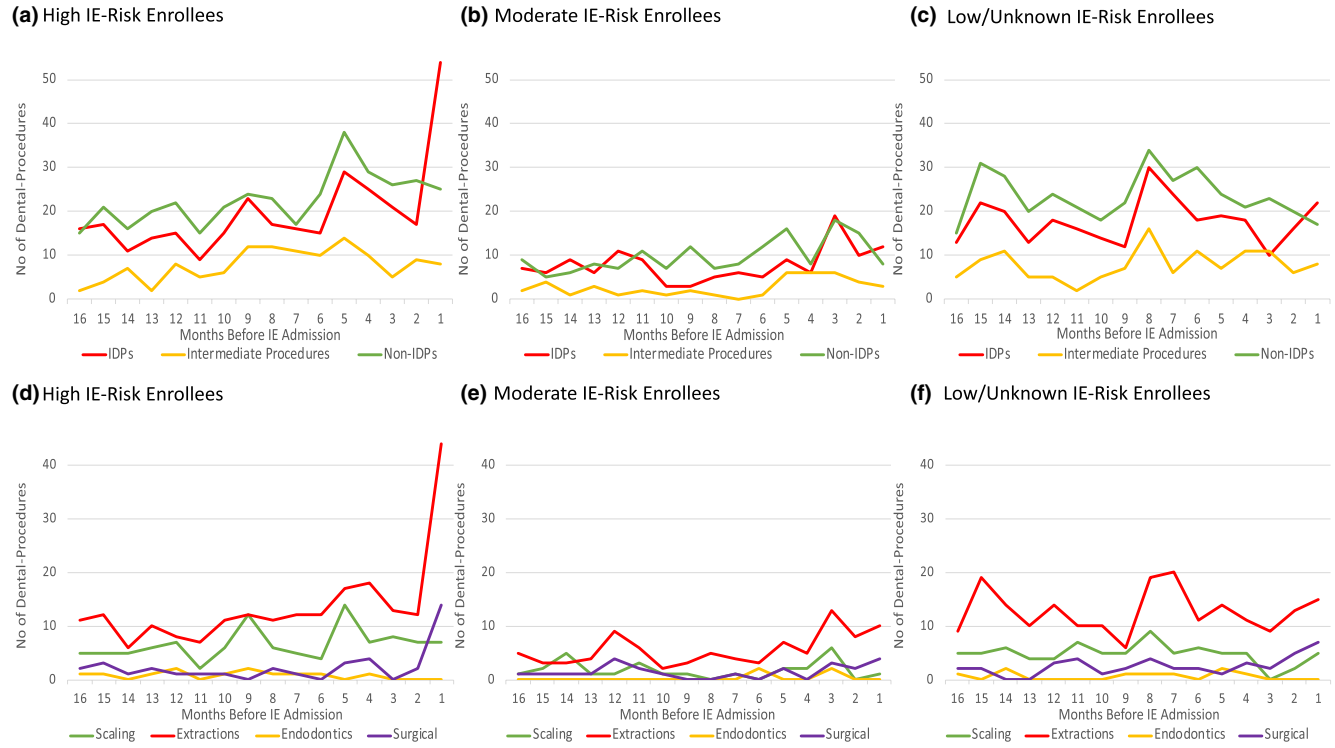
To address the rare outcome of interest (2647 IE-cases in a population of 1.68 million), we applied Firth logistic regression—a penalized-likelihood statistical method designed to address the possibility of rare outcomes causing small sample size bias (particularly in subanalyses) when using traditional maximum likelihood logistic regression that can lead to non-convergence of regression estimates (Doerken et al., 2019; Firth, 1991). The odds of IE following IDP (including subtypes) or intermediate-dental procedures were estimated by comparison with IE-incidence following non-IDPs (the control group) to test the null hypothesis that there was no increase in IE-incidence in the 30 days (or 4 months) following IDPs (the dental procedures model). We also compared IE-incidence following dental procedures with or without AP cover to test the null hypothesis that AP does not reduce IE-incidence in the 30 days (or 4 months) following a dental procedure (the antibiotic prophylaxis model). For both models, we set a $p < 0.05$ criterion for determining significance but first applied Bonferroni correction to account for multiple comparisons. If AP cover of IDPs reduced IE incidence in the 30 days after the procedure, then the number needed to prevent (NNP) was also calculated (i.e., the number of IDP that would need AP cover to prevent one IE case).

2.5 | Case-Crossover study

The monthly exposure of 2647 IE-patients to different IDPs was quantified over the 16 months before IE-hospital admission and plotted to identify the timing of any association. Accordingly, the incidence of IDPs, extractions, and surgical procedures was found to peak in the 30 days before IE-admission in those at high IE-risk (Figure 1 and Figure S1).

2.5.1 | Statistical analysis (Case-Crossover study)

Conditional logistic regression (with fixed effects to control for time invariant patient characteristics) was used to compare exposure to dental procedures during the 30-day case period with the preceding 12-month control period (months 2–13) (Maclure, 1991; Mittleman et al., 1995). To permit comparison with previous case-crossover studies where longer case periods (3–4 months) were used (Chen et al., 2015; Porat Ben-Amy et al., 2009; Tubiana et al., 2017), we performed further analyses using a 4-month case period and



Notes: AP = antibiotic prophylaxis, IDPs = invasive dental procedures, IE = infective endocarditis, intermediate procedures = intermediate dental procedures, Non-IDPs = non-invasive dental procedures.

FIGURE 1 Number of different dental procedures over the 16 months before infective endocarditis (IE)-related hospital admission (case-crossover study) Number of IDPs, intermediate or non-invasive dental procedures in those at (a) high, (b) moderate, or (c) low/unknown IE-risk. Number of different types of IDPs (scaling, extractions, or oral surgery) in those at (d) high, (e) moderate, or (f) low/unknown IE-risk.

12-month control period (months 5–16). Again, Bonferroni correction was applied for multiple comparisons.

3 | RESULTS

3.1 | Cohort study (dental procedures model)

Of the 1,678,190 Medicaid enrollees, 2647 were hospitalized with IE (1577 IE-cases/million), of whom 1381 (52.2%) were at high IE-risk, 314 (11.9%) at moderate IE-risk and 952 (36.0%) at low/unknown IE-risk (Table 1). The overall adjusted IE-incidence within 30 days of a dental procedure was 1952.7, 130.1, and 12.6 per million procedures among high, moderate, and low/unknown IE-risk patients, respectively (Table 2).

The odds of developing IE were significantly higher following IDPs compared to non-IDPs in those at high IE-risk (OR 6.58, 95% CI 2.76–20.33, $p < 0.0005$) (Table 2). Moreover, subanalysis of IDPs demonstrated that the odds of developing IE following extractions (OR 14.17, 95% CI 5.40–52.11, $p < 0.0001$) or oral surgery procedures (OR 29.98, 95% CI 9.66–119.34, $p < 0.0001$) were even higher.

When a 4-month exposure period was used (Table S8), the association between IDPs and IE remained statistically significant in those at high IE-risk, although the effect was smaller (OR 1.71, 95% CI 1.15–2.58 $p < 0.05$). The same was true for extractions (OR 2.56, 95% CI 1.70–3.94, $p < 0.0005$) and oral surgery procedures (OR 6.18, 95% CI 3.42–10.84, $p < 0.0001$).

3.2 | Cohort study (antibiotic prophylaxis model)

AP was prescribed before 25.9%, 10.5%, and 3.8% of IDPs in those at high, moderate, and low/unknown IE-risk, respectively (Table 1). For those at high IE-risk, AP was associated with a significant reduction in IE-risk (OR 0.20, 95% CI 0.06–0.53, $p < 0.0001$) compared to no AP, particularly following extractions (OR 0.29, 95% CI 0.08–0.77, $p < 0.01$). Although AP before oral surgery was also associated with a reduction in IE-risk (OR 0.40, 95% CI 0.04–1.75), this did not reach significance (Table 2, Figure 3), probably because of the relatively low number of procedures performed under AP cover in those at high risk (Table 1). Similarly, there were insufficient scaling or endodontic procedures performed with AP cover in those at high IE-risk to determine if AP was effective or not. The NNP (i.e., the number of IDPs that would need to be AP covered to prevent one IE case) in those at high IE-risk was 244, 143, and 71 for IDPs, extractions and oral surgical procedures, respectively. There was no significant effect of AP on the odds of developing IE following any type of dental procedure in individuals at moderate or low/unknown IE-risk, and the effects of AP in reducing IE incidence were not significant in any scenario when using a 4-month exposure period (Table S9).

TABLE 1 Demographic and descriptive data for the Medicaid cohort and case-crossover study populations in comparison with a Commercial/Medicare-Supplemental population.

Population data	Medicaid	Commercial/ Medicare-supplemental	OR comparing Medicaid with commercial/Medicare-suppl
Total Population	1,678,190 (100%)	7,951,972 (100%)	
Age 18–34	1,045,184 (62.3%)	2,435,930 (30.6%)	OR 3.739, 95% CI 3.726–3.752[a]
Age 35–44	264,375 (15.8%)	1,573,862 (19.8%)	OR 0.758, 95% CI 0.754–0.761[a]
Age 45–54	190,581 (11.4%)	1,794,556 (22.6%)	OR 0.440, 95% CI 0.437–0.442[a]
Age 55–64	117,443 (7.0%)	1,473,689 (18.5%)	OR 0.331, 95% CI 0.329–0.333[a]
Age 65+	60,607 (3.6%)	673,935 (8.5%)	OR 0.405, 95% CI 0.401–0.408[a]
Male	501,408 (29.9%)	3,691,739 (46.4%)	OR 0.492, 95% CI 0.490–0.494[a]
Female	1,176,782 (70.1%)	4,260,233 (53.6%)	OR 2.034, 95% CI 2.027–2.041[a]
CCI (Previous 12 m)			
0	1,396,086 (83.2%)	6,592,951 (82.9%)	OR 1.020, 95% CI 1.016–1.025[a]
1	172,541 (10.3%)	851,964 (10.7%)	OR 0.955, 95% CI 0.950–0.960[a]
2	47,651 (2.8%)	287,476 (3.6%)	OR 0.779, 95% CI 0.772–0.787[a]
3+	61,912 (3.7%)	219,851 (2.8%)	OR 1.347, 95% CI 1.335–1.360[a]
Cardiac risk			
High risk	8210 (0.5%)	36,773 (0.5%)	OR 1.058, 95% CI 1.033–1.084[a]
Moderate risk	86,739 (5.2%)	563,689 (7.1%)	OR 0.714, 95% CI 0.709–0.720[a]
Low/unknown risk	1,605,802 (95.7%)	7,617,072 (95.8%)	OR 0.975, 95% CI 0.967–0.983[a]
Dental procedure data			
All dental procedures	5,256,191 (100%)	58,058,148 (100%)	
Invasive-dental procedures (IDPs)	2,733,491 (52.0%)	39,468,691 (68.0%)	OR 0.510, 95% CI 0.509–0.511[a]
Intermediate-dental procedures	1,034,435 (19.7%)	9,685,382 (16.7%)	OR 0.111, 95% CI 0.110–0.111[a]
Non-invasive dental procedures (non-IDPs)	1,488,265 (28.3%)	8,904,075 (15.3%)	OR 2.181 95% CI 2.176–2.185[a]
Types of IDP			
Scaling	1,552,435 (29.5%)	35,472,509 (61.1%)	OR 0.266, 95% CI 0.266–0.267[a]
Extractions	1091,431 (20.8%)	2,122,760 (3.7%)	OR 6.906, 95% CI 6.888–6.923[a]
Endodontic	114,867 (2.2%)	1,465,025 (2.5%)	OR 0.8631, 95% CI 0.858–0.868[a]
Oral surgery	99,603 (1.9%)	529,863 (0.9%)	OR 2.097, 95% CI 2.083–2.112[a]
AP cov. All dental proc	218,258 (4.2%)	2,116,931 (3.7%)	OR 1.145, 95% CI 1.140–1.150[a]
AP cov. All IDPs	115,365 (4.2%)	1,378,332 (3.5%)	OR 1.218, 95% CI 1.210–1.225[a]
AP cov. All intermediate-dental procedures	40,504 (3.9%)	383,499 (4.0%)	OR 0.989, 95% CI 0.978–0.999[a]
AP cov. All non-IDPs	62,389 (4.2%)	355,100 (4.0%)	OR 1.053, 95% CI 1.044–1.063[a]
AP cov. IDPs—HR	3470 (25.9%)	59,045 (32.6%)	OR 0.793, 95% CI 0.763–0.824[a]
AP cov. IDPs—MR	14,222 (10.5%)	272,133 (9.5%)	OR 1.108, 95% CI 1.089–1.128[a]
AP cov. IDPs—LR	97,673 (3.8%)	1,047,154 (2.9%)	OR 1.301, 95% CI 1.292–1.310[a]
IE within 4 m of proc.	577 (0.011%)	2057 (0.004%)	OR 3.100, 95% CI 2.825–3.398[a]
Details of IE admissions (used in case-crossover study)			
IE admissions and rate	2647 (100%) (1577/mil)	3774 (100%) (475/mil)	OR 3.327, 95% CI 3.166–3.497[a]
Age 18–34	785 (29.7%) (751/mil)	279 (7.4%) (115/mil)	OR 6.506, 95% CI 5.675–7.458[a]
Age 35–44	608 (23.0%) (2300/mil)	269 (7.1%) (171/mil)	OR 13.501, 95% CI 11.696–15.586[a]
Age 45–54	655 (24.7%) (3437/mil)	654 (17.3%) (364/mil)	OR 9.460, 95% CI 8.488–10.543[a]
Age 55–64	450 (17.0%) (3832/mil)	1180 (31.3%) (801/mil)	OR 4.800, 95% CI 4.305–5.351[a]
Age 65+	149 (5.6%) (2459/mil)	1392 (36.9%) (2066/mil)	OR 1.191, 95% CI 1.005–1.410

(Continues)

TABLE 1 (Continued)

Population data	Medicaid	Commercial/ Medicare-supplemental	OR comparing Medicaid with commercial/Medicare-suppl
Male	1091 (41.2%) (2176/mil)	2338 (62.0%) (633/mil)	OR 3.441, 95% CI 3.202–3.698[a]
Female	1556 (58.8%) (1322/mil)	1436 (38.0%) (337/mil)	OR 3.927, 95% CI 3.655–4.219[a]
CCI (Previous 12 m)			
0	1229 (46.4%)	2532 (67.1%)	OR 0.425, 95% CI 0.384–0.471[a]
1	425 (16.1%)	432 (11.5%)	OR 1.480, 95% CI 1.281–1.709[a]
2	277 (10.5%)	274 (7.3%)	OR 1.493, 95% CI 1.253–1.778[a]
3+	716 (27.1%)	536 (14.2%)	OR 2.240, 95% CI 1.976–2.539[a]
Cardiac risk			
High risk	1381 (52.2%)	1292 (34.2%)	OR 2.096, 95% CI 1.893–2.320[a]
Moderate risk	314 (11.9%)	831 (22.0%)	OR 0.477, 95% CI 0.414–0.549[a]
Low/unknown risk	952 (36.0%)	1651 (43.8%)	OR 0.722, 95% CI 0.652–0.800[a]

Abbreviations: AP, antibiotic prophylaxis; CCI, Charlson Comorbidity Index score; cov, covered; IDPs, invasive dental procedures; IE, infective endocarditis; HR, individuals at high IE-risk; LR, individuals at low/unknown IE-risk; m, months; mil, million; MR, individuals at moderate IE-risk; non-IDPs, non-invasive dental procedures; proc, procedures; suppl, supplemental.

[a]$p < 0.05$ after Bonferroni correction.

3.3 | Case-Crossover study (dental procedures model)

Within the 2647 IE-admissions cohort, the incidence of IDPs, extractions, and oral surgery procedures peaked in the 30 days before IE-admission for those at high IE-risk (Figure 1 and Figure S1). In this group, there was a significant positive association between IDPs and IE-related hospital admission (OR 2.91, 95% CI 2.15–3.95, $p < 0.001$; Table 3) when comparing the 30-day case period with the preceding 12-month control period (months 2–13). Subanalysis revealed a significant association with extractions (OR 3.74, 95% CI 2.65–5.27, $p < 0.005$) and oral surgery procedure (OR 10.66, 95% CI 5.18–21.92, $p < 0.0001$) in the 30 days before IE admission. There were no significant positive associations between IDPs and IE for those at moderate or low/unknown IE-risk.

Use of a 4-month case period in those at high IE-risk also confirmed significant associations between IDPs (particularly extractions and oral surgery) and IE (Table S12). A significant association also persisted between IDPs, extractions, and IE in those at moderate IE-risk, but not in those at low/unknown IE-risk.

3.4 | Case-Crossover (antibiotic prophylaxis model)

The peak in the incidence of IDP's, extractions, and surgical procedures observed in the 30 days before IE admission in the case-crossover model was abrogated when these procedures were performed after AP (Figure 2). However, although AP before IDPs in individuals at high IE-risk was associated with reduced likelihood of IE, this association did not reach statistical significance (Table 3).

3.5 | IE disparities between Medicaid and commercial/Medicare-Supplemental cohorts

The Medicaid population was younger with a higher proportion of women than the Commercial/Medicare population but contained a higher proportion of individuals with higher (>3) CCI scores and had a 3.3-fold greater likelihood of developing IE (1577 vs. 475 IE cases/million). Moreover, IE occurred more often in younger individuals, with 53% of all Medicaid IE-cases occurring in those aged <45 years (compared to only 15% in the Commercial/Medicare population, Table 1).

We also observed differences in the types of dental procedures performed; extractions accounted for 20.8% of all dental procedures in Medicaid patients but only 3.7% in the Commercial/Medicare cohort (OR 6.91, 95% CI 6.89–6.92, $p < 0.05$). In contrast, scaling accounted for 61.1% of all dental procedures in Commercial/Medicare patients, but only 29.5% in the Medicaid cohort (OR 0.27, 95% CI 0.27–0.27, $p < 0.05$). Furthermore, the odds of developing IE within 4-months of a dental procedure were three-times higher in Medicaid than Commercial/Medicare patients (OR 3.10, 95% CI 2.83–3.40, $p < 0.05$). Although the use of AP in high-risk individuals undergoing IDPs was low in both populations, it was significantly lower in Medicaid compared to Commercial/Medicare patients (25.9% vs. 32.6%, $p < 0.05$).

4 | DISCUSSION

The association between IDPs and IE, and the efficacy (or not) of AP in preventing IE have long been debated in the absence of robust clinical evidence. No randomized controlled trial of AP

TABLE 2 Cohort Study (a) Dental Procedures Model—adjusted IE Incidence within 30 days of a dental procedure and (b) antibiotic prophylaxis model—adjusted IE Incidence following procedures covered or not covered by antibiotic prophylaxis.

(a) Cohort dental procedures model

Prior IE risk	High IE-risk individuals		Moderate IE-risk individuals		Low/unknown IE-risk individuals	
Type of dental procedure	**Adjusted IE/million proc**	**Odds ratio (95% CI)**	**Adjusted IE/million proc**	**Odds ratio (95% CI)**	**Adjusted IE/million proc**	**Odds ratio (95% CI)**
All	1952.7		130.1		12.6	
Control; non-invasive dental proc. (non-IDPs)	531.1	1	150.1	1	8.4	1
Intermediate-dental proc.	561.4	1.079 (0.188–4.879)	67.2	0.494 (0.017–2.009)	11.7	1.706 (0.710–4.097)
Invasive dental procedures (IDPs)	3367.3	6.579 (2.755–20.330), $p < 0.0005$	153.1	1.072 (0.499–2.410)	15.2	2.058 (1.067–4.329)
Scaling	148.2	0.293 (0.002–3.086)	57.0	0.425 (0.080–1.523)	8.2	1.254 (0.509–3.093)
Extractions	7770.8	14.169 (5.403–52.109), $p < 0.0001$	234.8	1.454 (0.651–3.341)	24.2	2.690 (1.316–5.858)
Endodontic	-	-				
Oral surgery	18,571.5	29.979 (9.662–119.336), $p < 0.0001$	832.3	4.085 (1.182–11.987)	120.6	10.972 (4.422–26.861)

(b) Cohort antibiotic prophylaxis model

Prior IE risk	High IE-risk individuals		Moderate IE-risk individuals		Low/unknown IE-risk individuals	
Type of dental procedure	**Adjusted IE/million proc**	**Odds ratio (95% CI) NNP**	**Adjusted IE/million proc**	**Odds ratio (95% CI)**	**Adjusted IE/million proc**	**Odds ratio (95% CI)**
Non-IDPs—AP	1330.2	1.798 (0.163–13.710)	363.8	2.169 (0.410–7.870)	nc	nc
Non-IDPs—No AP	747.2		150.2		nc	
Intermediate-dental proc. —AP	696.8	0.460 (0.003–5.660)	nc	nc	121.8	5.547 (3.905–6.712)
Intermediate-dental proc. —No AP	1666.7		nc		20.8	
IDPs—AP	1060.6	0.202 (0.055–0.530), $p < 0.0001$	195.6	1.203 (0.236–3.960)	27.2	1.305 (0.266–3.940)
IDPs—No AP	5155.9		160.1		15.2	
Scaling—AP	nc	nc	143.0	1.541 (0.011–20.240)	40.3	3.175 (0.335–14.260)
Scaling—No AP	nc		93.1		8.3	
Extract—AP	2816.2	0.290 (0.079–0.767), $p < 0.01$	372.2	1.523 (0.295–5.200)	34.3	1.160 (0.128–4.550)
Extract—No AP	9827.6		241.6		24.9	
Endo—AP	nc	nc	nc	nc	nc	nc
Endo—No AP	nc		nc		nc	
Oral surgery—AP	9805.3	0.396 (0.042–1.747)	2683.9	3.229 (0.310–19.910)	331.7	2.508 (0.267–11.170)
Oral surgery—No AP	23,980.3		924.9		125.4	

Note: IE rates are adjusted data corrected for differences in the age, sex, and Charlson Comorbidity Index (CCI) score between groups compared in each estimation and therefore differ between the dental procedures (Table 3a) and antibiotic prophylaxis models (Table 3b). Oral surgery procedures include both oral and periodontal surgery. Bonferroni-corrected p values shown where $p < 0.05$ (other p values not significant).

Abbreviations: AP, antibiotic prophylaxis; Extract, extractions; Endo, endodontic procedures; IDPs, invasive-dental procedures; IE, Infective endocarditis; nc, not calculable (insufficient numbers to permit calculation); non-IDPs, non-invasive dental procedures; Proc, procedure. Odds ratio significantly higher than control non-invasive dental procedures (non-IDP) (dental procedures model), or AP significantly reduced IE incidence compared to no AP (antibiotic prophylaxis efficacy model).

TABLE 3 Case-Crossover Analysis: (a) Dental Procedures Model – comparing the incidence of different dental procedures in the 1-month case period (months 0–1 before IE admission) and 12-month control period (months 2–13 before IE admission); (b) Antibiotic Prophylaxis Model–comparing the effect of antibiotic prophylaxis (AP) cover with no AP cover of dental procedures in the case control periods.

(a) Case-crossover dental procedures model (all IE admissions 2647)

Prior IE risk	High IE-risk individuals (1381)			Moderate IE-risk individuals (314)			Low/unknown IE-risk individuals (952)		
Type of dental procedure	Proc/m in 1 m case period	Proc/m in 12 m control period	OR (95% CI)	Proc/m in 1 m case period	Proc/m in 12 m control period	OR (95% CI)	Proc/m in 1 m case period	Proc/m in 12 m control period	OR (95% CI)
Non-invasive dental proc. (non-IDPs)	25	30.8	0.973 (0.643–1.473)	4	14.1	0.317 (0.117–0.86)	18	31.2	0.744 (0.459–1.205)
Intermediate-dental proc.	7	10.7	0.727 (0.338–1.567)	1	3.8	0.329 (0.045–2.415)	8	10	1.022 (0.494–2.112)
Invasive dental proc. (IDPs)	53	22.3	2.914 (2.147–3.954), $p < 0.001$	11	10.2	1.299 (0.694–2.434)	25	22.7	1.419 (0.933–2.159)
Types of IDP									
Scaling	6	7.9	0.911 (0.396–2.095)	1	2.2	0.706 (0.094–5.304)	6	5.8	1.336 (0.573–3.117)
Extractions	44	14.3	3.737 (2.651–5.268), $p < 0.005$	9	7.1	1.409 (0.703–2.827)	17	16.2	1.368 (0.824–2.272)
Endodontic	0	1.2	0 (0-Inf)	0	0.3	0 (0-Inf)	0	0.8	0 (0-Inf)
Oral surgery	14	1.8	10.66 (5.184–21.923), $p < 0.0001$	3	1.4	2.605 (0.74–9.175)	8	2.8	3.057 (1.395–6.696)

(b) Case-Crossover Antibiotic Prophylaxis Model (all IE admissions 2647)

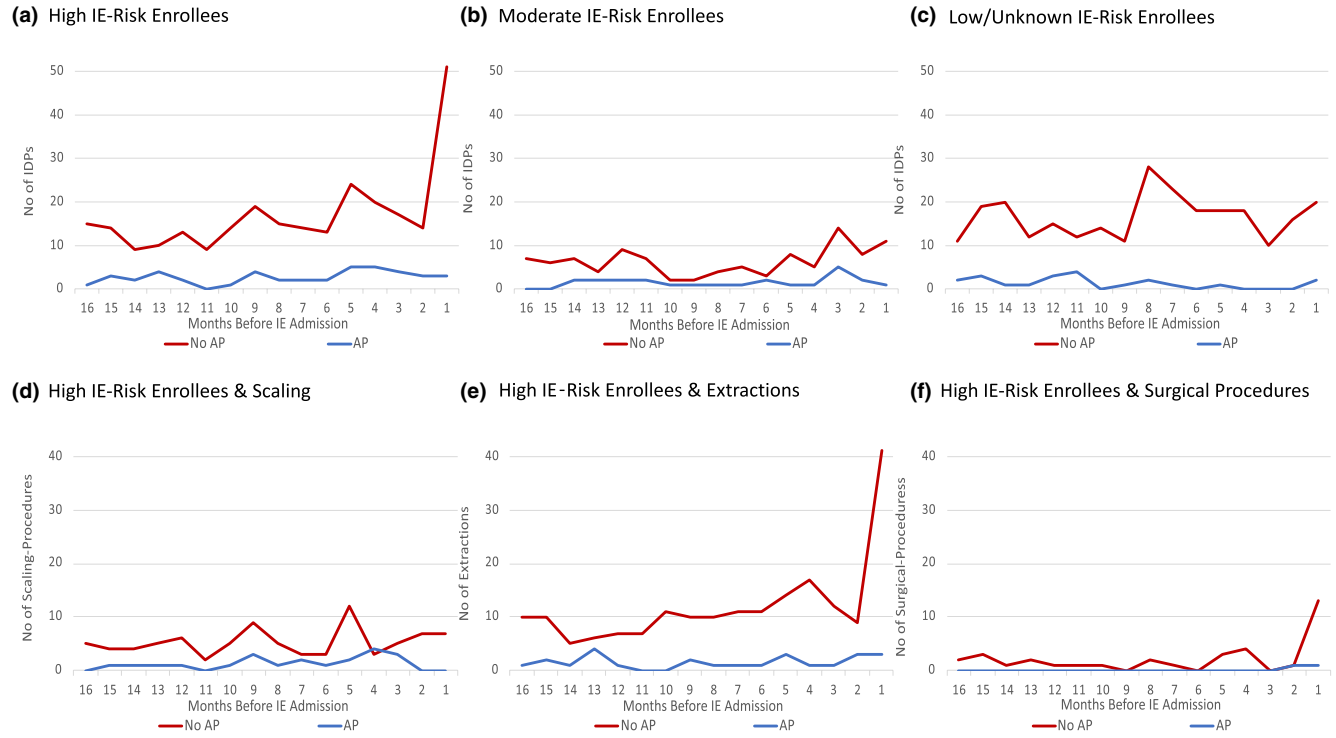
Prior IE Risk	High IE-Risk Individuals (1381)			Moderate IE-Risk Individuals (314)			Low/Unknown IE-Risk Individuals (952)		
Type of Dental Procedure	Proc/m in 1 m Case Period	Proc/m in 12 m Control Period	OR (95% CI)	Proc/m in 1 m Case Period	Proc/m in 12 m Control Period	OR (95% CI)	Proc/m in 1 m Case Period	Proc/m in 12 m Control Period	OR (95% CI)
Non-invasive dental proc. (non-IDPs)—AP	4	3.1	1.609 (0.563–4.599)	0	2.8	0 (0-Inf)	3	1.7	2.597 (0.740–9.120)
Non-IDPs–No AP	21	27.8	0.903 (0.575–1.416)	4	11.2	0.389 (0.143–1.061)	15	29.5	0.649 (0.384–1.099)
Non-IDPs, AP v No AP			1.778 (0.568–5.571)			0 (0-Inf)			3.99 (1.023–15.560)
Intermediate-dental proc. —AP	1	0.9	1.503 (0.187–12.095)	0	0.9	0 (0-Inf)	2	0.4	8.000 (1.337–47.877)
Intermediate-dental proc. —No AP	6	9.8	0.670 (0.293–1.530)	1	2.8	0.411 (0.056–3.032)	6	9.6	0.789 (0.344–1.810)
Intermediate-dental proc., AP v No AP			2.239 (0.238–21.072)			0 (0-Inf)			10.139 (1.410–72.883)

TABLE 3 (Continued)

(b) Case-Crossover Antibiotic Prophylaxis Model (all IE admissions 2647)									
Prior IE Risk	**High IE-Risk Individuals (1381)**			**Moderate IE-Risk Individuals (314)**			**Low/Unknown IE-Risk Individuals (952)**		
Type of Dental Procedure	**Proc/m in 1 m Case Period**	**Proc/m in 12 m Control Period**	**OR (95% CI)**	**Proc/m in 1 m Case Period**	**Proc/m in 12 m Control Period**	**OR (95% CI)**	**Proc/m in 1 m Case Period**	**Proc/m in 12 m Control Period**	**OR (95% CI)**
Invasive-dental proc. (IDPs)—AP	4	3.3	1.566 (0.546–4.437)	0	2.2	0 (0-Inf)	2	1.5	1.854 (0.416–8.268)
IDPs—No AP	49	19	3.136 (2.277–4.319), $p < 0.001$	11	8	1.664 (0.880–3.146)	23	21.2	1.390 (0.898–2.151)
IDPs, AP v No AP			0.499 (0.167–1.492)			0 (0-Inf)			1.337 (0.282–6.342)
Types of IDP									
Scaling—AP	0	1.8	0 (0–1.374e+294)	0	0.5	0 (0-Inf)	1	0.2	4.000 (0.416–38.454)
Scaling—No AP	6	6.2	1.182 (0.509–2.744)	1	1.7	0.923 (0.121–7.056)	5	5.6	1.178 (0.469–2.961)
Scaling, AP v No AP			0 (0–1.176e+294)			0 (0-Inf)			3.396 (0.296–39.034)
Extractions—AP	4	1.8	3.264 (1.069–9.971)	0	1.2	0 (0-Inf)	1	1.3	1.091 (0.140–8.483)
Extractions—No AP	40	12.5	3.788 (2.641–5.434), $p < 0.0001$	9	5.8	1.730 (0.854–3.504)	16	14.9	1.390 (0.824–2.345)
Extractions, AP v No AP			0.865 (0.268–2.797)			0 (0-Inf)			0.787 (0.095–6.528)
Endodontic—AP				0	0.2	0 (0-Inf)			
Endodontic—No AP	0	1.2	0 (0-Inf)	0	0.2	0 (0-Inf)	0	0.8	0 (0-Inf)
Endodontic, AP v No AP						1 (0-Inf)			
Oral surgery—AP	2	0.1	24 (2.176–264.677)	0	0.4	0 (0-Inf)	1	0.1	3,269,138 (0-Inf)
Oral surgery—No AP	12	1.7	9.753 (4.546–20.926), $p < 0.0001$	3	1	3.624 (0.992–13.234)	7	2.8	2.667 (1.166–6.100)
Oral surgery, AP v No AP			2.462 (0.198–30.551)			0 (0-Inf)			331,406 (0-Inf)

Note: Oral surgery includes both oral and periodontal surgery procedures. Bonferroni corrected p values shown only where $p < 0.05$ (other p values not significant).

Abbreviations: AP, antibiotic prophylaxis; IDPs, invasive-dental procedures; IE, infective endocarditis; Inf, infinity; m, month; non-IDPs, non-invasive dental procedures; OR, odds ratio; Proc, procedures, v, versus (compared with). OR for case period significantly higher than for control non-invasive dental procedures (non-IDP) (dental procedures model) or AP odds significantly reduced when compared with no AP odds (antibiotic prophylaxis efficacy model).



Notes: AP = antibiotic prophylaxis, IDPs = invasive dental procedures, IE = infective endocarditis, intermediate procedures = intermediate dental procedures, Non-IDPs = non-invasive dental procedures.

FIGURE 2 Number of IDPs with or without AP cover over the 16 months before infective endocarditis (IE)-related hospital admission (case-crossover study) Number of IDPs in individuals receiving or not receiving antibiotic prophylaxis (AP) in the 16 months before IE-related hospital admission in those at (a) high, (b) moderate, or (c) low/unknown IE-risk. Number of (d) scaling, (e) extractions, and (f) oral surgery procedures in high IE-risk individuals receiving or not receiving antibiotic prophylaxis (AP) in the 16 months before IE-related hospital admission.

efficacy has been conducted to date due to the need for an extremely large cohort to demonstrate a clinically significant effect of AP on IE incidence (a comparatively rare diagnosis). In the present study, performed in the United States, we used two different methodologies (cohort and case-crossover) to demonstrate an association between IDPs and IE, and the effectiveness of AP in its prevention, in a US population exceeding 1.6 million. In addition, significant health disparities between US patients on Medicaid and those with employer-provided Commercial/Medicare-Supplemental medical and dental cover were identified as possible contributors to IE risk.

The case-crossover study design was first proposed as a method for evaluating the role of transient events in triggering subsequent outcomes while eliminating control selection bias and confounding, each individual (having constant intra-subject characteristics) serving as their own control (Maclure, 1991). This design avoids selection bias and confounders (such as differences in oral-hygiene between cases and controls) and provides a powerful method for investigating potential triggers for outcomes such as IE (Maclure, 1991; Maclure & Mittleman, 2000). Our study revealed a statistically significant association between IE and IDPs (particularly extractions and oral surgery procedures) undertaken during the preceding 30 days in those at high IE-risk (Table 3, Figure 1). This was confirmed in the cohort study, where the odds of developing IE were also significantly higher in the 30 days following IDPs (particularly extractions and oral surgery) compared with non-IDPs (Table 2, Figure 3). The use of a 4-month (instead of a 30-day) case period revealed a weaker (but still significant) association between extractions or oral surgery procedures and IE using both methodologies (Tables S8 and S12).

Although there were no significant associations between dental procedures and IE at 30 days in those at moderate IE-risk (Table 3), there were between IDPs, extractions, and IE at 4 months (Table S12) in the case-crossover analysis. Furthermore, the time-course data (Figure 1 and Figure S1) suggest that any association between IDPs and IE in those at moderate IE-risk might extend over a longer (3- to 4-month) time frame before IE-related hospital admission than was observed in those at high risk. This may reflect a higher index of suspicion for an IE diagnosis (and therefore more rapid diagnosis) in those at high IE-risk compared to those at moderate risk or the possibility that high IE-risk patients experience a more rapid disease onset.

Data regarding the time between precipitating events and IE are sparse. Studies to date have used different time periods (3 months being the most common) (Duval et al., 2017; Imperiale & Horwitz, 1990; Lacassin et al., 1995; Strom et al., 1998; Tubiana et al., 2017; Van der Meer et al., 1992), but the only study to

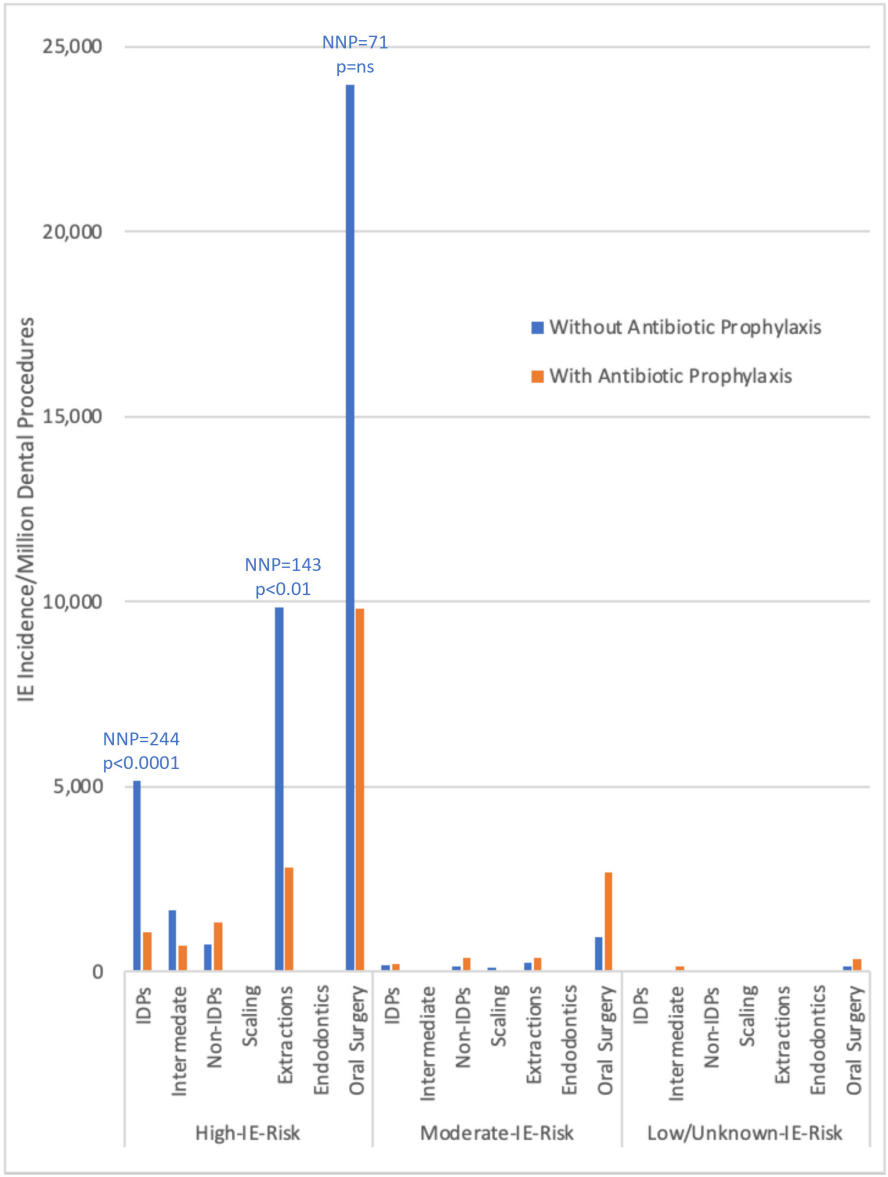


FIGURE 3 Incidence of IE within 1 month of dental procedures performed with or without AP in individuals at high, moderate, or low/unknown IE-risk (cohort study).

NOTE: AP = antibiotic prophylaxis, IDPs = invasive-dental procedure, IE = infective endocarditis, Non-IDPs = non-invasive dental procedures. NNP= Number needed to prevent

specifically examine the IE-incubation period reported a median of 7 days with 90% of diagnoses being made within 4 weeks of a potentially causal event (Starkebaum et al., 1977). Another study reported <4 weeks symptom duration in 52.3% of IE-cases (Issa et al., 2003). Finally, a recent study demonstrated that IE resulting from traumatic wounds occurred within 1–4 weeks of injury (Ohbe et al., 2021). These observations are consistent with our finding of a 30-day case/exposure period for those at high IE-risk and suggest that studies using longer case/exposure periods may underestimate any association (particularly in those at high IE-risk).

Notably, our Medicaid cohort study also demonstrated that AP significantly reduced IE-incidence following IDPs (particularly extractions) in those at high IE-risk. This is consistent with our recently reported results in the Commercial/Medicare-Supplemental population where AP significantly reduced IE incidence in high IE-risk subjects after IDP, extractions or oral surgery procedures (M. H. Thornhill et al., 2022). In the Medicaid population, however, case-crossover analysis failed to confirm a statistically significant effect of AP on IE incidence. This is most likely because of the relatively small number of procedures covered by AP in the month before diagnosis (Table 1).

Two previous small case-crossover studies ($n = 739$ and 170, respectively) (Chen et al., 2015; Porat Ben-Amy et al., 2009) failed to demonstrate a significant association between IDPs and IE, most likely because of their small sample size, insufficient statistical power and failure to specifically examine those at high IE-risk (Chen et al., 2015; Porat Ben-Amy et al., 2009). Another case-crossover study of 648 high-risk patients with prosthetic-valve IE reported a significant association between IDPs and IE, but failed to demonstrate a significant association between AP and reduced IE-risk (probably due to lack of statistical power) (Tubiana et al., 2017). Although our Medicaid case-crossover study had more high IE-risk

patients ($n = 1381$), it also failed to demonstrate a significant effect of AP. However, our larger cohort Medicaid study and our even larger cohort and case-crossover studies in the Commercial/Medicare-Supplemental population all demonstrated significant reduction in IE incidence following IDPs performed with AP in high IE-risk patients (M. H. Thornhill et al., 2022). Furthermore, when these findings are combined with data from a recent health economic analysis, they suggest AP is likely to be cost-effective in reducing IE in those at high IE-risk (Franklin et al., 2016).

4.1 | Disparities between Medicaid and commercial/Medicare-Supplemental cohorts

The associations between extractions, oral surgery procedures, and subsequent IE, and the effectiveness of AP demonstrated in this study, are similar to those we recently reported in a Commercial/Medicare-Supplemental population (M. H. Thornhill et al., 2022). However, there were significant healthcare disparities between these two populations (Table 1). In particular, IE-incidence was three times higher in Medicaid than Commercial/Medicare Supplemental patients (despite younger age), possibly reflecting a higher prevalence of injection drug use (IDU) in this population (Baddour et al., 2021;Deo et al., 2018; Fleischauer et al., 2017). Recent studies have reported that >40% of IDU-related IE-hospitalizations occur in Medicaid enrollees (Deo et al., 2018; Fleischauer et al., 2017).

We also identified differences in both the number and type of IDPs performed in these two populations. A significantly lower proportion of all dental procedures performed in Medicaid patients were IDPs (52%) compared to Commercial/Medicare patients (68%, see Table 1). Despite this, extractions accounted for 20.8% of all dental procedures performed in Medicaid patients but only 3.7% of those performed in the Commercial/Medicare cohort. In contrast, scaling accounted for 61.1% of procedures in Commercial/Medicare patients but only 29.5% in the Medicaid cohort. These findings suggest reduced emphasis on preventive dental care and oral hygiene in Medicaid patients and a greater resort to extractions. This could contribute to their higher IE-incidence and threefold higher likelihood of developing IE compared with Commercial/Medicare patients.

Our data showed that 9928 (74.1%) of the 13,398 IDPs performed in high-risk Medicaid patients were not covered by AP this compared with 122,075 (67.4%) of the 181,120 IDPs performed in the Commercial/Medicare cohort. Use of AP in accordance with AHA recommendations (i.e., in high-risk individuals undergoing IDPs) was, therefore, low in both populations but significantly lower in Medicaid patients (25.9 vs. 32.6%%) and may have contributed to the increased IE-incidence in Medicaid compared to Commercial/Medicare patients (Table 1).

Differences in general and dental health, access to care (Allen et al., 2021; Kennedy et al., 2017), and use of AP in the Medicaid and Commercial/Medicare populations are likely to explain the sixfold higher IE-incidence following IDPs in high IE-risk Medicaid patients compared to those with employer-provided medical and dental benefits (3367.3 vs. 521.1 cases/million procedures) (M. H. Thornhill et al., 2022). Nonetheless, such a large difference in the risk for developing IE should be of concern to healthcare providers and public health authorities in the United States.

4.2 | Study limitations

Misclassification is frequent in administrative databases, particularly for challenging diagnoses such as IE. Nonetheless, a recent study using ICD-10 codes (equivalent to the ICD-9 codes used in this study) reported 0.95 (95% CI 0.86–0.99) sensitivity, 1.0 (95% CI 1.0–1.0) specificity, and 0.6 (95% CI 0.49–0.69) positive predictive value for the identification of definite IE-cases according to the modified Duke criteria (Tan et al., 2016). Administrative databases also afford larger sample sizes than their clinical counterparts and capture the entire spectrum of IE-related hospitalizations (thereby reducing potential referral bias). Although we corrected for age, sex, and CCI differences when comparing IE-incidence in the cohort study, other uncorrected differences or unmeasured confounders may have influenced the outcome. Reassuringly, however, the cohort and case-crossover studies provided consistent results.

To increase our chance of demonstrating an association between IDPs and IE, we would have preferred to restrict our analysis to the 30%–40% of IE cases caused by oral streptococci. This was impossible, however, since the MarketScan databases do not record microbiological data, preventing comment on the bacterial cause of each case.

CPT and ICD-9 codes were used to identify those at moderate or high risk of IE. However, records of procedures or diagnoses that would categorize individuals as being at moderate or high risk were incomplete before January 2000, resulting in potential misclassification of some high- or moderate-risk individuals as low/unknown risk. This may explain the small but significant association between extractions or surgical procedures and IE in those at low/unknown IE-risk (Tables 2 and 3).

Low levels of AP use in those at high IE-risk and continued use in those for whom it is no longer recommended enabled our analysis of AP effects. However, some use of AP in those at moderate or low/unknown IE-risk may have been in individuals with prosthetic joints (as recommended by many orthopedic surgeons). Combined with misclassification, this could explain the apparent adverse effect of AP on IE-incidence in some of those at moderate or low/unknown IE-risk.

Varying dental AP prescribing strategies (particularly the use of a single prescription for multiple AP courses) made it difficult to verify whether AP was used for specific dental procedures. Even when a single AP dose was prescribed immediately before a dental procedure, we could not verify with certainty that it had been taken. Conversely, even when there was no evidence of AP prescribing, we cannot be certain that a patient was not provided AP by other means. However, we have previously validated the methodology

used in this study and demonstrated 88% (95% CI 82–92%) sensitivity and 96% (95% CI 94–97%) specificity for identifying when AP was prescribed (and distinguishing this from antibiotic prescribing to treat infections) (M.H. Thornhill et al., 2020).

Although the present study focused on the relationship between IDPs and IE, it is possible that more cases of oral streptococcal IE occurred due to daily activities such as toothbrushing, flossing, and mastication (particularly in those with poor oral hygiene) (Lockhart et al., 2009). Use of AP does not, therefore, diminish the importance of maintaining good oral hygiene as an IE prevention strategy.

5 | CONCLUSIONS

Using two different methodologies, we demonstrate a significant temporal association between IDPs (particularly extractions and oral surgery procedures) and the subsequent development of IE in those at high IE-risk. We also demonstrated that use of AP significantly reduced IE-incidence following these procedures, thus supporting current AHA and ESC guideline recommendations that all those at high IE-risk should receive AP before undergoing invasive dental procedures (Habib et al., 2009; W. Wilson et al., 2007; W. R. Wilson et al., 2021). Finally, our data also highlighted an increased risk of IE in the Medicaid population.

AUTHOR CONTRIBUTIONS

Martin H. Thornhill: Conceptualization; funding acquisition; investigation; methodology; original draft preparation. **Teresa B. Gibson:** Data curation; formal analysis; investigation; methodology; review and editing. **Frank Yoon:** formal analysis; methodology; review and editing. **Mark J. Dayer:** conceptualization; visualization; review and editing. **Bernard D. Prendergast:** conceptualization; review and editing. **Peter B. Lockhart:** conceptualization; review and editing. **Patrick T. O'Gara:** conceptualization; review and editing. **Larry M. Baddour:** conceptualization; review and editing.

ACKNOWLEDGMENTS

We acknowledge the indispensable free advice, comments, and assistance of colleagues in general and specialist dental practice on matters of dental practice and coding. In particular, we acknowledge the assistance of Dr Richard Potter DDS and colleagues of the Texas Dental Association 20th District, San Antonio District Dental Society, Dr Julianne K. Ruppel DDS, MS (Ruppel Orthodontics, St. Louis, Missouri), Dr Thomas Paumier DDS (general dentist, Ohio), Dr Jeffery Johnston DDS, MS (Delta Dental of Michigan, Ohio, and Indiana), and Dr Jed Jacobson DDS (Ann Arbor, Michigan). Their views may not reflect those expressed in this paper.

FUNDING INFORMATION

This study was funded by a grant from the Delta Dental of Michigan Research Committee and Renaissance Health Service Corporation. The funding source had no role in the study's design, conduct, or reporting.

CONFLICT OF INTEREST STATEMENT

Drs Thornhill, Lockhart, and O'Gara received support from the Delta Dental Research and Data Institute for the submitted work. Dr O'Gara reports support in the last 3 years from Medtronic, Edwards Scientific and the National Heart Lung Blood Institute, which was unconnected to the submitted work; Dr Dayer reports support from Biotronik in the last 3 years, which was unconnected to the submitted work; none of the other authors reports a financial relationship in the previous 3 years with companies that might have an interest in the submitted work. Dr Prendergast reports unrestricted research and educational grants from Edwards LifeSciences, lecture fees from Abbott, Anteris and Edwards Lifesciences, and consultancy fees while serving on the Scientific Advisory Board for Anteris and Microport (all unconnected to the submitted work). Dr Baddour has received royalty payments (authorship duties) from UpToDate, Inc., and consulting fees from Boston Scientific and Roivant Sciences. Drs Thornhill, Gibson, Yoon, and O'Gara have no non-financial interests that may be relevant to the submitted work. Drs Baddour and Lockhart were members of the American Heart Association Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease and were involved in drafting the 2007 and 2021 American Heart Association guidelines on the prevention of infective endocarditis. Dr Dayer was a consultant to the review committee that produced the 2015 update to NICE clinical guideline 64 on prophylaxis against infective endocarditis. Dr Prendergast was a member of the Task Force on the Prevention, Diagnosis and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC) that produced the 2009 ESC guidelines and acted as an external advisor to the committee that produced the NICE clinical guideline 64 on Prophylaxis Against Infective Endocarditis in March 2008.

DATA AVAILABLITY STATEMENT

All de-identified summary data related to the study have been made available in the manuscript and supplementary appendix. The original data was were obtained from the MarketScan® Medicaid, commercial medical, Medicare-supplemental, prescription benefits, and dental databases under a data sharing agreement with IBM Watson Health. Researchers wishing to access this original data can do so by entering into a similar agreement (https://www.ibm.com/uk-en/products/marketscan-research-databases).

ORCID

Martin H. Thornhill https://orcid.org/0000-0003-0681-4083
Patrick T. O'Gara https://orcid.org/0000-0003-0601-1088

REFERENCES

Allen, H., Gordon, S. H., Lee, D., Bhanja, A., & Sommers, B. D. (2021). Comparison of utilization, costs, and quality of Medicaid vs subsidized private health Insurance for low-Income Adults. *JAMA*

Network Open, *4*(1), e2032669. https://doi.org/10.1001/jamanetworkopen.2020.32669

American Dental Association (ADA). (2019). Code on dental procedures and nomenclature (CDT code). Retrieved from https://www.ada.org/en/publications/cdt

Baddour, L. M., Thornhill, M. H., & Dayer, M. J. (2021). Injection drug use: A minor criterion with major implications for infective endocarditis. *Journal of the American College of Cardiology*, *77*(5), 556–558. https://doi.org/10.1016/j.jacc.2020.11.058

Bikdeli, B., Wang, Y., Kim, N., Desai, M. M., Quagliarello, V., & Krumholz, H. M. (2013). Trends in hospitalization rates and outcomes of endocarditis among Medicare beneficiaries. *Journal of the American College of Cardiology*, *62*(23), 2217–2226. https://doi.org/10.1016/j.jacc.2013.07.071

Bolger, A., & Kazi, D. S. (2022). Antibiotic prophylaxis against endocarditis prior to invasive dental procedures: Filling in the gaps. *Journal of the American College of Cardiology*, *80*(11), 1042–1044. https://doi.org/10.1016/j.jacc.2022.07.003

Cahill, T. J., Harrison, J. L., Jewell, P., Onakpoya, I., Chambers, J. B., Dayer, M., Lockhart, P., Roberts, N., Shanson, D., Thornhill, M., Heneghan, C. J., & Prendergast, B. D. (2017). Antibiotic prophylaxis for infective endocarditis: A systematic review and meta-analysis. *Heart*, *103*(12), 937–944. https://doi.org/10.1136/heartjnl-2015-309102

Centers for Disease Control and Prevention (CDC). (2019). International classification of diseases, ninth revision, clinical modification (ICD-9-CM). Retrieved from https://www.cdc.gov/nchs/icd/icd9cm.htm

Centers for Medicare and Medicaid Services. (2020). Medicare Supplement Insurance. Retrieved from https://www.medicare.gov/Pubs/pdf/11575-Medigap-Getting-Started.pdf

Centers for Medicare and Medicaid Services. (n.d). Medicaid.gov keeping America healthy. Retrieved from https://www.medicaid.gov

Charlson, M. E., Pompei, P., Ales, K. L., & MacKenzie, C. R. (1987). A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *Journal of Chronic Diseases*, *40*(5), 373–383. https://doi.org/10.1016/0021-9681(87)90171-8

Chen, P. C., Tung, Y. C., Wu, P. W., Wu, L. S., Lin, Y. S., Chang, C. J., Kung, S., & Chu, P. H. (2015). Dental procedures and the risk of infective endocarditis. *Medicine (Baltimore)*, *94*(43), e1826. https://doi.org/10.1097/MD.0000000000001826

Chu, V. H., Sexton, D. J., Cabell, C. H., Reller, L. B., Pappas, P. A., Singh, R. K., Fowler, V. G., Jr., Corey, G. R., Aksoy, O., & Woods, C. W. (2005). Repeat infective endocarditis: Differentiating relapse from reinfection. *Clinical Infectious Diseases*, *41*(3), 406–409. https://doi.org/10.1086/431590

Dajani, A. S., Taubert, K. A., Wilson, W., Bolger, A. F., Bayer, A., Ferrieri, P., Gewitz, M. H., Shulman, S. T., Nouri, S., Newburger, J. W., Hutto, C., Pallasch, T. J., Gage, T. W., Levison, M. E., Peter, G., & Zuccaro, G., Jr. (1997). Prevention of bacterial endocarditis. Recommendations by the American Heart Association. *Circulation*, *96*(1), 358–366.

Deo, S. V., Raza, S., Kalra, A., Deo, V. S., Altarabsheh, S. E., Zia, A., Khan, M. S., Markowitz, A. H., Sabik, J. F., 3rd, & Park, S. J. (2018). Admissions for infective endocarditis in intravenous drug users. *Journal of the American College of Cardiology*, *71*(14), 1596–1597. https://doi.org/10.1016/j.jacc.2018.02.011

DeSimone, D. C., Tleyjeh, I. M., Correa de Sa, D. D., Anavekar, N. S., Lahr, B. D., Sohail, M. R., Steckelberg, J. M., Wilson, W. R., & Baddour, L. M. (2015). Temporal trends in infective endocarditis epidemiology from 2007 to 2013 in Olmsted County, MN. *American Heart Journal*, *170*(4), 830–836. https://doi.org/10.1016/j.ahj.2015.07.007

Doerken, S., Avalos, M., Lagarde, E., & Schumacher, M. (2019). Penalized logistic regression with low prevalence exposures beyond high dimensional settings. *PLoS One*, *14*(5), e0217057. https://doi.org/10.1371/journal.pone.0217057

Duval, X., Millot, S., Chirouze, C., Selton-Suty, C., Moby, V., Tattevin, P., Alla, F., & EI-dents Association pour l'Etude et la Prévention de l'Endocardite Infectieuse (AEPEI) Study Group. (2017). Oral streptococcal endocarditis, Oral hygiene habits, and recent dental procedures: A case-control study. *Clinical Infectious Diseases*, *64*(12), 1678–1685. https://doi.org/10.1093/cid/cix237

Firth, D. (1991). Bias reduction of maximum likelihood estimates. *Biometrika*, *80*(1), 27–38.

Fleischauer, A. T., Ruhl, L., Rhea, S., & Barnes, E. (2017). Hospitalizations for endocarditis and associated health care costs among persons with diagnosed drug dependence–North Carolina, 2010-2015. *MMWR. Morbidity and Mortality Weekly Report*, *66*(22), 569–573. https://doi.org/10.15585/mmwr.mm6622a1

Franklin, M., Wailoo, A., Dayer, M., Jones, S., Prendergast, B., Baddour, L. M., Lockhart, P. B., & Thornhill, M. H. (2016). The cost-effectiveness of antibiotic prophylaxis for patients at risk of infective endocarditis. *Circulation*, *134*, 1568–1578.

Habib, G., Hoen, B., Tornos, P., Thuny, F., Prendergast, B., Vilacosta, I., & ESC Committee for Practice Guidelines. (2009). Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): The task force on the prevention, diagnosis, and treatment of infective endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for infection and cancer. *European Heart Journal*, *30*(19), 2369–2413. https://doi.org/10.1093/eurheartj/ehp285

IBM Watson Health. (2019). The IBM MarketScan research databases for life sciences researchers–data brochure. Retrieved from Somers, NY: https://www.ibm.com/downloads/cas/OWZWJ0QO

Imperiale, T. F., & Horwitz, R. I. (1990). Does prophylaxis prevent post-dental infective endocarditis? A controlled evaluation of protective efficacy. *The American Journal of Medicine*, *88*(2), 131–136. https://doi.org/10.1016/0002-9343(90)90461-I

Issa, V. S., Fabri, J., Jr., Pomerantzeff, P. M., Grinberg, M., Pereira-Barreto, A. C., & Mansur, A. J. (2003). Duration of symptoms in patients with infective endocarditis. *International Journal of Cardiology*, *89*(1), 63–70. https://doi.org/10.1016/s0167-5273(02)00424-2

Jensen, A. D., Østergaard, L., Petersen, J. K., Graversen, P. L., Butt, J. H., Hadji-Turdeghal, K., Dahl, A., Bruun, N. E., Iversen, K., Bundgaard, H., Køber, L., & Fosbøl, E. L. (2022). Temporal trends of mortality in patients with infective endocarditis: A nationwide study. *European heart journal. Quality of care & clinical outcomes*, *9*, 24–33. https://doi.org/10.1093/ehjqcco/qcac011

Jones, T. D., Baumgartner, L., Bellows, M. T., Breese, B. B., Kuttner, A. G., McCarty, M., & Rammelkamp, C. H. (1955). Prevention of rheumatic fever and bacterial endocarditis through control of streptococcal infections. *Circulation*, *11*, 317–320.

Kennedy, J., Wood, E. G., & Frieden, L. (2017). Disparities in insurance coverage, health services use, and access following implementation of the affordable care act: A comparison of disabled and nondisabled working-age adults. *Inquiry*, *54*, 46958017734031. https://doi.org/10.1177/0046958017734031

Lacassin, F., Hoen, B., Leport, C., Selton-Suty, C., Delahaye, F., Goulet, V., & Briancon, S. (1995). Procedures associated with infective endocarditis in adults. A case control study. *European Heart Journal*, *16*(12), 1968–1974. https://doi.org/10.1093/oxfordjournals.eurheartj.a060855

Lewis, T., & Grant, R. (1923). Observations relating to subacute infective endocarditis. *Heart*, *10*, 21–77.

Lockhart, P. B., Brennan, M. T., Thornhill, M., Michalowicz, B. S., Noll, J., Bahrani-Mougeot, F. K., & Sasser, H. C. (2009). Poor oral hygiene as a risk factor for infective endocarditis-related bacteremia. *Journal of the American Dental Association (1939)*, *140*(10), 1238–1244.

Maclure, M. (1991). The case-crossover design: A method for studying transient effects on the risk of acute events. *American Journal of Epidemiology*, *133*(2), 144–153.

Maclure, M., & Mittleman, M. A. (2000). Should we use a case-crossover design? *Annual Review of Public Health*, *21*, 193–221. https://doi.org/10.1146/annurev.publhealth.21.1.193

Mittleman, M. A., Maclure, M., & Robins, J. M. (1995). Control sampling strategies for case-crossover studies: An assessment of relative efficiency. *American Journal of Epidemiology*, *142*(1), 91–98. https://doi.org/10.1093/oxfordjournals.aje.a117550

Mylonakis, E., & Calderwood, S. B. (2001). Infective endocarditis in adults. *The New England Journal of Medicine*, *345*(18), 1318–1330.

Ohbe, H., Iwagami, M., Sasabuchi, Y., & Yasunaga, H. (2021). Increased risk of infective endocarditis after traumatic skin wound. *Heart*, *107*, 1868–1874. https://doi.org/10.1136/heartjnl-2020-318632

Porat Ben-Amy, D., Littner, M., & Siegman-Igra, Y. (2009). Are dental procedures an important risk factor for infective endocarditis? A case-crossover study. *European Journal of Clinical Microbiology & Infectious Diseases*, *28*(3), 269–273. https://doi.org/10.1007/s10096-008-0622-3

Rudowitz, R., Garfield, R., & Hinton, E. (2019). Medicaid. Retrieved from https://www.kff.org/medicaid/issue-brief/10-things-to-know-about-medicaid-setting-the-facts-straight/

Starkebaum, M., Durack, D., & Beeson, P. (1977). The "incubation period" of subacute bacterial endocarditis. *The Yale Journal of Biology and Medicine*, *50*(1), 49–58.

STROBE. (n.d). STrengthening the reporting of OBservational studies in epidemiology (STROBE) guidelines. Retrieved from https://www.strobe-statement.org

Strom, B. L., Abrutyn, E., Berlin, J. A., Kinman, J. L., Feldman, R. S., Stolley, P. D., Levison, M. E., Korzeniowski, O. M., & Kaye, D. (1998). Dental and cardiac risk factors for infective endocarditis. A population-based, case-control study. *Annals of Internal Medicine*, *129*(10), 761–769.

Tan, C., Hansen, M., Cohen, G., Boyle, K., Daneman, N., & Adhikari, N. K. (2016). Accuracy of administrative data for identification of patients with infective endocarditis. *International Journal of Cardiology*, *224*, 162–164. https://doi.org/10.1016/j.ijcard.2016.09.030

Thornhill, M. H., Dayer, M. J., Forde, J. M., Corey, G. R., Chu, V. H., Couper, D. J., & Lockhart, P. B. (2011). Impact of the NICE guideline recommending cessation of antibiotic prophylaxis for prevention of infective endocarditis: Before and after study. *BMJ*, *342*, d2392.

Thornhill, M. H., Gibson, T. B., Cutler, E., Dayer, M. J., Chu, V. H., Lockhart, P. B., O'Gara, P. T., & Baddour, L. M. (2018). Antibiotic prophylaxis and incidence of endocarditis before and after the 2007 AHA recommendations. *Journal of the American College of Cardiology*, *72*(20), 2443–2454. https://doi.org/10.1016/j.jacc.2018.08.2178

Thornhill, M. H., Gibson, T. B., Durkin, M. J., Dayer, M. J., Lockhart, P. B., O'Gara, P. T., & Baddour, L. M. (2020). Prescribing of antibiotic prophylaxis to prevent infective endocarditis. *Journal of the American Dental Association (Chicago, IL)*, *151*(11), 835–845. https://doi.org/10.1016/j.adaj.2020.07.021

Thornhill, M. H., Gibson, T. B., Yoon, F., Dayer, M. J., Prendergast, B. D., Lockhart, P. B., O'Gara, P. T., & Baddour, L. M. (2022). Antibiotic prophylaxis against infective endocarditis before invasive dental procedures. *Journal of the American College of Cardiology*, *80*(11), 1029–1041. https://doi.org/10.1016/j.jacc.2022.06.030

Thornhill, M. H., Jones, S., Prendergast, B., Baddour, L. M., Chambers, J. B., Lockhart, P. B., & Dayer, M. J. (2018). Quantifying infective endocarditis risk in patients with predisposing cardiac conditions. *European Heart Journal*, *39*(7), 586–595. https://doi.org/10.1093/eurheartj/ehx655

Toyoda, N., Chikwe, J., Itagaki, S., Gelijns, A. C., Adams, D. H., & Egorova, N. N. (2017). Trends in infective endocarditis in California and New York state, 1998-2013. *JAMA*, *317*(16), 1652–1660. https://doi.org/10.1001/jama.2017.4287

Tubiana, S., Blotière, P. O., Hoen, B., Lesclous, P., Millot, S., Rudant, J., Weill, A., Coste, J., Alla, F., & Duval, X. (2017). Dental procedures, antibiotic prophylaxis, and endocarditis among people with prosthetic heart valves: Nationwide population based cohort and a case crossover study. *BMJ*, *358*, j3776. https://doi.org/10.1136/bmj.j3776

US Department for Health and Human Services. (1996). Health insurance portability and accountability act 1996. Retrieved from https://www.hhs.gov/hipaa/index.html

US Department of Health & Human Services. (2021). Does Medicaid cover dental care? Retrieved from https://www.hhs.gov/answers/medicare-and-medicaid/does-medicaid-cover-dental-care/index.html

Van der Meer, J. T., Van Wijk, W., Thompson, J., Vandenbroucke, J. P., Valkenburg, H. A., & Michel, M. F. (1992). Efficacy of antibiotic prophylaxis for prevention of native-valve endocarditis. *Lancet*, *339*(8786), 135–139.

Wilson, W., Taubert, K. A., Gewitz, M., Lockhart, P. B., Baddour, L. M., Levison, M., Bolger, A., Cabell, C. H., Takahashi, M., Baltimore, R. S., Newburger, J. W., Strom, B. L., Tani, L. Y., Gerber, M., Bonow, R. O., Pallasch, T., Shulman, S. T., Rowley, A. H., Burns, J. C., … Quality of Care and Outcomes Research Interdisciplinary Working Group. (2007). Prevention of infective endocarditis: Guidelines from the American Heart Association: A guideline from the American Heart Association rheumatic fever, endocarditis, and Kawasaki disease committee, council on cardiovascular disease in the young, and the council on clinical cardiology, council on cardiovascular surgery and anesthesia, and the quality of care and Outcomes research interdisciplinary working group. *Circulation*, *116*(15), 1736–1754. https://doi.org/10.1161/CIRCULATIONAHA.106.183095

Wilson, W. R., Gewitz, M., Lockhart, P. B., Bolger, A. F., De Simone, D., Kazi, D. S., Couper, D. J., Beaton, A., Kilmartin, C., Miro, J. M., Sable, C., Jackson, M. A., Baddour, L. M., & American Heart Association Young Hearts Rheumatic Fever, Endocarditis and Kawasaki Disease Committee of the Council on Lifelong Congenital Heart Disease and Heart Health in the Young; Council on Cardiovascular and Stroke Nursing; and the Council on Quality of Care and Outcomes Research. (2021). Prevention of Viridans Group Streptococcal Infective Endocarditis: A Scientific Statement From the American Heart Association. *Circulation*, *143*(20), e963–e978. https://doi.org/10.1161/CIR.0000000000000969

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Thornhill, M. H., Gibson, T. B., Yoon, F., Dayer, M. J., Prendergast, B. D., Lockhart, P. B., O'Gara, P. T., & Baddour, L. M. (2023). Endocarditis, invasive dental procedures, and antibiotic prophylaxis efficacy in US Medicaid patients. *Oral Diseases*, *00*, 1–15. https://doi.org/10.1111/odi.14585