



This is a repository copy of *Temporal trends of infective endocarditis in North America from 2000 to 2017 – a systematic review*.

White Rose Research Online URL for this paper:  
<https://eprints.whiterose.ac.uk/178733/>

Version: Published Version

---

**Article:**

Talha, K.M., Dayer, M.J., Thornhill, M.H. [orcid.org/0000-0003-0681-4083](https://orcid.org/0000-0003-0681-4083) et al. (9 more authors) (2021) Temporal trends of infective endocarditis in North America from 2000 to 2017 – a systematic review. *Open Forum Infectious Diseases*. ISSN 2328-8957

<https://doi.org/10.1093/ofid/ofab479>

---

**Reuse**

This article is distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs (CC BY-NC-ND) licence. This licence only allows you to download this work and share it with others as long as you credit the authors, but you can't change the article in any way or use it commercially. More information and the full terms of the licence here: <https://creativecommons.org/licenses/>

**Takedown**

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing [eprints@whiterose.ac.uk](mailto:eprints@whiterose.ac.uk) including the URL of the record and the reason for the withdrawal request.



[eprints@whiterose.ac.uk](mailto:eprints@whiterose.ac.uk)  
<https://eprints.whiterose.ac.uk/>

# Temporal Trends of Infective Endocarditis in North America from 2000 to 2017 – A Systematic Review

Khawaja M. Talha, M.B.B.S.<sup>1</sup>; Mark J. Dayer, M.B.B.S., Ph.D., F.R.C.P.<sup>2</sup>; Martin H. Thornhill, M.B.B.S., B.D.S., Ph.D.<sup>3</sup>; Wajeeha Tariq, M.B.B.S.<sup>1</sup>; Verda Arshad, M.B.B.S.<sup>1</sup>; Imad M. Tleyjeh, M.D., M.Sc.<sup>1,4-6</sup>; Kent R. Bailey, Ph.D.<sup>7</sup>; Raj Palraj, M.D.<sup>1</sup>; Nandan S. Anavekar, M.D.<sup>8</sup>; M. Rizwan Sohail, M.D.<sup>9</sup>; Daniel C. DeSimone, M.D.<sup>1,8</sup>; Larry M. Baddour, M.D.<sup>1,8</sup>

<sup>1</sup>Division of Infectious Diseases, Department of Medicine, Mayo Clinic School of Medicine and Science, Rochester, Minnesota, USA; <sup>2</sup>Department of Cardiology, Somerset Foundation Trust, Taunton, UK; <sup>3</sup>Academic Unit of Oral & Maxillofacial Medicine Surgery & Pathology, University of Sheffield School of Clinical Dentistry, Sheffield, UK; <sup>4</sup>Division of Epidemiology, Mayo Clinic School of Medicine and Science, Rochester, Minnesota, USA; <sup>5</sup>Infectious Diseases Section, Department of Medical Specialties, King Fahad Medical City, Riyadh, Saudi Arabia; <sup>6</sup>College of Medicine, Alfaisal University, Riyadh, Saudi Arabia; <sup>7</sup>Department of Biomedical Statistics and Informatics, Mayo Clinic School of Medicine and Science, Rochester, Minnesota, USA; <sup>8</sup>Department of Cardiovascular Disease, Mayo Clinic School of Medicine and Science, Rochester, Minnesota, USA; <sup>9</sup>Section of Infectious Diseases, Baylor College of Medicine, Houston, Texas, USA.

© The Author(s) 2021. Published by Oxford University Press on behalf of Infectious Diseases Society of America.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (<https://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact [journals.permissions@oup.com](mailto:journals.permissions@oup.com)

Correspondence: Daniel C. DeSimone, MD  
Division of Infectious Diseases,  
Mayo Clinic,  
200, 1<sup>st</sup> Street SW, Rochester, MN, USA, 55905,  
Desimone.daniel@mayo.edu  
(507)-284-2511

Accepted Manuscript

Financial Disclosure: Larry M. Baddour, M.D. reports Boston Scientific, consultant duties; UpToDate, royalty payments (authorship duties); Botanix Pharmaceuticals, consulting duties; Roivant Sciences Inc., consultant duties. M. Rizwan Sohail, M.D. reports receiving funds from TYRX Inc and Medtronic for prior research unrelated to this study administered according to a sponsored research agreement between Mayo Clinic and study sponsor that prospectively defined the scope of the research effort and corresponding budget; and honoraria/consulting fees from Medtronic Inc., Philips, and Aziyo Biologics, Inc. Research Grant: Medtronic. Dr Mark Dayer reports payments from Biotronik unrelated to this study. The remaining authors have nothing to disclose.

Funding: N/A

Abbreviations: IE (infective endocarditis), IDU (injection drug use), PWID (persons who inject drugs, VGS (viridans group streptococci)



## INTRODUCTION

Among the variety of diseases involving the cardiovascular system, infective endocarditis (IE) is less commonly seen. Nevertheless, due to the high (up to ~40%) one-year mortality rate, frequent need for surgical intervention and common requirement of prolonged hospital stays, the syndrome deserves close surveillance. Moreover, the ever-changing epidemiology of IE coupled with an increasing incidence demonstrated in some investigations warrants a contemporary review.

The expected IE patient “phenotype” of older, particularly male, patients predominates and has for decades. Factors responsible for this clinical profile are multiple and include implantation of an ever-increasing array of cardiovascular devices with the bulk of these devices placed in older patients, often with comorbid conditions. Degenerative cardiac valve disease is also important in IE epidemiology among older patients. The survival of patients with congenital heart disease into adulthood has also influenced the epidemiology of IE where a broader age range of adult patients has been observed. In contrast, the almost complete elimination of rheumatic carditis in North America has impacted the prevalence of IE among younger adults in North America.

Injection drug use (IDU) as a complication of the ongoing opioid epidemic has changed the epidemiologic landscape of many regions of North America. Unlike IE seen decades ago, more rural areas have described escalating rates of IE among younger, otherwise healthy people who inject drugs (PWID), with a predominance of infection due to *Staphylococcus aureus*, one of the most virulent pathogens that causes IE. Moreover, IDU-related IE has not been limited to right-sided IE as both left-sided and bilateral involvement have often been seen with increased morbidity and mortality. Despite the prevalence of PWID/IE in some rural areas, larger tertiary care centers in urban environments have also

been impacted, in part related to the referral of IE patients for management expertise. For example, the prevalence of PWID in adult patients with IE seen recently in Boston, Massachusetts and Lexington, Kentucky has reached 46% and 73%, respectively.

Marked restrictions in the use of antibiotic prophylaxis (AP) introduced by the 2007 American Heart Association (AHA) guidelines, which have been adopted by both Canada and the United States, represent another factor that could impact the epidemiology, and to a lesser extent, the incidence of IE in North America. These restrictions accounted for ~90% reduction in AP for invasive dental procedures and prompted concerns that more cases of IE due to viridans group streptococci (VGS) would occur. Ongoing investigations continue to evaluate for this possibility, but based on work published to date, a clear determination of an increase in VGS IE following introduction of these guidelines is lacking, in part due to the lack of microbiologic data reported in these publications. Furthermore, no specific International Classification of Diseases (ICD) codes exist to date, remarkably, for VGS. The updated (2021) AHA Statement largely reflects the changes in the 2007 version but was revised to focus only on invasive dental procedures and IE due to VGS. In response to the many factors outlined above, we conducted a systematic review of population-based studies that evaluated temporal trends of IE epidemiology in the adult population of North America from 2000 onwards.

## **METHODS**

A literature search was performed with a focus on the incidence and epidemiology of IE. It was conducted in June 2020 in Ovid EBM Reviews™, Ovid Embase™, Ovid Medline™, Scopus™, and Web of Science™ for papers published between January 1, 2000 and May 31, 2020. The search was limited to the English language. Search strategies are outlined in the Supplement. All results were exported to Endnote where obvious duplicates

were deleted. Two reviewers (K.M.T and L.M.B) performed the literature review and any disagreements were solved by discussion with two additional reviewers (M.J.D. and D.C.D). Corresponding authors of studies were contacted via email in cases where queries existed.

### **Patient Consent Statement**

The study was exempt from patient consent, as it does not include factors necessitating patient consent. The Mayo Clinic Institutional Review Board approved the study

### Inclusion and exclusion criteria

All studies which provided information on population-based trends of IE in the adult ( $\geq 18$  years) population of North America from 2000 onwards were included in the review. Single-center and multi-center studies, clinical trials, case reports, conference abstracts, systematic reviews and animal studies were excluded, as were investigations that reported crude incidence without a population-based estimate. In addition, studies that determined IE incidence that was specific to infecting pathogens or unique patient populations (e.g. HIV-infected, congenital heart disease) were also excluded. Details of the search strategy are provided in the Supplement.

### Data extraction

Data that described authors, publication year, study location, population covered, average age, incidence rate, IE microbiology, mortality, IDU, and cases requiring surgery as part of treatment were extracted from all included studies.



## Study definition and outcomes

The primary outcome was incidence of IE, while secondary outcomes were prevalence of PWID among IE patients, pathogen prevalence, proportion of patients that required valvular surgery and mortality (stratified as inpatient, six-month and one-year mortality). All included studies defined IE using primary or secondary diagnosis based on International Classification of Diseases ninth revision (ICD 9) and tenth revision (ICD 10). Studies that defined IE using either Duke criteria or modified Duke criteria as possible or definite IE were also included.

## Risk of bias

Two reviewers (K.M.T and W.T.) independently rated the methodologic quality of each study. We assessed the quality of each population-based survey based on four key features: adequacy of population definition, sampling techniques, disease definition, and completeness of case ascertainment, as summarized in Table 2. We deemed the population definition to be inadequate if residency status population of interest was not confirmed. Optimal sampling techniques include complete enumeration or random sampling techniques. Adequacy of case ascertainment was assessed based on case-finding procedures, inclusion of postmortem diagnoses, and number of hospitals serving the population under study that participated in the study. Author statements about shortfall in case ascertainment were also considered an indication of inadequate case ascertainment. Based on these criteria, we excluded studies that had considerable shortfalls in case ascertainment and/or lacked a case definition. Reviewer disagreements were resolved by consensus after review of the article. A detailed version of the quality assessment tool is included in the Supplement.



2). There were a few studies which included yearly trends of IE incidence before 2000. However, the current systematic review was limited to contemporary trends of IE over the past two decades.

Overall, there was great variability observed in trends of overall incidence of IE, with no appreciable increase noted over time (Figure 2). The study by Kadri 2019 described a much higher IE incidence compared to that of other investigations performed during the same time frame, and hence was plotted on a secondary axis in Figure 2.

### Patient Demographics

IE was predominately seen in older patients. The lowest mean age (59.1 years) recorded was by Thornhill and the highest mean age (76.0 years) was reported by Bikdeli . The studies by Mendiratta and Bikdeli et al only included patients aged  $\geq 65$  years, which accounts for a comparatively higher mean age reported in both studies (76.0 and 79.4, respectively). IE was more common in men as reported by all but two studies (Thornhill and Bikdeli ) (Table 1).

### Injection Drug Use

Five of 14 studies, from different study populations, reported trends of percentage changes in IE in PWID. Wong 2020 reported incidence numbers for IE in PWID, instead of percentages, as illustrated on the secondary axis of Figure 3. There has been a notable increase in percentage prevalence of opioid use and IDU among patients with IE as reported by individual studies (see Supplement). There were 3 studies that reported only the overall percentage prevalence of IDU in an IE cohort during their respective study periods. DeSimone reported an overall PWID prevalence of 10% among patients with IE which did not change in IE patients seen between 2014 and 2017. Garg reported a PWID-IE prevalence

of 16.6%, as a proportion of total IE cases while Tleyjeh reported a PWID-IE prevalence of 3% over a 30 year study period.

### Microbiology

Nine studies detailed pathogens (Table 1). Seven studies reported *S. aureus* as the most common pathogen with VGS as the most common in 2 studies. The prevalence of enterococci was reported in 4 studies with the highest (22%) prevalence described by DeSimone . Coagulase-negative staphylococci were reported as an exclusive entity by 5 studies and Correa and DeSimone et al. reported the highest (10%) prevalence.

### Outcomes

The percentage of patients who required cardiac valvular surgery for IE was documented in seven studies (range: 6.4 – 16.0%). Other outcomes examined included inpatient, six-month and one-year mortality rates. Inpatient mortality was reported in seven studies, with rates ranging from 3.7% to 14.4%. Six-month mortality was described in three studies and rates were much higher, ranging from 26.7% to 31.8%. Four studies reported rates of one-year mortality, which was very consistent, ranging from 36.2% to 37.1% (Table 1).

## **DISCUSSION**

The overall incidence of IE has remained stable in North America in the years 2000-2017, based on the findings of our systematic review. This finding may be somewhat unanticipated as results from single- and multi-center investigations predominate in the literature and are subject to referral and other biases. Thus, our reliance on only population-based studies in this review.

IDU, perhaps, is a predisposing condition of IE in North America, particularly in the United States, that has garnered the most attention over the past ~20 years. The increase in prevalence of IDU among IE patients that was demonstrated in this review is not surprising, given the ongoing opioid epidemic in North America, which has resulted in an 11-fold increase in deaths related to opioid drug overdose between 2013 and 2019. The prevalence of IDU represents a major change in more traditional risk factors associated with the development of IE and has had a direct effect on the demographics of IE patients. Wong et al., for example, highlighted a marked increase in incidence of IE among persons aged 18–29 years between 2007 and 2017, likely attributable to PWID. This population poses a sizable burden to the healthcare system in North America. Fleischauer et al highlighted that 42% of PWID with IE in North Carolina were either uninsured or on Medicaid, for example. The dramatic increase in PWID-IE cases seen in this state alone between 2010 and 2015 was striking, with resultant increases of 1,800 percent in hospital expenditures. Moreover, the patients affected were young to middle-aged adults, which represents a population subset that forms an essential part of a country’s economic workforce. Coupled with a concomitant burden of hepatitis C, HIV infection and risk of recurrent IE in patients who survive initial bouts of IE, there is a justified cause for concern as public health and other agencies involved in healthcare delivery devise strategies to reduce the tremendous burden of complications, including IE, due to the opioid epidemic.

Because this burden has received considerable attention, and rightfully so, the assumption has been that IDU has resulted in an increase in IE incidence and impacted the epidemiology of IE throughout North America. Our systematic review, however, did not demonstrate an incidence increase which could be due to a phenomenon of “geographic heterogeneity” in regard to IDU and areas of the United States. Because of variability of rates of IDU based on geographic location, “local” incidence of IE could widely vary. This,

coupled with the recognition that population-based studies in North America included in this review have surveyed only specific portions of the entire population of either Canada or the United States, could explain, in part, the lack of increase in IE incidence.

There has been variability of reported IE incidence among other global sites. For example, investigations from England have demonstrated a rising incidence of IE following a total restriction in AP for certain dental procedures has occurred, but a causal relationship between increasing incidence and AP restrictions was not established. Of note, the authors raised concerns regarding the inconsistent use of ICD coding and primary and secondary diagnoses that have been used to define IE cases in different studies which could have markedly influenced estimates of IE incidence. These factors were closely linked to the number of different ICD-9/10 codes used to identify IE cases, as reflected in incidence rates displayed in Figure 2. It is notable that all studies with an incidence in the 5-10 cases per 100,000 range used a restricted number of ICD-9/10 codes (with either primary or a restricted number of primary/secondary diagnosis codes) (See Supplement) or Duke/modified Duke criteria. In contrast, studies with higher IE incidence rates used a much broader set of ICD-9 and 10 codes in both the primary and secondary position. Interestingly, Fawcett et al. reported that more than half of the cases that were coded using ICD-10 as IE in study centers were not, in fact, confirmed cases. For example, the code I38 from ICD-10, used in both Wong and Kadri 9, had a PPV of less than 6%. They reported that sensitivity and positive predictive values (PPV) of ICD-9 codes were 70%. This is lower than measures reported in Toyoda (sensitivity 94%; PPV 94%) (Table 4). Moreover, there is a discrepancy in the use of surrogate codes for IE in PWID, since there are no specific ICD 9/10 codes for PWID, resulting in studies reporting varying data for hospitalization of patients for the same year using the same database. Furthermore, it is suggested that studies which use ICD-10 for coding of IE in PWID should be viewed with caution, owing to the risk of missing or

misclassifying more than half the patients, prompting questions regarding the accuracy of codes. This demonstrates a need for ICD codes to be standardized and validated with other records before conducting population-based studies.

ICD-9 codes were most often used in our shortlisted studies, since it was only after 2015 that medical centers in North America fully adopted ICD-10 coding. However, there are several nuances that should be considered when using ICD-9 coding to determine incidence of IE. ICD-9 codes used until 2015 in the US were not confined to diagnosis codes; they also included many procedure codes – and procedure codes are more important than diagnosis codes for billing purposes. This is not the case with ICD-10 codes used in Europe since they only include diagnosis codes and other systems are used for coding when procedures have been performed. It most likely affects the way coders record information and different coding strategies adopted in Europe and the US for identifying IE cases, since healthcare systems in Europe converted to ICD-10 coding before the year 2000. This also suggests that data recorded after 2015 in North America may differ from those recorded before 2015.

Another key aspect to consider is the large difference in incidence reported by Kadri 2019 as compared to that by the remainder of studies. The authors examined the NIS database, which was used by 4 other studies included in this review. However, Kadri et al. observed an incidence range of 179 to 289 cases per 100,000, compared to 2.61 to 39.10 cases per 100,000, reported in other studies. One possible reason for the prevailing difference is the large number of ICD codes (12 ICD-9 codes and 10 ICD-10 codes) used to identify patients. Kadri et al also reported a steep rise in IE incidence following 2010. Thus, it is tempting to speculate that a real increase in IE incidence may not have occurred due to use of ICD-10 with a delay in transition to its implementation in hospitals by 2015.

Bikdeli et al. also detected a high incidence of IE in their cohort as compared to that seen in other studies. This should have been expected since their cohort included Medicare patients and IE has been characteristically predominant among older individuals. Nevertheless, it was intriguing to note the vast disparity in incidence as determined by use of primary codes only versus use of both primary and secondary codes (Figure 2). This observation should be viewed with caution, however, as it highlights the high sensitivity and low specificity of secondary codes in incidence studies, and is most likely an overestimation of true IE incidence.

Since population-based studies are the underpinnings of evidence to detect even the slightest of changes in incidence for an uncommon, yet life-threatening disease like IE, there is a need for standardization of study protocols and ICD code linkage and validation in order to ascertain a more generalizable and precise measurement of IE incidence across the world. In North America, different databases use a variety of combinations of standard codes to ascertain incidence of IE, which leads to a disparity in available evidence. Similar studies conducted in Europe that used more robust, standardized nationwide registries, have also fallen prey to pitfalls of coding issues. Therefore, the authors have proposed recommendations for conducting future incidence and epidemiologic studies of IE. (Table 5)

Trends in the incidence of IE from 2000 to 2017 in North America are of importance in part because of the AHA guideline update in 2007 widely followed in both the US and Canada, where the population indicated for pre-operative AP was restricted to patients at highest risk of IE. The lack of increase in IE incidence demonstrated in our investigation following availability of the 2007 AHA guidelines is reassuring. Work from Mackie and colleagues deserves highlighting. It was based on data from Canada and they made a similar observation and reported a slight increase in IE hospitalizations in all age groups from 2002 to 2013; however, there was no significant difference observed in the rate of increase



following implementation of AHA guidelines. These data were not included in the systematic review, however, due to inability to segregate age groups of interest.

Among causative pathogens, *S. aureus* was reported as the most common cause followed by VGS. The increase in *S. aureus*-related IE can be attributed to a multitude of factors, including increasing PWID and healthcare-associated procedures. The prevalence of VGS has been declining recently; Slipzcuk et al. reported a decrease in VGS prevalence from 27.4% to 17.6% in IE patients over the past five decades in their systematic review. VGS coding deserves special comment as we address IE incidence due to this group of pathogens. Although there have been specific ICD-9/10 codes for many organisms, including *S. aureus*, no codes exist for VGS. Therefore, assigning infection due to VGS has been a process of elimination, by excluding other types of streptococci that harbour specific ICD-9/10 codes (e.g. ICD 10 code A49.1 for streptococcal infection at an unspecified site). This practice, coupled with use of “big data” studies, has resulted in estimates of VGS IE incidence that have been suboptimal or incorrect. Moreover, it is difficult to ascertain the impact of 2007 AHA prevention guidelines on VGS IE incidence as the true number might be skewed due to factors that impact the recording of supplementary and secondary codes for VGS IE. In addition, because *Enterococcus faecalis*, a prevalent cause of IE in the elderly, was listed as “*Streptococcus faecalis*” in ICD-9 coding, in at least one survey this likely impacted the reported increase in “streptococcal” IE incidence.

The need for surgical intervention in IE patients ranged from 6.4 to 16.0%. This in contrast to previously conducted studies that reported surgery in up to 25% to 50% of IE patients. Since most of these studies are not population-based and were conducted at surgical tertiary care centers, they are prone to referral bias resulting in inflated figures for surgical intervention.

The range of in-hospital mortality rates demonstrated in this review was lower as compared to that described in previous systematic reviews by Slipzcuk et al. (8 to 40%) and Tleyjeh et al (16 to 21%). Despite these relatively low in-hospital mortality rates, 1-year mortality persisted; just over 1 in 3 patients were dead by 1 year (36.2 to 37.1%, Table 1).

A recently published systematic review compared incidence of IE before and after implementation of major guidelines changes for AP use and invasive procedures . In contrast to the number (n=14) of North American studies included in our review, the Williams publication included only eight investigations that focused on trend comparisons in “before and after” guideline changes. Moreover, we used time plots to observe changes in IE incidence over the past 20 years, irrespective of changes in international guidelines. This was done to assess factors other than AP use that might have impacted the incidence of IE. Williams et al. included three studies that were excluded from our review because the cohorts in those studies included pediatric IE cases . Furthermore, we included more contemporary studies that extended to May 2020. It is also important to highlight that there are considerable demographic differences between North American and European populations with IE that were combined in the Williams’ review, which deserve separate analysis; Europe has not been affected to the same degree by the opioid epidemic seen in North America, for example.

### Limitations

Despite the thoroughness of the current systematic review, there were certain limitations that deserve mention. Only studies with patients aged 18 years and older were included, which resulted in the exclusion of a small number of robust population-based investigations. There were two studies that included patients age  $\geq 65$  and one that included patients limited to ages 18-64. These studies were included as the authors of this review believe it was necessary to include all adult-based studies, since the epidemiology of pediatric

IE is different than that seen in adults and bacterial pathogens that cause IE are similar among all adult age groups, albeit with a higher prevalence for enterococcal species in older patients. Only one study from Canada fit the study's inclusion criteria, which might not be an adequate representation of IE incidence in that country. There was also great heterogeneity in the variety of ICD codes used in each included investigation, and a lack of availability of trends data for causal pathogens and risk factors prohibited us from conducting a meta-regression analysis. Lastly, trends for VGS IE were not available, which would have been of interest to accurately assess the impact of antibiotic prophylaxis guidelines regarding dental procedures on incidence of VGS IE over the past two decades. The addition of a secondary code specific for VGS is expected to be supported in the next version (ICD-11) of coding updates. (Table 5).

## CONCLUSION

Based on findings of this systematic review, the incidence of IE in North America has remained stable between 2000-2017, despite increasing rates of IDU-related IE. A standardized approach to the use of ICD coding to optimally define IE incidence is needed in subsequent population-based investigations. In addition, sustained efforts are needed to ensure the ICD-11 coding version includes specific genus and species designations of VGS.

## ACKNOWLEDGMENTS

The authors are extremely grateful for the philanthropic support provided by a gift from Eva and Gene Lane (L.M.B.), which was paramount in our work to advance the science of cardiovascular infections, which has been an ongoing focus of investigation at Mayo Clinic for over 60 years. We also recognize the unique expertise of Danielle J. Gerberi, M.L.S., AHIP for conducting the systematic review literature search and Barbara A. Abbott for data retrieval from the Rochester Epidemiology Project (REP).

## POTENTIAL CONFLICTS OF INTEREST

Potential conflicts of interest. LMB reports consultant duties for Boston Scientific and Roivant Sciences Inc., and royalty payments (authorship duties) from UpToDate. MRS reports research grant from Medtronic, receiving funds from TYRX Inc and Medtronic for prior research unrelated to this study administered according to a sponsored research agreement between Mayo Clinic and study sponsor that prospectively defined the scope of the research effort and corresponding budget; and honoraria/consulting fees from Medtronic Inc., Philips, and Aziyo Biologics, Inc. MJD reports payments from Biotronik unrelated to this study. The remaining authors have no conflicts.

## REFERENCES

1. Bin Abdulhak AA, Baddour LM, Erwin PJ, et al. Global and regional burden of infective endocarditis, 1990-2010: a systematic review of the literature. *Glob Heart*. 2014/03// 2014;9(1):131-143.
2. Kadri AN, Wilner B, Hernandez AV, et al. Geographic Trends, Patient Characteristics, and Outcomes of Infective Endocarditis Associated With Drug Abuse in the United States From 2002 to 2016. *J Am Heart Assoc*. Oct 2019;8(19):e012969.
3. Alkhouli M, Alqahtani F, Alhajji M, Berzingi CO, Sohail MR. Clinical and Economic Burden of Hospitalizations for Infective Endocarditis in the United States. *Mayo Clin Proc*. May 2020;95(5):858-866.
4. Erichsen P, Gislason GH, Bruun NE. The increasing incidence of infective endocarditis in Denmark, 1994-2011. *Eur J Intern Med*. Nov 2016;35:95-99.
5. Bor DH, Woolhandler S, Nardin R, Bruschi J, Himmelstein DU. Infective endocarditis in the U.S., 1998-2009: a nationwide study. *PLoS One*. 2013;8(3):e60033.
6. Parikh MP, Octaria R, Kainer MA. Methicillin-Resistant Staphylococcus aureus Bloodstream Infections and Injection Drug Use, Tennessee, USA, 2015-2017. *Emerg Infect Dis*. 2020;26(3):446-453.
7. Huang G, Davis KA, Petty SA, Tan WA, Barnes EW, Peacock JE, Jr. Left-sided infective endocarditis in persons who inject drugs. *Infection*. Jun 2020;48(3):375-383.
8. Balda J, Alpizar-Rivas R, Elarabi S, Jaber BL, Nader C. Recent Trends in Infective Endocarditis among Patients with and without Injection Drug Use: An Eight-Year Single Center Study. *Am J Med Sci*. 2021;18(21):00279-00272.
9. Blevins SR, Stivers T, Sabitus K, Weeks R, Porterfield JZ, Thornton A. 83. A Descriptive Analysis of a Multi-disciplinary Approach to Opioid Use Disorder Treatment Within an Infectious Diseases Clinic: Open Forum Infect Dis. 2020 Dec 31;7(Suppl 1):S173. doi: 10.1093/ofid/ofaa439.393. eCollection 2020 Oct.
10. Wilson W, Taubert KA, Gewitz M, et al. 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*. Oct 9 2007;116(15):1736-1754.
11. Wilson WR, Gewitz M, Lockhart PB, et al. Prevention of Viridans Group Streptococcal Infective Endocarditis: A Scientific Statement From the American Heart Association. *Circulation*. 2021;143(20):e963-e978.
12. World Health O. International classification of diseases : [9th] ninth revision, basic tabulation list with alphabetic index. Geneva: World Health Organization; 1978.
13. World Health O. ICD-10 : international statistical classification of diseases and related health problems : tenth revision. 2nd ed ed. Geneva: World Health Organization; 2004.
14. Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Duke Endocarditis Service. *Am J Med*. Mar 1994;96(3):200-209.
15. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis*. Apr 2000;30(4):633-638.
16. Tleyjeh IM, Abdel-Latif A, Rahbi H, et al. A Systematic Review of Population-Based Studies of Infective Endocarditis. *Chest*. 2007/09/01/ 2007;132(3):1025-1035.
17. Page MJ, Shamseer L, Tricco AC. Registration of systematic reviews in PROSPERO: 30,000 records and counting. *Syst Rev*. 2018;7(1):32-32.

18. Tleyjeh IM, Steckelberg JM, Murad HS, et al. Temporal trends in infective endocarditis: a population-based study in Olmsted County, Minnesota. *Jama*. 2005;293(24):3022-3028.
19. de Sa DDC, Tleyjeh IM, Anavekar NS, et al. Epidemiological Trends of Infective Endocarditis: A Population-Based Study in Olmsted County, Minnesota. *Mayo Clinic Proceedings*. 2010/05/01/ 2010;85(5):422-426.
20. Thornhill MH, Gibson TB, Cutler E, et al. Antibiotic Prophylaxis and Incidence of Endocarditis Before and After the 2007 AHA Recommendations. *Journal of the American College of Cardiology*. 2018/11/13/ 2018;72(20):2443-2454.
21. Bikdeli B, Wang Y, Kim N, Desai MM, Quagliarello V, Krumholz HM. Trends in hospitalization rates and outcomes of endocarditis among Medicare beneficiaries. *Journal of the American College of Cardiology*. 2013/12/10/ 2013;62(23):2217-2226.
22. Mendiratta P, Tilford JM, Prodhon P, Cleves MA, Wei JY. Trends in Hospital Discharge Disposition for Elderly Patients with Infective Endocarditis: 1993 to 2003. *Journal of the American Geriatrics Society*. 2009;57(5):877-881.
23. Wong CY, Zhu W, Aurigemma GP, et al. Infective Endocarditis Among Persons Aged 18–64 Years Living with Human Immunodeficiency Virus, Hepatitis C Infection, or Opioid Use Disorder, United States, 2007–2017. *Clinical Infectious Diseases*. 2020.
24. DeSimone DC, Tleyjeh IM, Correa de Sa DD, et al. Temporal trends in infective endocarditis epidemiology from 2007 to 2013 in Olmsted County, MN. *American Heart Journal*. 2015/10/01/ 2015;170(4):830-836.
25. Garg P, Ko DT, Jenkyn KMB, Li L, Shariff SZ. Infective Endocarditis Hospitalizations and Antibiotic Prophylaxis Rates Before and After the 2007 American Heart Association Guideline Revision. *Circulation*. 2019;140(3):170-180.
26. Tleyjeh IM, Steckelberg JM, Murad HS, et al. Temporal Trends in Infective Endocarditis A Population-Based Study in Olmsted County, Minnesota. *JAMA*. 2005;293(24):3022-3028.
27. Mattson CL, Tanz LJ, Quinn K, Kariisa M, Patel P, Davis NL. Trends and Geographic Patterns in Drug and Synthetic Opioid Overdose Deaths - United States, 2013-2019. *MMWR Morb Mortal Wkly Rep*. Feb 12 2021;70(6):202-207.
28. Fleischauer AT, Ruhl L, Rhea S, Barnes E. Hospitalizations for Endocarditis and Associated Health Care Costs Among Persons with Diagnosed Drug Dependence - North Carolina, 2010-2015. *MMWR - Morbidity & Mortality Weekly Report*. 2017;66(22):569-573.
29. Coutinho RA. HIV and hepatitis C among injecting drug users. *BMJ*. 1998;317(7156):424-425.
30. Rigg KK, Monnat SM, Chavez MN. Opioid-related mortality in rural America: Geographic heterogeneity and intervention strategies. *Int J Drug Policy*. 2018;57:119-129.
31. Thornhill MH, Dayer MJ, Nicholl J, Prendergast BD, Lockhart PB, Baddour LM. An alarming rise in incidence of infective endocarditis in England since 2009: why? *Lancet*. 2020;395(10233):1325-1327.
32. Quan TP, Muller-Pebody B, Fawcett N, et al. Investigation of the impact of the NICE guidelines regarding antibiotic prophylaxis during invasive dental procedures on the incidence of infective endocarditis in England: An electronic health records study. *BMC Medicine*. 02 Apr 2020;18 (1) (no pagination)(84).
33. Cooley N. The new NICE guidance on antimicrobial prophylaxis against infective endocarditis. *Pharmaceutical Journal*. 19 Apr 2008;280(7498):476+481.
34. Fawcett N, Young B, Peto L, et al. 'Caveat emptor': the cautionary tale of endocarditis and the potential pitfalls of clinical coding data—an electronic health records study. *BMC Medicine*. 2019/09/04 2019;17(1):169.
35. Toyoda N, Chikwe J, Itagaki S, Gelijns AC, Adams DH, Egorova NN. Trends in Infective Endocarditis in California and New York State, 1998-2013. *JAMA*. 2017;317(16):1652-1660.
36. See I, Gokhale RH, Geller A, et al. National Public Health Burden Estimates of Endocarditis and Skin and Soft-Tissue Infections Related to Injection Drug Use: A Review. *The Journal of Infectious Diseases*. 2020;222(Supplement\_5):S429-S436.

37. Marks LR, Nolan NS, Jiang L, Muthulingam D, Liang SY, Durkin MJ. Use of ICD-10 Codes for Identification of Injection Drug Use-Associated Infective Endocarditis Is Nonspecific and Obscures Critical Findings on Impact of Medications for Opioid Use Disorder. *Open Forum Infect Dis*. Oct 2020;7(10):ofaa414.
38. International Classification of Diseases, (ICD-10-CM/PCS) Transition. 2015; <https://www.cms.gov/Medicare/Coding/ICD10>.
39. Burns EM, Rigby E, Mamidanna R, et al. Systematic review of discharge coding accuracy. *J Public Health (Oxf)*. 2012;34(1):138-148.
40. Mackie AS, Liu W, Savu A, Marelli AJ, Kaul P. Infective Endocarditis Hospitalizations Before and After the 2007 American Heart Association Prophylaxis Guidelines. *Can J Cardiol*. Aug 2016;32(8):942-948.
41. Slipczuk L, Codolosa JN, Davila CD, et al. Infective endocarditis epidemiology over five decades: a systematic review. *PLoS one*. 2013;8(12):e82665-e82665.
42. Pant S, Patel NJ, Deshmukh A, et al. Trends in infective endocarditis incidence, microbiology, and valve replacement in the United States from 2000 to 2011. *J Am Coll Cardiol*. May 19 2015;65(19):2070-2076.
43. DeSimone DC, Wilson WR, Baddour LM. Trends in Infective Endocarditis Incidence, Microbiology, and Valve Replacement in the United States From 2000 to 2011: The Devil Is in the Details. *J Am Coll Cardiol*. Sep 8 2015;66(10):1201-1202.
44. Pericas JM, Falces C, Moreno A, Marco F, Mestres CA, Miro JM. Neglecting Enterococci May Lead to a Misinterpretation of the Consequences of Last Changes in Endocarditis Prophylaxis American Heart Association Guidelines. *Journal of the American College of Cardiology*. 2015;66(19):2156-2156.
45. Prendergast BD, Tornos P. Surgery for infective endocarditis: who and when? *Circulation*. Mar 9 2010;121(9):1141-1152.
46. Castillo JC, Anguita MP, Ramírez A, et al. Long term outcome of infective endocarditis in patients who were not drug addicts: a 10 year study. *Heart*. 2000;83(5):525-530.
47. Murdoch DR, Corey GR, Hoen B, et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study. *Arch Intern Med*. Mar 9 2009;169(5):463-473.
48. Williams ML, Doyle MP, McNamara N, Tardo D, Mathew M, Robinson B. Epidemiology of infective endocarditis before versus after change of international guidelines: a systematic review. 2021;15:17539447211002687.
49. Moreyra AE, East S-a, Zinonos S, et al. Trends in Hospitalization for Infective Endocarditis as a Reason for Admission or a Secondary Diagnosis. *The American Journal of Cardiology*. 2019/08/01/ 2019;124(3):430-434.
50. McCarthy NL, Baggs J, See I, et al. Bacterial Infections Associated With Substance Use Disorders, Large Cohort of United States Hospitals, 2012–2017. *Clinical Infectious Diseases*. 2020.
51. Mori M, Brown KJ, Mahmood SUB, Geirsson A, Mangi AA. Trends in Infective Endocarditis Hospitalizations, Characteristics, and Valve Operations in Patients With Opioid Use Disorders in the United States: 2005–2013;2014. *Journal of the American Heart Association*. 2020;9(6):e012465.
52. Khera R, Krumholz HM. With great power comes great responsibility: big data research from the National Inpatient Sample. *Circulation: Cardiovascular Quality and Outcomes*. 2017;10(7):e003846.
53. Warren JL, Klabunde CN, Schrag D, Bach PB, Riley GF. Overview of the SEER-Medicare data: content, research applications, and generalizability to the United States elderly population. *Medical care*. 2002:IV3-IV18.

54. Thornhill MH, Gibson TB, Cutler E, et al. Antibiotic prophylaxis and incidence of endocarditis before and after the 2007 AHA recommendations. *Journal of the American College of Cardiology*. 2018;72(20):2443-2454.
55. Wong CY, Zhu W, Aurigemma GP, et al. Infective endocarditis among persons aged 18-64 years with HIV, hepatitis C infection, or opioid use disorder-United States, 2007-2017. *Clinical Infectious Diseases: an Official Publication of the Infectious Diseases Society of America*. 2020.

Accepted Manuscript



Table 1: Clinical features of patient populations in included studies.

Author	Database	Age (years)	Female (%)	Microbiology* (%)	Mortality (%)	Underwent surgery (%)
United States of America						
Tleyjeh 2005	REP	61.5 (mean)	27.0	VGS 44.0, <i>Staphylococcus aureus</i> 26.0, CoNS 7.0, <i>Enterococcus</i> species 6.0	Inpatient: NR	16.0
					6-month: NR	
					1-year: 37.1	
Mendiratta 2009	NIS	76.0 (mean)	47.0	NR	Inpatient: 20.0	NR
					6-month: NR	
					1-year: NR	
Correa 2010	REP	70.5 (median)	33.3	VGS 40.0, <i>Staphylococcus aureus</i> 19.3, CoNS 10.0, <i>Enterococcus</i> species 6.7	Inpatient: NR	16.0
					6-month: 26.7	
					1-year: NR	
Bikdeli 2013	Medicare inpatient Standard Analytic Files	79.4 (mean)	58.8	NR	Inpatient: 10.1	NR
					6-month: 31.8	
					1-year: 36.2	
DeSimone 2015	REP	68.8 (median)	41.0	<i>Staphylococcus aureus</i> - 33.0, <i>Enterococcus</i> species - 22.0, VGS 16.0, CoNS 10.0	Inpatient: NR	16.0
					6-month: 29.0	
					1-year: 37.0	
Toyoda 2017	Statewide Planning and Research Cooperative System database in New York and the Office of Statewide Health Planning and Development database in	62.3 (mean)	40.9	<i>Staphylococcus aureus</i> 31.9, Streptococci 26.6, Oral streptococci 10.1	Inpatient: NR	13.3
					6-month: NR	
					1-year: 37.1	

	California					
Thornhill 2018	Truven Database	59.1 (mean)	53.2	NR	NR	NR
Alkhouli 2019	NIS	61.5 (mean)	41.1	NR	Inpatient: 11.8	11.2
					6-month: NR	
					1-year: NR	
Kadri 2019	NIS	68.0 (median)	48.7	<i>Staphylococcus aureus</i> 24.6, Streptococci 15.5, GNB 1.2	Inpatient: 8.8	6.4
					6-month: NR	
					1-year: NR	
Moreyra 2019	Myocardial Infarction Data Acquisition System	63.5 (mean)	42.0	Staphylococci 54.0, Streptococci 40.0, GNB 4.0	Inpatient: 14.4	NR
					6-month: NR	
					1-year: NR	
McCarthy 2020	Premier Healthcare Database	NR	NR	<i>Staphylococcus aureus</i> 27.3, VGS 26.5, <i>Enterococcus</i> species 16.1	Inpatient 3.7	NR
					6-month: NR	
					1-year: NR	
Mori 2020	NIS	59.3 (mean)	40.6	Staphylococci 36.2, Streptococci 23.9, GNB 7.1	Inpatient: 8.3	11.4
					6-month: NR	
					1-year: NR	
Wong 2020	IBM MarketScan	NR	42.1	NR	NR	NR
Canada						
Garg 2019	Multiple population-based administrative healthcare databases in Ontario	63.0 (median)	36.3	<i>Staphylococcus aureus</i> 30.3, <i>Streptococcus</i> species 26.4, Other staphylococcal species 10.5, Gram-negative or <i>Candida</i> species 6.5	NR	NR
	NIS – National Inpatient Sample VGS - viridans group streptococci					

	CoNS – coagulase-negative staphylococci GNB – gram-negative bacilli REP – Rochester Epidemiology Project NR – Not reported
--	---

*\*The genus and species of the pathogens have been listed as presented in the individual studies. Since the pathogens were grouped differently in each study, it was not possible for us to standardize them.*

Accepted Manuscript

Table 2: Quality assessment of included studies.

<b>Study</b>	<b>Adequacy of population definition</b>	<b>Sampling techniques</b>	<b>Disease definition</b>	<b>Completeness of case ascertainment</b>
Tleyjeh 2005	Adequate	Adequate	Adequate	Adequate
Mendiratta 2009	Adequate	Adequate	Inadequate	Adequate
Correa 2010	Adequate	Adequate	Adequate	Adequate
Garg 2012	Adequate	Adequate	Inadequate	Adequate
Bikdeli 2013	Adequate	Adequate	Inadequate	Adequate
DeSimone 2015	Adequate	Adequate	Adequate	Adequate
Toyoda 2017	Adequate	Adequate	Inadequate	Adequate
Thornhill 2018	Adequate	Adequate	Inadequate	Adequate
Alkhouli 2019	Adequate	Adequate	Inadequate	Adequate
Kadri 2019	Adequate	Adequate	Inadequate	Adequate
Moreyra 2019	Adequate	Adequate	Inadequate	Adequate
McCarthy 2020	Adequate	Adequate	Inadequate	Adequate
Mori 2020	Adequate	Adequate	Inadequate	Adequate
Wong 2020	Adequate	Adequate	Inadequate	Adequate

Accepted Manuscript

Table 3: Description of population included in databases.

<b>Database</b>	<b>Definition</b>
Rochester Epidemiology Project	A collaboration of clinics, hospitals and other medical facilities in 27 counties in Minnesota and Wisconsin.
National Inpatient Sample (NIS)	Constructed annually by including 100% of the discharges from 20% of US hospitals.
Medicare Inpatient Standard Analytical Files	Medicare is the primary health insurer of 97% of the US population 65 years and older.
Statewide Planning and Research Cooperative System database	Prospectively collects data on every hospital discharge, ambulatory surgery, and emergency department visit in the state of New York.
Office of Statewide Health Planning and Development database	Prospectively collects data on every hospital discharge, ambulatory surgery, and emergency department visit in the state of California.
Myocardial Infarction Data Acquisition System (MIDAS)	Covers all discharges with the diagnosis of acute myocardial infarction in New Jersey, based on the New Jersey hospital discharge data system.
Premier Healthcare Database (PHD)	An electronic healthcare database from approximately 800 private and academic hospitals, representing approximately 20% of US inpatient discharges.
Truven Database	Includes those covered by employer-sponsored private health insurance involving more than 260 employers and 40 health plans, with 240 million covered lives and 32 billion service records.
IBM MarketScan	Includes diagnosis and procedure codes for 26 million persons who enrolled in approximately 350 employer-sponsored commercial health insurance plans in 2017 in all 50 US states.

Table 4: Summary of studies that performed ICD code validation

Study	Codes/criteria used	Comment	Validity
Toyoda 2017	ICD 9 and 10. Primary and secondary.	Independent validation	Sensitivity 94% Specificity 99% PPV 94%
Thornhill 2018	ICD 9. Primary and secondary	Record linkage using ICD codes	Sensitivity 95% Specificity 100%
Alkhoulī 2019	ICD 9 and 10. Primary and secondary.	Record linkage using ICD codes	Sensitivity 94% Specificity 99% PPV 94%
Mori 2020	ICD 9 and 10. Primary and secondary.	Record linkage using ICD codes	Sensitivity 94% Specificity 99% PPV 94%

Accepted Manuscript

Table 5: Recommendations for conducting incidence and epidemiologic studies of infective endocarditis.

1. Population-based studies should be designed and conducted to minimize the risk of bias and ensure the adequacy of case ascertainment, disease definition, sampling techniques and population definition.
2. Studies should report a separate analysis of adult (18 years and older) and pediatric patients, as the clinical aspects of IE are markedly different for the two groups.
3. Investigators should consider the date for implementation of ICD 10 codes, i.e. 2015 in the USA, when reporting trend data.
4. All studies should report separately ICD-10 code I33 in the primary position in order to facilitate comparison of rates across populations.
5. Designate a code for PWID as a modification for ICD 11, to prevent use of non-specific surrogate codes.
6. Designate codes for VGS-IE as a modification for ICD 11, as a common pathogen associated with IE.
7. There should be a separate code to designate current IDU.

Figure 1: Schematic representation of study selection using PRISMA.

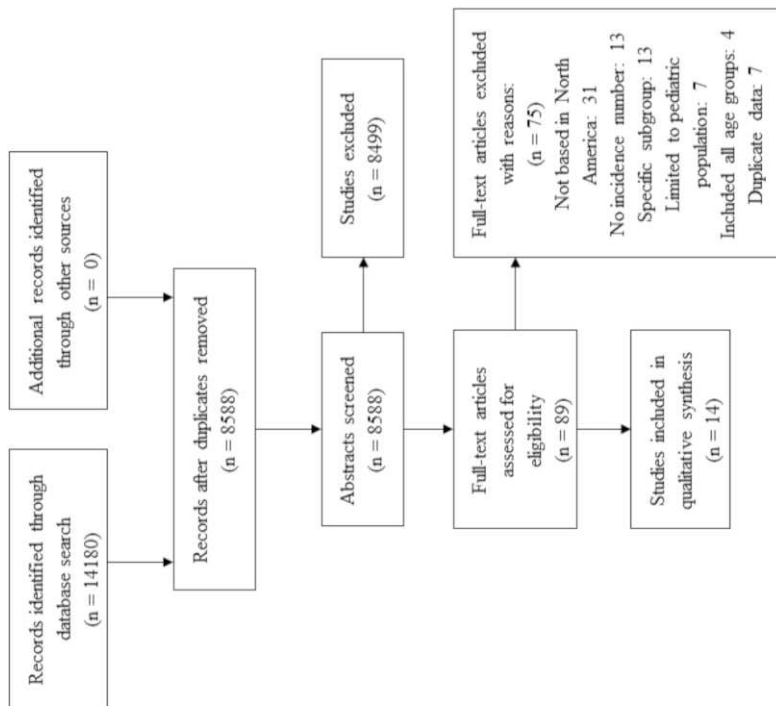
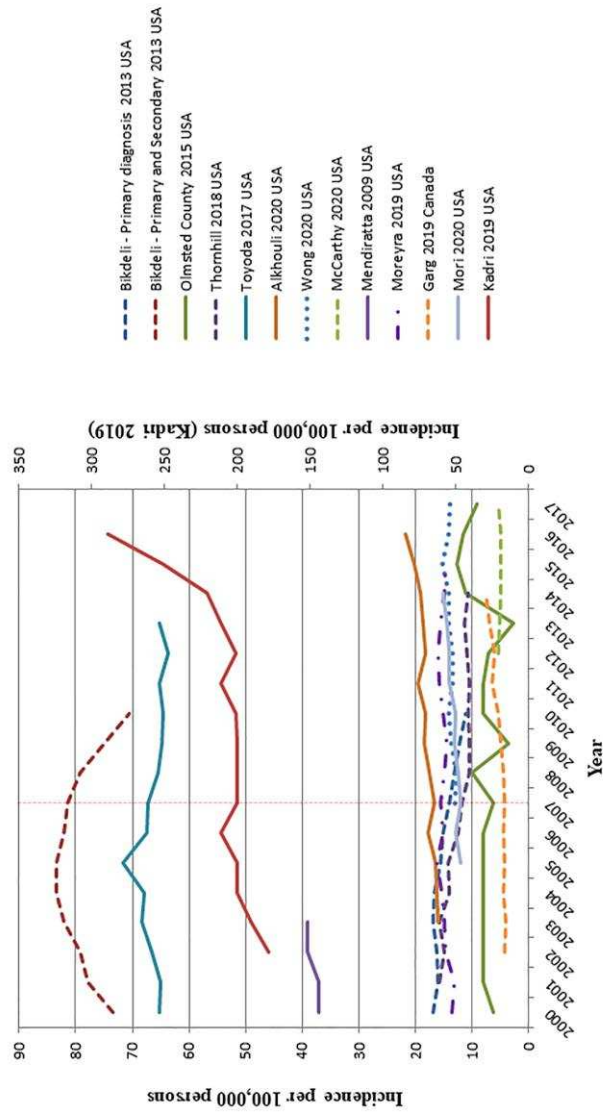


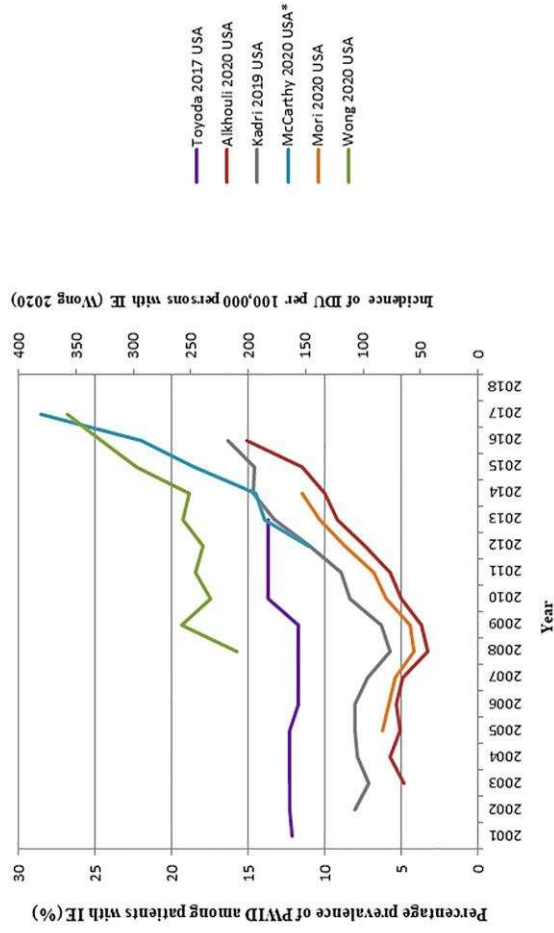


Figure 2: Temporal trends of infective endocarditis from 2000 – 2017. Incidences data per 100,000 persons was plotted against time (years) for all included studies. A secondary y-axis was used to plot data from Kadri 2019.



\* ..... AHA IE antibiotic prophylaxis guideline update - 2007

Figure 3: Prevalence of injection drug use among patients with IE. Percentage prevalence of PWID was plotted against time (years) on the primary y-axis. The secondary y-axis was used to plot incidence of IDU per 100,000 persons with IE from Wong 2020.



\*McCarthy 2020 reported percentage prevalence of opioid use disorders, used as a surrogate indicator of injection drug use in this study.