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MAJOR ARTICLE

Temporal Trends of Infective Endocarditis in North America From 2000 to 2017—A Systematic Review

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Background. The objective of this paper was to examine temporal changes of infective endocarditis (IE) incidence and epidemiology in North America.

Methods. A systematic review was conducted at Mayo Clinic, Rochester. Ovid EBM Reviews, Ovid Embase, Ovid Medline, Scopus, and Web of Science were searched for studies published between January 1, 2000, and May 31, 2020. Four referees independently reviewed all studies, and those that reported a population-based incidence of IE in patients aged 18 years and older in North America were included.

Results. Of 8588 articles screened, 14 were included. Overall, IE incidence remained largely unchanged throughout the study period, except for 2 studies that demonstrated a rise in incidence after 2014. Five studies reported temporal trends of injection drug use (IDU) prevalence among IE patients with a notable increase in prevalence observed. *Staphylococcus aureus* was the most common pathogen in 7 of 9 studies that included microbiologic findings. In-patient mortality ranged from 3.7% to 14.4%, while the percentage of patients who underwent surgery ranged from 6.4% to 16.0%.

Conclusions. The overall incidence of IE has remained stable among the 14 population-based investigations in North America identified in our systematic review. Standardization of study design for future population-based investigations has been highlighted for use in subsequent systematic reviews of IE.

Keywords. epidemiology; incidence; infective endocarditis; injection drug use; mortality; North America.

Among the variety of diseases involving the cardiovascular system, infective endocarditis (IE) is less commonly seen. Nevertheless, due to the high (up to ~40%) 1-year mortality rate, frequent need for surgical intervention, and common requirement of prolonged hospital stays [1], 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 [2–5].

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 [6]. 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 [7]. 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

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recently in Boston, Massachusetts, and Lexington, Kentucky, has reached 46% and 73%, respectively [8, 9].

Marked restrictions in the use of antibiotic prophylaxis (AP) introduced by the 2007 American Heart Association (AHA) guidelines [10], 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 a ~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 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 [11]. 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 Supplementary Data. 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 resolved by discussion with 2 additional reviewers (M.J.D. and D.C.D.). Corresponding authors of studies were contacted via email in cases where queries existed.

Patient Consent

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 that provided information on population-based trends of IE in the adult (≥18 years) population of North America from 2000 onwards were included in the review. Single-center and multicenter 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 (eg, HIV-infected, congenital heart disease) were also excluded. Details of the search strategy are provided in the Supplementary Data.

Data Extraction

Data that described the 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 who required valvular surgery, and mortality (stratified as inpatient, 6-month, and 1-year mortality). All included studies defined IE using primary or secondary diagnosis based on the International Classification of Diseases, Ninth Revision (ICD-9) [12] and Tenth Revision (ICD-10) [13]. Studies that defined IE using either Duke criteria [14] or modified Duke criteria [15] 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 4 key features: adequacy of population definition, sampling techniques, disease definition, and completeness of case ascertainment, as summarized in Table 2 [16]. We deemed the population definition to be inadequate if residency status population of interest was not confirmed. Optimal sampling techniques included 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 Supplementary Data.

The study was registered with the international prospective register of systematic reviews (PROSPERO), which is an international database of prospectively registered systematic reviews in health and social care (Registration ID: CRD42020191196) [17].

Data Assessment

A formal statistical analysis was not conducted as part of the systematic review due to overlapping data sets for studies using the same database (see the "Results" section). Moreover, there was a lack of availability of trend data for variables of interest.

RESULTS

Study Selection

A total of 8588 studies were identified from the search engines after deduplication. Study abstracts were screened, and 89 studies were identified for full-text review. Fourteen studies met inclusion criteria and are included in the systematic review (Figure 1). General characteristics of the included studies are listed in Table 1. Of the 14 studies, 5 examined the Nationwide Inpatient Sample (NIS) database over different and overlapping time periods. Thirteen studies were conducted in the United States, and 1 study was done in Canada (Table 1). A summary of a population description is included in each database (Table 3). The list of diagnosis codes used by each study is provided in the Supplementary Data.

Overall Incidence

All included studies described an overall incidence of IE. Figure 2 illustrates contemporary trends of IE incidence per 100 000 people from the year 2000 through 2017. Data from 4 Olmsted County studies [18–21] using the Rochester Epidemiology Project (REP) were included as a single study of IE incidence temporal trends in Olmsted County (Figure 2). There were a few [22, 23] studies that included yearly trends of IE incidence before 2000. However, the current systematic review was limited to contemporary trends of IE over the past 2 decades.

Overall, there was great variability observed in trends of overall incidence of IE, with no appreciable increase noted over time (Figure 2). A study by Kadri et al. [2] described a much higher IE incidence compared with 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 et al. [24], and the highest mean age (76.0 years) was reported by Bikdeli et al. [25]. The studies by Mendiratta et al. [18] and Bikdeli et al. [25] only included patients aged ≥65 years, which accounts for a comparatively higher mean age reported in both studies (76.0 and 79.4 years, respectively). IE was more common in men, as reported by all but 2 studies (Thornhill et al. [24] and Bikdeli et al. [25]) (Table 1).

Injection Drug Use

Five of 14 studies, from different study populations, reported trends of percent changes in IE in PWID. Wong et al. [19] reported incidence numbers for IE in PWID, instead of

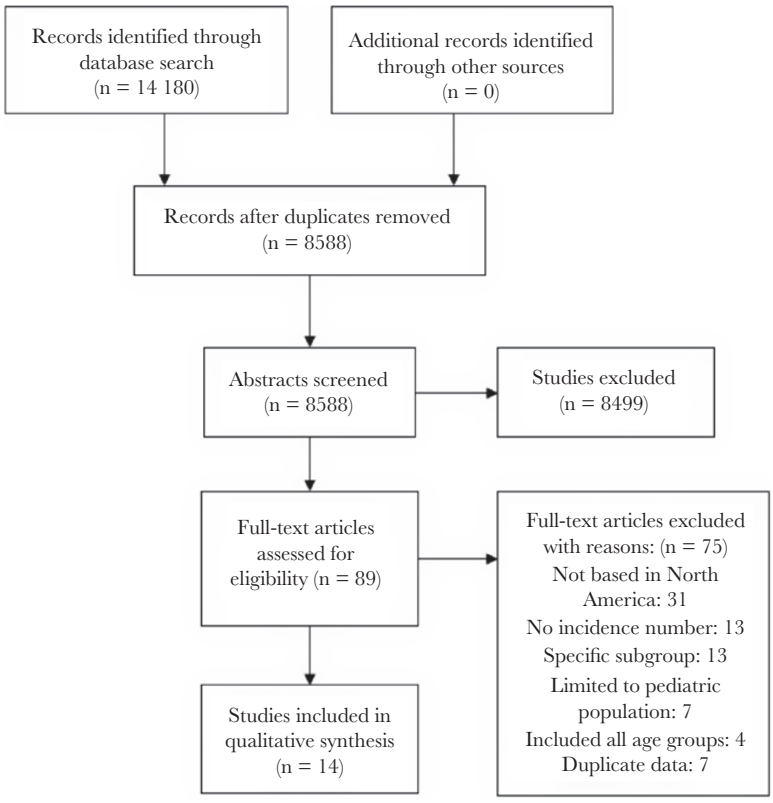


Figure 1. Schematic representation of study selection using PRISMA.

Table 1. Clinical Features of Patient Populations in Included Studies

Author	Database	Age, y	Female, %	Microbiology,[a] %	Mortality, %	Underwent Surgery, %
United States of America						
Tleyjeh 2005 [26]	REP	61.5 (mean)	27.0	VGS 44.0, *Staphylococcus aureus* 26.0, CoNS 7.0, *Enterococcus* species 6.0	Inpatient: NR 6-month: NR 1-year: 37.1	16.0
Mendiratta 2009 [18]	NIS	76.0 (mean)	47.0	NR	Inpatient: 20.0 6-month: NR 1-year: NR	NR
Correa 2010 [23]	REP	70.5 (median)	33.3	VGS 40.0, *Staphylococcus aureus* 19.3, CoNS 10.0, *Enterococcus* species 6.7	Inpatient: NR 6-month: 26.7 1-year: NR	16.0
Bikdeli 2013 [25]	Medicare inpatient Standard Analytic Files	79.4 (mean)	58.8	NR	Inpatient: 10.1 6-month: 31.8 1-year: 36.2	NR
DeSimone 2015 [20]	REP	68.8 (median)	41.0	*Staphylococcus aureus* 33.0, *Enterococcus* species 22.0, VGS 16.0, CoNS 10.0	Inpatient: NR 6-month: 29.0 1-year: 37.0	16.0
Toyoda 2017 [35]	Statewide Planning and Research Cooperative System database in New York and the Office of Statewide Health Planning and Development database in California	62.3 (mean)	40.9	*Staphylococcus aureus* 31.9, Streptococci 26.6, Oral streptococci 10.1	Inpatient: NR 6-month NR 1-year: 37.1	13.3
Thornhill 2018 [24]	Truven Database	59.1 (mean)	53.2	NR	NR	NR
Alkhouli 2019 [3]	NIS	61.5 (mean)	41.1	NR	Inpatient: 11.8 6-month: NR 1-year: NR	11.2
Kadri 2019 [2]	NIS	68.0 (median)	48.7	*Staphylococcus aureus* 24.6, Streptococci 15.5, GNB 1.2	Inpatient: 8.8 6-month: NR 1-year: NR	6.4
Moreyra 2019 [49]	Myocardial Infarction Data Acquisition System	63.5 (mean)	42.0	Staphylococci 54.0, Streptococci 40.0, GNB 4.0	Inpatient: 14.4 6-month: NR 1-year: NR	NR
McCarthy 2020 [50]	Premier Healthcare Database	NR	NR	*Staphylococcus aureus* 27.3, VGS 26.5, *Enterococcus* species 16.1	Inpatient 3.7 6-month: NR 1-year: NR	NR
Mori 2020 [51]	NIS	59.3 (mean)	40.6	Staphylococci 36.2, Streptococci 23.9, GNB 7.1	Inpatient: 8.3 6-month: NR 1-year: NR	11.4
Wong 2020 [19]	IBM MarketScan	NR	42.1	NR	NR	NR
Canada						
Garg 2019 [21]	Multiple population-based administrative health care databases in Ontario	63.0 (median)	36.3	*Staphylococcus aureus* 30.3, *Streptococcus* species 26.4, Other staphylococcal species 10.5, Gram-negative or *Candida* species 6.5	NR	NR

Abbreviations: CoNS, coagulase-negative staphylococci; GNB, gram-negative bacilli; NIS, National Inpatient Sample; NR, not reported; REP; Rochester Epidemiology Project; VGS, viridans group streptococci.

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

percentages, as illustrated on the secondary axis of Figure 3. There has been a notable increase in the percent prevalence of opioid use and IDU among patients with IE as reported by individual studies (Supplementary Data). There were 3 studies that reported only the overall percent prevalence of IDU in an IE cohort during their respective study periods. DeSimone et al. [20] reported an overall PWID prevalence of 10% among patients with IE, which did not change in IE patients seen between 2014 and 2017. Garg et al. [21] reported a PWID-IE prevalence of 16.6% as a proportion of total IE cases, while Tleyjeh et al. [26] reported a PWID-IE prevalence of 3% over a 30-year study period.

Table 2. Quality Assessment of Included Studies

Study	Adequacy of Population Definition	Sampling Techniques	Disease Definition	Completeness of Case Ascertainment
Tleyjeh 2005 [16]	Adequate	Adequate	Adequate	Adequate
Mendiratta 2009 [18]	Adequate	Adequate	Inadequate	Adequate
Correa 2010 [23]	Adequate	Adequate	Adequate	Adequate
Garg 2019 [21]	Adequate	Adequate	Inadequate	Adequate
Bikdeli 2013 [25]	Adequate	Adequate	Inadequate	Adequate
DeSimone 2015 [20]	Adequate	Adequate	Adequate	Adequate
Toyoda 2017 [35]	Adequate	Adequate	Inadequate	Adequate
Thornhill 2018 [24]	Adequate	Adequate	Inadequate	Adequate
Alkhouli 2019 [3]	Adequate	Adequate	Inadequate	Adequate
Kadri 2019 [2]	Adequate	Adequate	Inadequate	Adequate
Moreyra 2019 [49]	Adequate	Adequate	Inadequate	Adequate
McCarthy 2020 [50]	Adequate	Adequate	Inadequate	Adequate
Mori 2020 [51]	Adequate	Adequate	Inadequate	Adequate
Wong 2020 [19]	Adequate	Adequate	Inadequate	Adequate

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 et al. [20]. Coagulase-negative staphylococci were reported as an exclusive entity by 5 studies, and Correa et al. [23] and DeSimone et al. [20] reported the highest (10%) prevalence.

Outcomes

The percentage of patients who required cardiac valvular surgery for IE was documented in 7 studies (range, 6.4%–16.0%). Other outcomes examined included inpatient, 6-month, and 1-year mortality rates. Inpatient mortality was reported in 7 studies, with rates ranging from 3.7% to 14.4%. Six-month mortality was described in 3 studies, and rates were much higher, ranging from 26.7% to 31.8%. Four studies reported rates of 1-year mortality, which was very consistent, ranging from 36.2% to 37.1% (Table 1).

DISCUSSION

The overall incidence of IE 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 multicenter investigations predominate in the literature and are subject to referral and other biases—hence our reliance on only population-based studies in this review.

IDU may be the predisposing condition for 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

Table 3. Description of Population Included in Databases

Database	Definition
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 [52]
Medicare Inpatient Standard Analytical Files	Medicare is the primary health insurer of 97% of the US population 65 years and older [53]
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 health care database from ~800 private and academic hospitals, representing ~20% of US inpatient discharges [50]
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 [54]
IBM MarketScan	Includes diagnosis and procedure codes for 26 million persons who enrolled in ~350 employer-sponsored commercial health insurance plans in 2017 in all 50 US states [19]

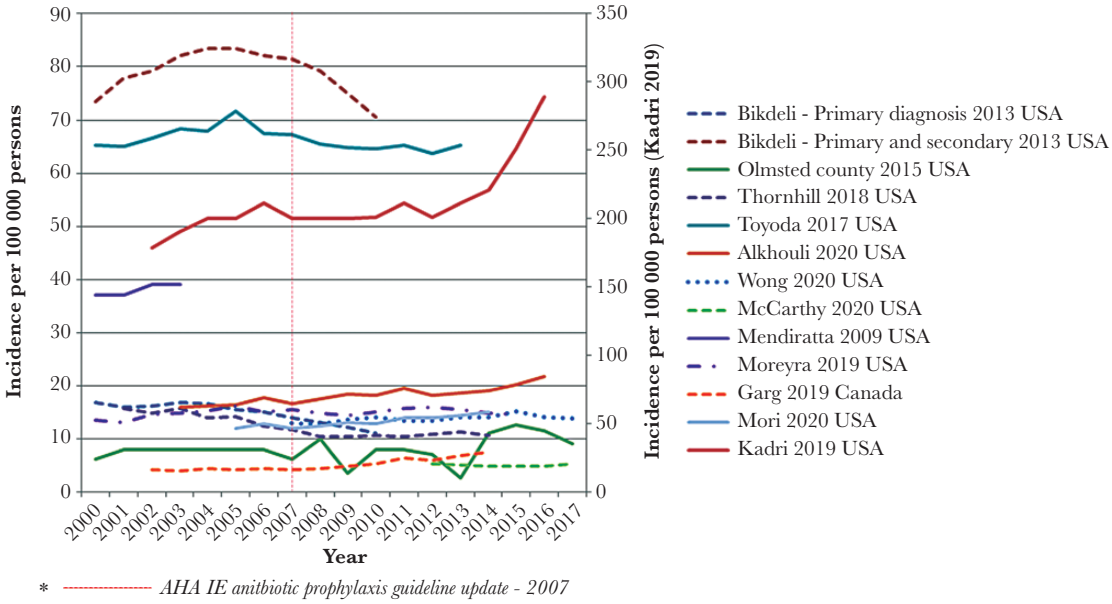
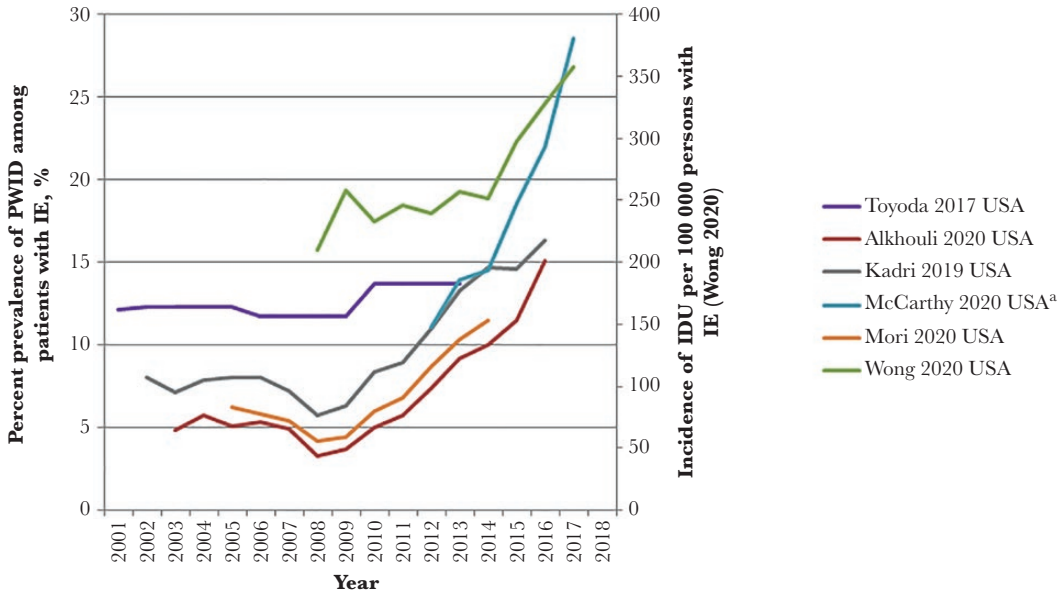


Figure 2. Temporal trends of infective endocarditis from 2000 to 2017. Incidence data per 100 000 persons were plotted against time (years) for all included studies. A secondary y-axis was used to plot data from Kadri et al. [2]. Abbreviations: AHA, American Heart Association; IE, infective endocarditis.

[27]. 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. [19], 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 health care system in North America. Fleischauer et al. [28] 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 1800% in hospital expenditures. Moreover,



[a]*McCarthy 2020 reported percentage prevalence of opioid use disorder; used as a surrogate indicator of injection drug use in this study.*

Figure 3. Prevalence of injection drug use among patients with IE. Percent prevalence in 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 et al. [19]. Abbreviations: IDU, injection drug use; IE, infective endocarditis; PWID, persons who inject drugs.

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 [29], there is a justified cause for concern as public health and other agencies involved in health care 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 [30] 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 the 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 [31, 32] have demonstrated a rising incidence of IE following a total restriction in AP for certain dental procedures [33], but a causal relationship between increasing incidence and AP restrictions has not been 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 the incidence rates displayed in Figure 2. 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 codes or a restricted number of primary/secondary diagnosis codes) (Supplementary Data) 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 positions. Interestingly, Fawcett et al. [34] 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 [19] and Kadri 9 [2], had a PPV of <6%. They reported that the sensitivity and positive predictive values (PPVs) of the ICD-9 codes were 70%. This is lower than measures reported in Toyoda (sensitivity, 94%; PPV, 94%) (Table 4) [35]. Moreover, there is a discrepancy in the use of surrogate codes for IE in PWID, as 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 [36]. Furthermore, it has been suggested that studies that 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 [37]. 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, as it was only after 2015 that medical centers in North America fully adopted ICD-10 coding [38]. However, there are several nuances that should be considered when using ICD-9 coding to determine the incidence of IE. ICD-9 codes used until 2015 in the United States 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, as they only include diagnosis codes and other systems are used for coding when procedures have been performed [39]. It most likely affects the way coders record information and different coding strategies adopted in Europe and the United States for identifying IE cases, as health care systems in Europe converted to ICD-10 coding before the year 2000. This also suggests that

Table 4. Summary of Studies that Performed ICD Code Validation

Study	Codes/Criteria Used	Comment	Validity
Toyoda 2017 [35]	ICD-9 Primary and secondary	Independent validation	Sensitivity 94% Specificity 99% PPV 94%
Thornhill 2018 [24]	ICD-9. Primary and secondary	Record linkage using ICD codes	Sensitivity 95% Specificity 100%
Alkhouli 2019 [3]	ICD-9 and -10. Primary and secondary	Record linkage using ICD codes	Sensitivity 94% Specificity 99% PPV 94%
Mori 2020 [51]	ICD-9 Primary and secondary	Record linkage using ICD codes	Sensitivity 94% Specificity 99% PPV 94%

Abbreviations: ICD, *International Classification of Diseases*; PPV, positive predictive value.

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 et al. [2] as compared with the remainder of the 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 179–289 cases per 100 000, compared with 2.61–39.10 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. [25] also detected a high incidence of IE in their cohort as compared with that seen in other studies. This should have been expected as 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 vs 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 [34].

As 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 [34]. 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 United States and Canada, where the population indicated for preoperative AP was restricted to patients at highest risk of IE [10]. 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 [40] 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.

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 2 groups.
3. Investigators should consider the date for implementation of ICD-10 codes, that is, 2015 in the United States, 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 nonspecific 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.

Abbreviations: ICD, International Classification of Diseases; IDU, injection drug use; IE, infective endocarditis; PWID, persons who inject drugs; VGS, viridans group streptococci.

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 health care–associated procedures. The prevalence of VGS has been declining recently; Slipzcuk et al. [41] reported a decrease in VGS prevalence from 27.4% to 17.6% in IE patients over the past 5 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 harbor specific ICD-9/10 codes (eg, ICD-10 code A49.1 for streptococcal infection at an unspecified site). This practice, coupled with the 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 1 survey this likely impacted the reported increase in "streptococcal" IE incidence [42–44].

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%–50% of IE patients [45–47]. As most of these studies were not population-based and were conducted at surgical tertiary care centers, they were

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 with that described in previous systematic reviews by Slipzcuk et al. (8%–40%) [41] and Tleyjeh et al. (16%–21%) [16]. 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%–37.1%) (Table 1).

A recently published systematic review compared incidence of IE before and after implementation of major guideline changes for AP use and invasive procedures [48]. In contrast to the number (n = 14) of North American studies included in our review, the Williams publication included only 8 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 3 studies that were excluded from our review because the cohorts in those studies included pediatric IE cases [5, 40, 42]. 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 as 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 2 studies [18, 25] that included patients aged ≥65 and 1 [19] that included patients aged 18–64. These studies were included as the authors of this review believed it was necessary to include all adult-based studies, as the epidemiology of pediatric IE is different than that seen in adults and because bacterial pathogens that cause IE are similar among all adult age groups, albeit with a higher prevalence for enterococcal species in older patients. Only 1 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 the incidence of VGS IE over the past 2 decades. The addition of a secondary code specific to VGS is expected to be supported in the next version (ICD-11) of coding updates (Table 5).

CONCLUSIONS

Based on findings of this systematic review, the incidence of IE in North America has remained stable between 2000 and 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 that the ICD-11 coding includes specific genus and species designations of VGS.

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