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MAJOR ARTICLE

Temporal Trends of Infective Endocarditis in Olmsted County, Minnesota, Between 1970 and 2018: A Population-Based Analysis

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Background. A population-based study of infective endocarditis (IE) in Olmsted County, Minnesota, provides a unique opportunity to define temporal and seasonal variations in IE incidence over an extended time period.

Methods. This was a population-based review of all adults (≥18 years) residing in Olmsted County, Minnesota, with definite or possible IE using the Rochester Epidemiology Project from January 1, 1970, through December 31, 2018. Poisson regression was used to characterize the trends in IE incidence; models were fitted with age, sex, calendar time, and season, allowing for nonlinearity and nonadditivity of their effects.

Results. Overall, 269 cases of IE were identified over a 49-year study period. The median age of IE cases was 67.2 years, and 33.8% were female. The overall age- and sex-adjusted incidence of IE was 7.9 cases per 100 000 person-years (95% CI, 7.0–8.9), with corresponding rates of 2.4, 2.4, 0.9, and 0.7 per 100 000 person-years for *Staphylococcus aureus*, viridans group streptococci (VGS), *Enterococcus* species, and coagulase-negative staphylococci IE, respectively. Temporal trends varied by age, sex, and season, but on average IE incidence increased over time ($P = .021$). Enterococcal IE increased the most ($P = .018$), while *S. aureus* IE appeared to increase but mostly in the winter months ($P = .018$). Between 1996 and 2018, the incidence of VGS IE was relatively stable, with no statistically significant difference in the trends before and after the 2007 AHA IE prevention guidelines.

Conclusions. Overall, IE incidence, and specifically enterococcal IE, increased over time, while *S. aureus* IE was seasonally dependent. There was no statistically significant difference in VGS IE incidence in the periods before and after publication of the 2007 AHA IE prevention guidelines.

Keywords. dental prophylaxis; enterococci; guidelines; incidence; infective endocarditis; *Staphylococcus aureus*; trends; viridans group streptococci.

Infective endocarditis (IE) is an uncommon infection but is associated with high morbidity and mortality, which warrants continued surveillance [1]. Particular attention to the changing epidemiology of IE is critical to the prevention, diagnosis, and management of IE. Our group has extensively examined the epidemiology of IE in population-based studies of Olmsted County, Minnesota, since 1970, with periodic updates to provide a contemporary characterization of IE [2–4]. More recent evaluations of this population have shown an increase in IE among females [3] and a shift from viridans group streptococci (VGS) to *Staphylococcus aureus* as the predominant pathogen. In addition, IE incidence due to enterococci has increased [4], which has been seen in other locales in the United States and other countries [5–7]. Furthermore, several studies have shown an overall increase in the incidence of IE [5, 7–9]; however, there was no significant increase in IE incidence in Olmsted County in our most recent evaluation between 2007 and 2013, as compared with that between 1970 and 2006 [4].

In the United States, population-based studies are extremely difficult to perform, as compared with some countries with national patient health record databases. Olmsted County, Minnesota, provides the opportunity to conduct these studies. We sought to provide a variation over time in incidence of IE with a more contemporary analysis to further evaluate the impact, if any, of the 2007 American Heart Association (AHA) IE prevention guidelines on VGS IE incidence that extended our observation period for an additional 5 years. Moreover, we included an examination of seasonality in IE incidence of Olmsted County cases, which had not been done previously and has been of interest in other investigations.

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METHODS

We identified adults, age 18 years or older, who resided in Olmsted County, Minnesota, and were diagnosed with definite or possible IE between January 1, 1970, and December 31, 2018. Cases were ascertained using the Endocarditis Registry of the Division of Infectious Diseases and the Rochester Epidemiology Project (REP). The REP is a medical records linkage system established in 1966 that provides the capability for population-based studies of disease causes and outcomes; it is unique in the United States [10]. Among the resources utilized for this study, the REP provides a dynamic method of census enumeration as well as software to facilitate incidence calculations incorporating population estimates. Our investigation spans nearly 50 years, during which time the adult population in Olmsted County ranged from ~58 000 in 1970 to 96 000 in 2000 and 122 000 in 2018. Cases of cardiac implantable electronic device–related IE were excluded.

Review of the entire medical record for each patient was performed, and extensive information, including demographic, clinical, radiological, microbiological, outcome, and mortality data, was collected. We used a standardized data abstraction form with detailed definitions of the variables. These were stored in Research Electronic Data Capture (REDCap) to provide a secure repository of patient data for research purposes [11].

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.

Statistical Analysis

Demographic and clinical characteristics are described by medians and interquartile ranges (IQRs) or by percentages and absolute frequencies. Incidence rates of IE were calculated overall and by pathogen based on number of cases divided by person-time of follow-up, with the denominator estimated by census figures of adults living in Olmsted County during the study period (expressed per 100 000 person-years). To make our estimates more generalizable, age- and sex-adjusted rates were computed via direct standardization against the overall age and sex distribution of the 2010 US White population. All analyses were done using R software, version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria). A threshold of $P < .05$ was used to indicate evidence of statistical significance.

For examining trends in IE incidence, 4 variables—age, sex, calendar time, and season—were considered potential sources of variability. A data set suitable for modeling incidence was constructed by stratifying the data to obtain separate records for each combination of these variables' values, with age and time each stratified finely by single-year intervals to allow analysis of these as continuous variables. A multivariable Poisson regression model with overdispersion correction was used to model the count of incident IE cases on the basis of the 4 aforementioned variables as predictors. The model included stratified population counts (on a logarithmic scale) as an offset variable to convert the outcome into rates and to adjust for population changes over time. Both the age and calendar time variables were modeled flexibly with regression splines to relax linearity assumptions. To assess the model assumption of additivity, we initially fit a nonadditive model with all 2-way interactions and constructed a joint likelihood ratio (LR) test for all the interaction effects combined. If significant or equivocal ($P < .10$), we proceeded with testing, for each of the 4 predictors separately (ie, 1 at a time), all 2-way interactions involving that predictor. On the basis of this partial joint LR test, all interactions with a given predictor were either retained or omitted in the final model. This approach limits collinearity and multiple comparison problems that are likely to arise when testing all 2-way interactions individually. The results of the fitted model were displayed graphically and with effect estimates; specifically, incidence ratios were calculated to represent the fold increase in incidence rate associated with changes in the model inputs.

In secondary analyses, the modeling approach described above was repeated for incidence of microorganism-specific IE. In addition, a subset analysis spanning the last 22 years of the study period (1996 to 2018) was done to examine temporal trends in IE due to VGS before and after the introduction of the AHA prevention guidelines in April 2007. The study period of 1996 to 2018 gives ~11 years before and after the publication of the 2007 AHA guidelines. An interrupted time series analysis was performed with Poisson regression based on a hypothesized slope change model. The time trend was fitted with a spline function that assumed piecewise linearity within 2 intervals and a slope change at the point in time the guidelines were implemented. The model formulation included a main effect term for (linear) calendar time and a cross-product of time with a constructed variable indicating the postguideline period. Difference in slopes between the 2 linear trends was determined by a Wald test for the interaction effect.

We constructed a 4-level variable for seasonality based on the meteorological definition, with seasons assumed to begin on the first day of the months that include the equinoxes and solstices: spring (March 1 to May 31), summer (June 1 to August 31), fall (September 1 to November 30), and winter (December 1 to February 28). For sensitivity analysis, we also considered a more quantitative measure in modeling incidence as a nonlinear, continuous function of seasonality using the month of the year (at the index date of IE).

RESULTS

IE Incidence Trends

A total of 269 incident cases of IE were identified in Olmsted County, Minnesota, between 1970 and 2018. The demographics, clinical characteristics, microbiology, and clinical outcomes of these persons are summarized in Table 1. Crude incidence rates of IE for men and women are shown by groupings of age, calendar time, season, and pathogen in Figure 1. Overall, the age- and sex-adjusted incidence rate of IE (cases per 100 000 person-years) was 7.9 (95% CI, 7.0–8.9), with higher rates in men (12.1; 95% CI, 10.3–13.9) compared with women (4.5; 95% CI, 3.6–5.5). Incidence rates by pathogen showed that *S. aureus* IE and VGS IE were the most common, each 2.4 (95% CI, 1.9–2.9), followed by 0.9 (95% CI, 0.6–1.2) and 0.7 (95% CI, 0.5–1.0) for enterococci and coagulase-negative staphylococci (CoNS) IE, respectively.

In the multivariable regression for determining the prognostic factors associated with IE incidence, we considered the possibility that some effects of age, sex, calendar time, and seasonality may interact; that is, the effect of 1 factor on incidence may depend on the level of another factor and vice versa. A global test of all possible interactions showed preliminary evidence of such patterns (LR $\chi^2 = 44.4$; $P = .033$; 29 d.f.), but upon further testing only interactions involving calendar time were significant as a group (LR $\chi^2 = 29.1$; $P = .029$; 18 d.f.). This finding suggests that the temporal trend in IE incidence was dependent on age, sex, or season. Figure 2 displays the model-estimated trends in incidence of IE for selected predictor combinations. The results revealed highly significant effects of age and sex on IE incidence (both $P < .001$) (Figure 2A). The overall effect for calendar time, when taking the interactions into account, was also significant ($P = .021$; 21 d.f.), with rates generally increasing across the study period (Figure 2B–D). However, there was no evidence of a seasonal effect, either overall ($P = .271$) or differentially by calendar year ($P = .200$ for time × season interaction). As the interaction patterns with respect to calendar year were difficult to discern and seemed to be of minor importance, the multivariable regression analysis was repeated without the interaction terms to simplify the interpretation of effects. Based on the resulting estimates of age and sex, which were averaged across time, an IQR increase in age (from 52 to 78 years) was associated with a 4-fold increase in IE incidence (average incidence ratio [aIR], 3.99; 95% CI, 3.30–4.82), and rates were 2.6-fold higher in men than in women (aIR, 2.59; 95% CI, 2.01–3.33). Finally, consistent with the prior observation of an increasing temporal trend, an IQR increase in calendar year (from 1992 to 2014) was associated with a 39% increase in the incidence of IE (aIR, 1.39; 95% CI, 1.03–1.86).

Table 1. Patient Characteristics of Incident IE Cases in Olmsted County From 1970 to 2018

Variable	No.	% (No.) Missing	Total (n = 269)
Calendar year, median (IQR)	269	0	2004 (1992–2014)
Age, median (IQR), y	269	0	67.2 (52.3–78.5)
Female gender	269	0	33.8 (91)
IV drug abuse	264	1.9 (5)	5.3 (14)
Valve surgery, 6 wk	267	0.7 (2)	16.1 (43)
Valve surgery, 1 y	265	1.5 (4)	21.9 (58)
Mortality, 6 mo	265	1.5 (4)	27.2 (72)
Underlying valve disease			
Rheumatic	267	0.7 (2)	8.2 (22)
Mitral valve prolapse	267	0.7 (2)	12.4 (33)
Congenital heart disease	267	0.7 (2)	6.7 (18)
Bicuspid aortic valve	267	0.7 (2)	8.2 (22)
Native	267	0.7 (2)	75.7 (202)
Prosthetic	267	0.7 (2)	24.0 (64)
Previous IE	268	0.4 (1)	6.7 (18)
Valve affected			
Aortic	269	0	38.3 (103)
Mitral only	269	0	36.4 (98)
Aortic and mitral	269	0	8.6 (23)
Right-sided or bilateral	269	0	4.1 (11)
Pathogen			
Viridans group streptococci	269	0	30.1 (81)
Staphylococcus aureus	269	0	30.9 (83)
Enterococcus species	269	0	10.8 (29)
Coagulase-negative staphylococci	269	0	9.3 (25)
HACEK	269	0	3.0 (8)

Abbreviations: HACEK, *Haemophilus* species, *Aggregatibacter, Cardiobacterium, Eikenella, Kingella*; IE, infective endocarditis; IQR, interquartile range.

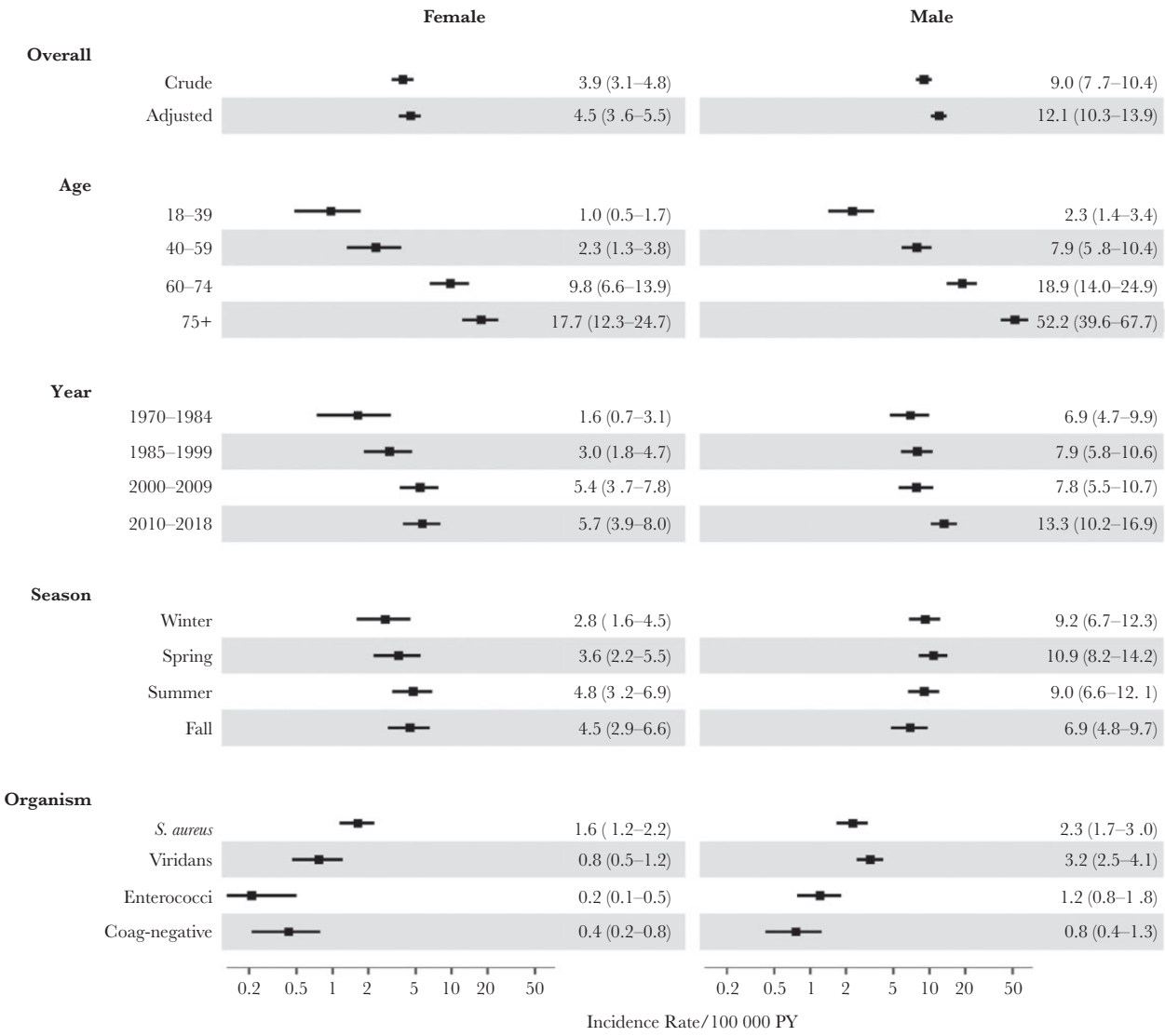

Figure 1. Incidence rates of IE (per 100 000 person-years) computed for adult residents of Olmsted County from 1970 to 2018, stratified by sex and further stratified by demographic or microorganism categories. All values represent crude (unadjusted) rates, with the exception of the "adjusted" rates, which are standardized to the age and sex distributions of the 2010 US White population. Error bars represent 95% CIs. Abbreviations: IE, infective endocarditis; PY, person-years.

Trends in IE by Pathogen

In separate models for incidence of IE by pathogen, the model for *S. aureus* IE showed evidence of interaction effects by season. Overall tests for each factor's combined effect (main effect and seasonal interaction) showed a significant association of age ($P < .001$), sex ($P = .035$), and calendar year ($P = .018$) with the incidence of *S. aureus* IE. Seasonality also explained variation in the incidence (Wald $\chi^2 = 21.5$; $P = .043$ for overall association), but mostly as an effect modifier for the other factors (Wald $\chi^2 = 19.2$; $P = .024$ for season-related interactions). Of the individual interactions with season, calendar time ($P = .052$) and sex ($P = .081$) were strongest, yet both only trended toward significance. As illustrated in Figure 3, these 2 results suggest that much of the trend of increasing *S. aureus* IE occurred in winter months (from 1992 to 2014, the increase in incidence was about 28-fold in winter and 0.7-, 3.2-, and 1.4-fold in spring, summer, and fall, respectively) and that the higher incidence in males was only apparent in winter and spring. Sensitivity analysis revealed similar but statistically significant seasonal patterns (interactions with calendar time, $P = .047$, and sex, $P = .006$) when the model was refit with seasonality as a nonlinear, continuous variable based on month of the year.

When the multivariable analyses were repeated for incidence of other pathogens of IE (VGS, enterococci, and CoNS IE) (Figure 4), only the model for enterococci IE showed a statistically significant increasing temporal trend in incidence ($P = .001$). An IQR increase in calendar year (from 1992 to 2014) was associated with a nearly 3-fold increase in the incidence of IE (aIR, 2.90; 95% CI, 1.53–5.50), or ~5.0% per year.

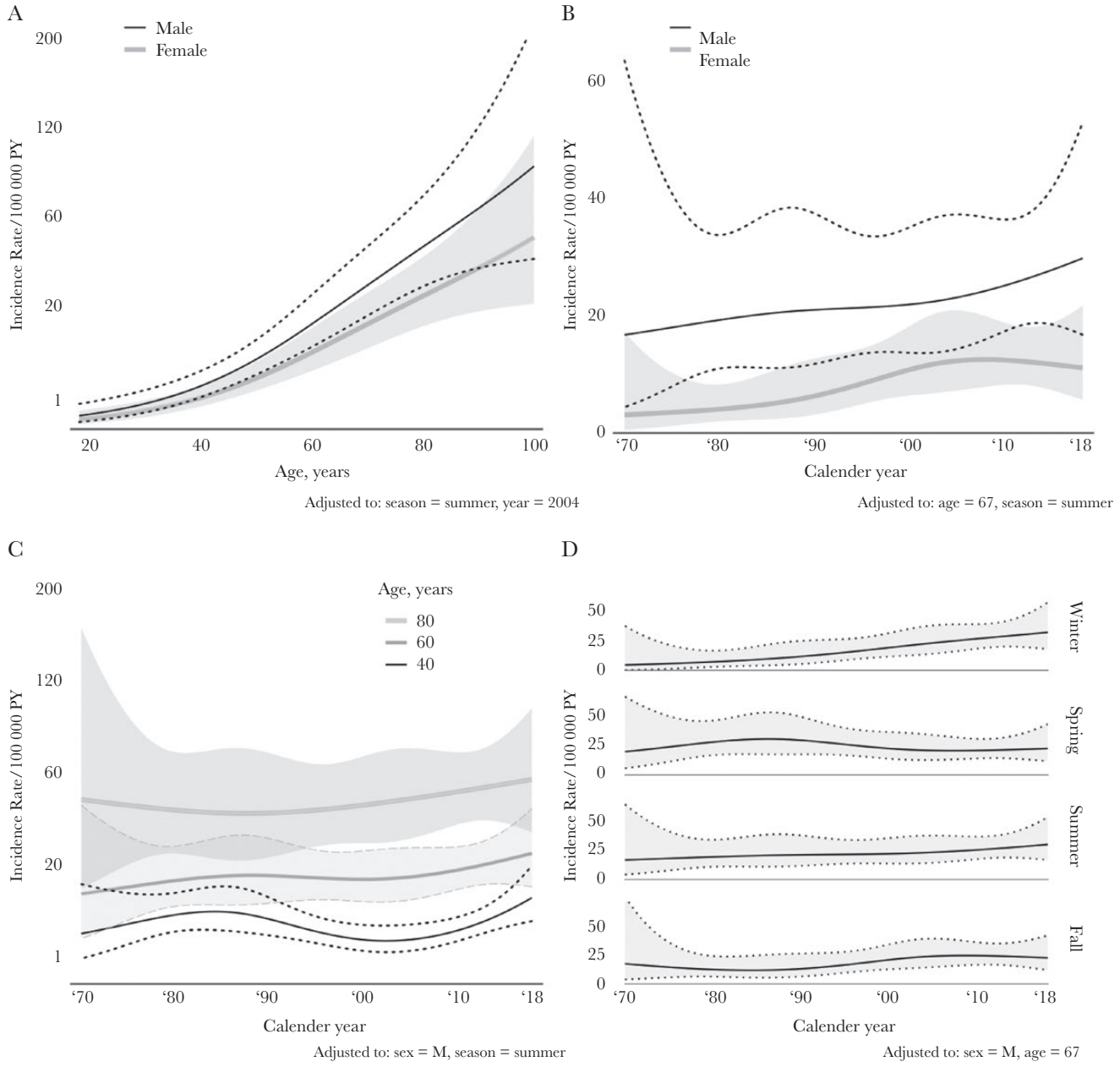

Figure 2. Multivariable Poisson regression analysis was used to investigate patterns in incidence rates and revealed that IE incidence was higher for men compared with women ($P < .001$) and increased with age ($P < .001$) in both sexes. There was also evidence for an overall association of calendar time with incidence ($P = .021$) and an overall interaction between time and all other factors (global test for interaction, $P = .029$); however, none of the individual interaction terms was statistically significant (eg, time × age, $P = .092$). There was no evidence of a seasonal effect either overall ($P = .271$) or differentially by calendar year ($P = .200$ for time × season interaction). On average, the calendar year effect represented an increasing trend in IE incidence over time. Abbreviations: IE, infective endocarditis; PY, person-years.

None of these models demonstrated evidence of seasonal variation.

VGS IE Incidence

For the subset analysis to assess the impact of the 2007 AHA prevention guidelines, 45 cases of VGS IE were identified in the Olmsted County adult population between the years 1996 and 2018, corresponding to an age- and sex-adjusted incidence rate of 2.1 (95% CI, 1.5–2.8) per 100 000 person-years. As shown by the model-predicted trend lines in Figure 5, the incidence of VGS IE does not appear to change appreciably in the interval *r* before vs after the intervention. The test for slope change showed no significant difference in these 2 trends ($\chi^2 = 0.49$, $P = .482$), and the overall test of the time effect (ie, test of whether a temporal trend exists within either period) was also nonsignificant ($\chi^2 = 0.66$; $P = .720$). When adjusting for age, sex, and seasonality by including these covariates in the model, the conclusions remained the

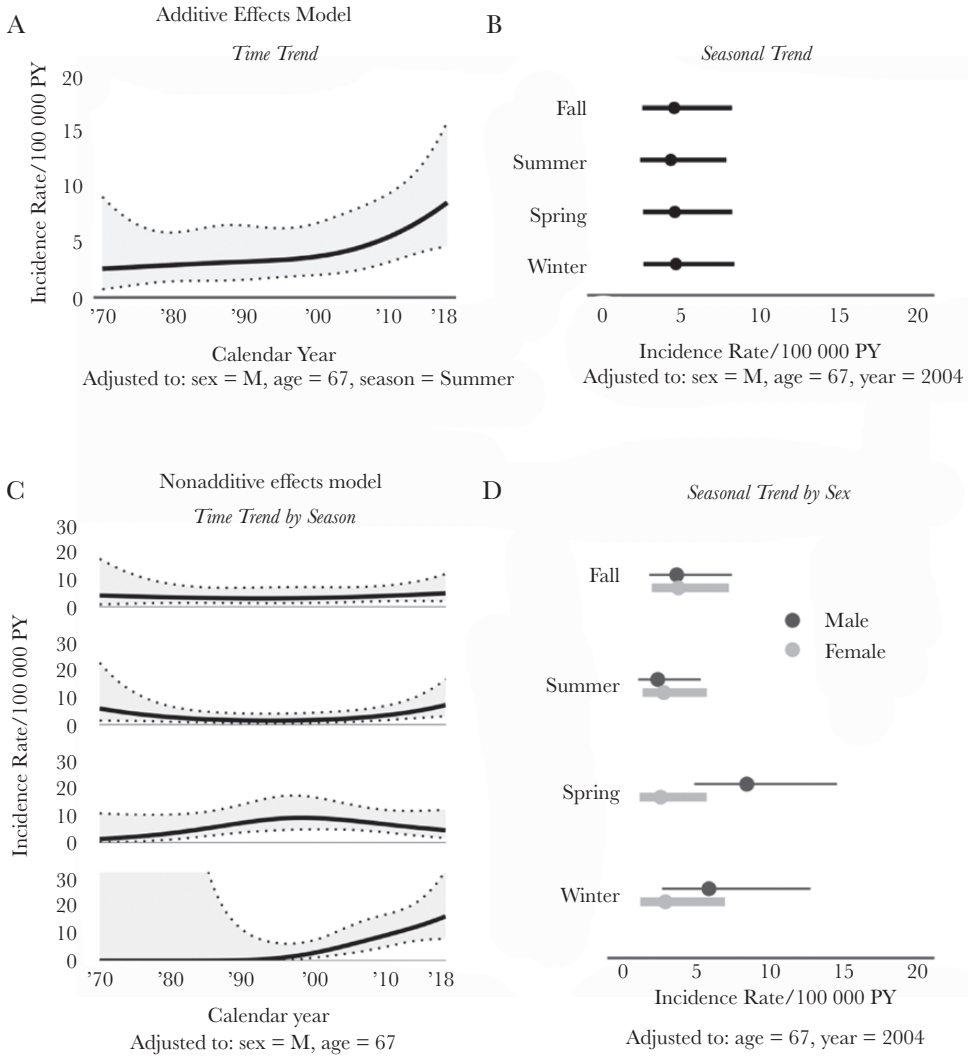

Figure 3. In multivariable analyses for pathogen-specific IE, only the model for *S. aureus* IE showed evidence of nonadditive (interaction) effects. For reference, (A) and (B) depict the temporal and seasonal effects from a simple additive model; (C) and (D) depict corresponding trends by levels of the interacting variable from the final nonadditive model. Whereas the main effects model showed, on average, increasing incidence of *S. aureus* IE over time with no apparent seasonal variation, the model with interactions demonstrated an overall seasonality effect ($P = .043$), mainly due to differential effects by time and by sex ($P = .024$ for season-related interactions). These results, although individually nonsignificant, reflect a stronger temporal trend in winter months ($P = .052$ for time × season interaction) and a tendency of higher male incidence during winter–spring only ($P = .081$ for sex × season interaction). Abbreviations: IE, infective endocarditis; PY, person-years.

same ($P = .289$ for slope change; $P = .280$ for time effect). Overall, these findings do not show any evidence of a statistically significant increase in the incidence of VGS IE relating to the 2007 AHA guideline changes.

DISCUSSION

To our knowledge, no other published IE incidence investigation involving a population-based cohort has included a study period spanning almost 5 decades. Moreover, this appears to be the most extensive population-based cohort study to examine VGS IE incidence before and after the 2007 AHA IE prevention guidelines within the United States. In addition, this is the only population-based cohort study to examine the impact of seasonality on incidence of IE.

Overall IE Temporal Trends

Noteworthy changes in the incidence and epidemiology of IE in Olmsted County, Minnesota, over a 49-year period have occurred. In the first 31 years (1970–2000), Tleyjeh et al. [2] found no significant change in the incidence of IE, while VGS was the predominant causative organism of IE. The addition of the years 2001–2006 to the previous period by Correa de Sa et al. [3] resulted in a significant long-term increase in IE incidence among females, but no significant increase in incidence of VGS or *S. aureus*; VGS continued to be the most common cause of IE. DeSimone et al. [4] showed higher rates of IE in men and older individuals among incidence cases identified between 2007 and 2013, with no significant change in the incidence of IE over this 7-year period. Moreover, this was the first time *S. aureus* and

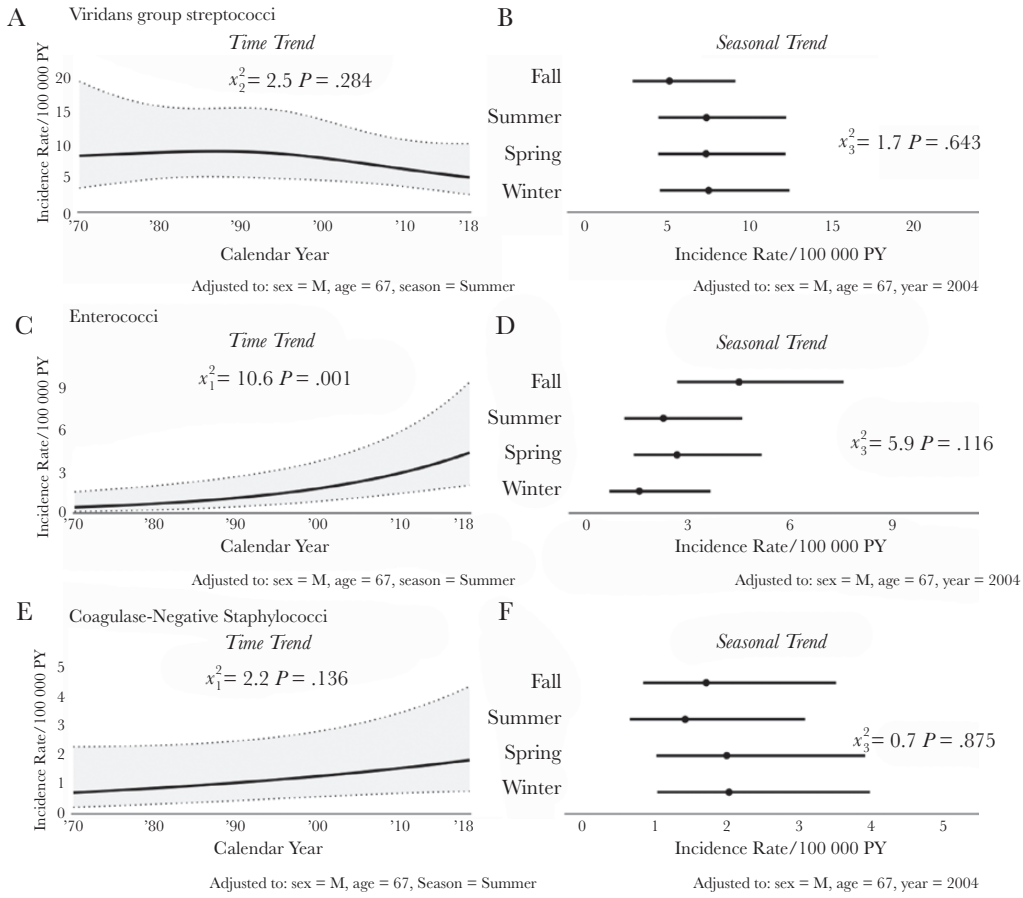

Figure 4. From multivariable analyses for examining trends in incidence of other organism-specific IE, only the model for enterococci IE demonstrated a significant temporal trend ($P = .001$), which reflected increasing incidence over time. None of these models demonstrated statistically significant seasonal variation in the incidence rate. Due to constraints imposed by the low number of cases with enterococci and CoNS IE, calendar time and age were each entered as linear terms into the model. Abbreviations: CoNS, coagulase-negative staphylococci; IE, infective endocarditis; PY, person-years.

enterococci outnumbered cases due to VGS; this observation was also seen in cases seen between 2013 and 2018.

The trends in IE incidence due to *S. aureus* deserve attention. When averaging the underlying seasonal effects, an increasing temporal trend was observed. This increase mostly occurred over the final 2 decades of the study period and may be in part due to increased health care–related exposures, such as implanted mechanical and bioprosthetic cardiac valves, hemodialysis, and an aging population that requires more interventions and facility exposures, with health care–associated infections complicating these exposures. One would assume that increasing IVDU among our cohort may be driving the increases in IE due to *S. aureus*, but the prevalence of IVDU was fairly low and increased only marginally over the study period. Furthermore, none of the aforementioned exposures explain the impact of seasonality on the temporal trend of *S. aureus* IE, in which the greatest increases across time occurred during the winter. This suggests that other factors may be playing a role.

The increase in enterococcal IE incidence is noteworthy and has been described by others. Health care exposure has also been operative in predisposing to enterococcal IE, which, in the past, was more often acquired in the community in the setting of genitourinary tract or gastrointestinal tract abnormalities. The prevalence of enterococcal IE among patients with transcatheter aortic valve implantations (TAVIs) has been a focus of concern [12] for several years, with a recent call [13] to revise surgical site infection prophylaxis to include coverage of enterococci; this would be a marked departure from current practice, which includes cefazolin as the recommended drug for use as surgical site infection (SSI) prophylaxis. Because a transfemoral approach is used in the bulk of patients who undergo TAVI, this anatomical site has been thought to account for the proclivity to cause complicating enterococcal contamination of the valve at the time of insertion.

VGS IE Incidence

The current study extends past results relating to surveillance of the Olmsted County adult population with VGS IE before and after the 2007 AHA IE prevention guidelines by including 5 additional years (2014–2018) in the postintervention period.

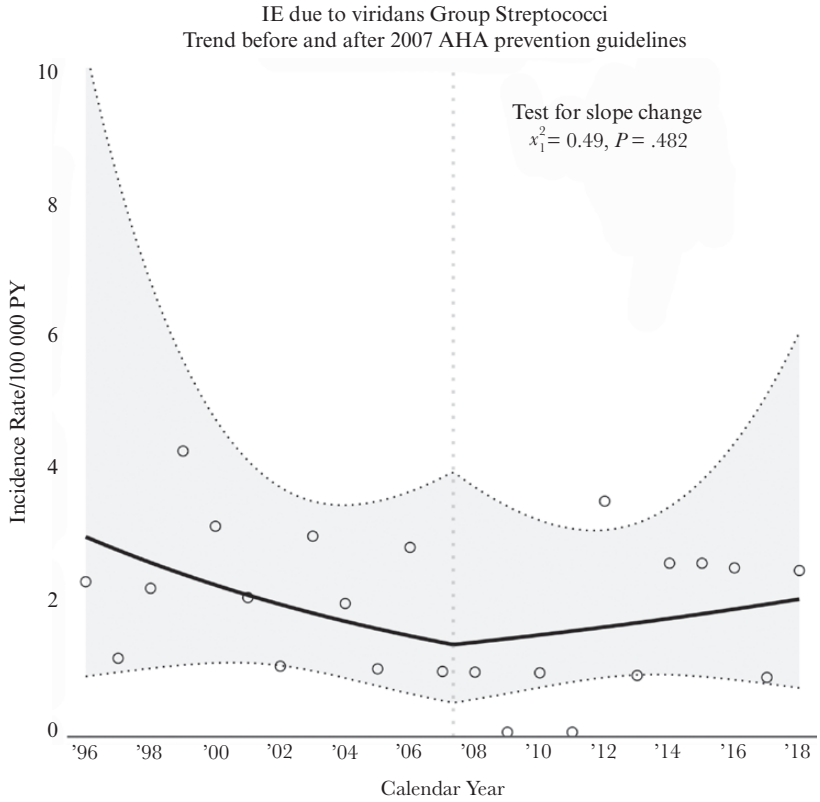

Figure 5. A subset analysis was used on data from the second half of our study period to examine temporal trends in IE incidence due to viridans group streptococci before and after the introduction of the AHA prevention guidelines in April 2007. This update to our previous investigation has extended the postguideline interval by 5 years, allowing us to better understand the intervention's impact. An interrupted time series analysis was performed with Poisson regression based on a hypothesized slope change model. Similar to past results, the present study shows no significant difference in the 2 trends before and after the guideline change, as indicated by a postintervention × time interaction effect ($\chi^2 = 0.49$, $P = .482$). A 2 d.f. test of the overall time effect (ie, a test of whether a temporal trend was demonstrated in either period) was also nonsignificant ($\chi^2 = 0.66$, $P = .720$). Abbreviations: AHA, American Heart Association; IE, infective endocarditis; PY, person-years.

Consistent with our previous findings, we found no statistically significant increase in the incidence of VGS IE since the change in guidelines [14, 15]. The findings of other investigations over the past decade mirror those reported herein [9, 16–19]. The more contemporary findings described in the current investigation are reassuring in the context of the marked (~90%) restrictions in antibiotic prophylaxis (AP) use for invasive dental procedures to only those with highest risk of IE adverse outcomes, as outlined in the 2007 AHA prevention guidelines [20].

It is important to note that in the United Kingdom, where AP use is not recommended for any patient group, there was no significant increase in IE cases within 2 years of the guideline change (March 2008–April 2010) [21]. Extending the study of the same population to March 2013, however, caused a significant increase in the number of IE cases per month above the projected historical trend—resulting in an additional 35 cases per month than would have been expected [22]. These findings led to a revision in the NICE guidelines in 2016 that included patient-centered clinical decision-making in deciding whether an individual patient warranted AP before an invasive dental procedure [23, 24].

To date, there has been only 1 study by Pant et al. [8] that reported an increase in streptococcal IE. However, they included ICD-9-CM codes for enterococci and non-VGS streptococci under the umbrella of "streptococcal" IE, which is a critical error, as enterococci are a major cause of IE and their occurrence has been increasing [25, 26].

There is a continued need for randomized clinical trials to attempt to address the question of whether AP before invasive dental procedures prevents VGS IE. However, this recognition has persisted for decades, and the likelihood of a trial being conducted is remote. Therefore, observational studies, in particular population-based investigations, will be critical in determining the impact of AP guidelines changes on VGS IE incidence. Moreover, prolonged examination of the same population-based cohort is critical, as "uptake" of new guideline recommendations may take years to ultimately impact clinical practice and the effect may take years to be recognized [21, 22].

Seasonality

Seasonality of infectious diseases extends beyond viral diseases. For example, it is well recognized that there is a spring/

summer prevalence of skin and soft tissue infections [27]. The pathogenic mechanisms responsible for this seasonal preference have been speculative to date. For other syndromes of bacterial infections, seasonality has either not been examined or has undergone limited investigation. Such is the case for infective endocarditis (IE), where only 2 studies have addressed seasonality, with mixed results. In 1 [28], a retrospective analysis that included patients seen between 1993 and 2001 who were identified through a referral to an echocardiography laboratory in a medical center in the United States was done. With only 60 IE cases included, the investigation demonstrated an increased prevalence of IE in fall/winter. In the other study [29], a Danish national database was used and concluded that there was a lack of seasonality in IE among >10 000 patients examined between 1994 and 2016. To investigate the possibility of a seasonal impact on the epidemiology of IE, we evaluated a population-based cohort seen in Olmsted County, Minnesota, between 1970 and 2018 for evidence of seasonality in IE occurrence.

The current investigation represents the first time that a population-based cohort has been examined to determine the effect, if any, of seasonality on IE incidence. Overall, seasonality was not associated with IE incidence. Likewise, when analyzed based on specific pathogen, there were no significant seasonal patterns in incidence of IE due to VGS, enterococci, or CoNS. However, for *S. aureus* IE, seasonality may have indirectly contributed to changes in incidence by modifying the effects of calendar time and sex. Marginally significant interaction effects with calendar year and sex suggested that increases in *S. aureus* IE over time were driven by trends during winter and that higher incidence among men applied only to the winter–spring months. Although these findings of *S. aureus* are unlikely to have any significant clinical implications, the role of seasonality warrants further investigation. There was no pathogen association with seasonality demonstrated in the Finkelhor study [30]; no examination of seasonality and causative organism in IE was done in the Danish national investigation [31].

CONCLUSIONS

There was a significant increase in overall incidence of IE from 1970 to 2018 in the current population-based investigation. *S. aureus* has remained the most common pathogen, and IE incidence due to this organism appeared to increase differentially by season, while *Enterococcus* species increased independent of season. There was no statistically significant increase in VGS IE incidence across the entire time frame or in a pre– vs post–2007 AHA IE prevention guideline comparison. Significant changes in IE incidence have occurred in this 49-year study period and will continue to occur in the future, highlighting the continued need for epidemiologic population-based studies to monitor and understand these trends.

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