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A M E R I C A N C O L L E G E O F
 C H E S T
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A Systematic Review of Population-Based Studies of Infective Endocarditis*

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Background: We sought to summarize and critically appraise the literature on the epidemiology of infective endocarditis (IE) in the general population.

Methods: We retrieved population-based IE surveys by searching MEDLINE and EMBASE. Two reviewers independently extracted relevant data. We performed a meta-regression to determine if temporal trends of IE characteristics exist.

Results: Fifteen population-based investigations with 2,371 IE cases from seven countries (Denmark, France, Italy, the Netherlands, Sweden, United Kingdom, and United States) from 1969 to 2000 were eligible. Different case definitions and procedures were used to capture all IE cases, including census of existing diagnoses, record-linkage system, and direct contact survey. In the unadjusted regression, there was a decline in the proportion of IE patients with underlying rheumatic heart disease (RHD; 12%; 95% confidence interval [CI], - 21 to - 3%; $p = 0.01$) and an increase in the proportion of patients undergoing valve surgery (9%; 95% CI, 3 to 16%) per decade. After adjusting for country, the decline in IE cases with underlying RHD became nonsignificant, but the proportions of IE patients undergoing valve surgery increased 7% per decade (95% CI, - 4 to 14%; $p = 0.06$), and those with underlying prosthetic valve increased 7% per decade (95% CI, - 1 to 16%; $p = 0.07$). There were no significant temporal trends in the causative organisms.

Conclusion: Evidence from well-planned, representative IE epidemiologic surveys is scarce in many countries. Available studies suggest a changing distribution of underlying valvular heart disease in patients with IE and an increase in its surgical treatment.

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Key words: epidemiology; infective endocarditis; survey; systematic review

Abbreviations: CI = confidence interval; IE = infective endocarditis; RHD = rheumatic heart disease

The clinical features of infective endocarditis (IE) as described by Osler have undergone many changes in developed countries.^{1,2} IE was a disease that commonly affected patients with predisposing valvular abnormalities caused by rheumatic carditis, and viridans group streptococci were the most common pathogens. This presentation is still seen in developing countries where rheumatic heart disease

(RHD) is prevalent. This group of at-risk patients is, however, being surpassed by new at-risk groups, including injection drug users, elderly people with valvular sclerosis, patients with cardiovascular prostheses, those with nosocomial exposure, and hemodialysis patients. Several studies² from passively re-

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ported case series suggest that *Staphylococcus aureus* is currently the most frequently identified pathogen. The apparent increase in the proportion of IE cases due to *S aureus* in institutional experiences from referral centers may be artifactual, due to changes in medical practice that affect likelihood and patterns of referral.³ Population-based investigations, in contrast, are more reliable in characterizing the epidemiology of IE because they avoid many of the biases that plague institutional surveys.

We performed a systematic review of all population-based IE surveys in order to more appropriately define the epidemiology of this disease. We also performed a metaregression to determine if temporal trends of IE characteristics exist. We outline the methodologic issues that we encountered and suggest directions for future research.

MATERIALS AND METHODS

Our systematic review included the following procedures: (1) establishment of a complete series of existing population-based IE surveys; (2) collection of methodologic details and results; (3) selection of well-designed studies; and (4) synthesis of findings that characterize IE epidemiology and its temporal trends.

Identification of Relevant Literature

A literature search was performed to identify all population-based IE surveys with the help of an experienced medical librarian. The search included MEDLINE, and EMBASE databases from inception until June 4, 2005. We searched the MEDLINE database using the search terms *endocarditis, registry, and population surveillance*. There was no restriction to language of publication. There were two studies in Danish, one in French, one in Italian, and one in Spanish that were eligible for our review. Physicians translated these articles and abstracted relevant data after discussion with one of the investigators (I.M.T.). Two investigators (I.M.T. and H.R.) independently reviewed abstracts of all identified references. Any study that could be relevant, based on findings that were described in the respective abstract, was reviewed in full text. We manually reviewed bibliographies of retrieved articles for additional citations and obtained the full text of all potentially relevant articles. We did not seek unpublished investigations.

A study had to be a population-based survey of IE, as defined below, to be included. We excluded studies restricted to specific subgroups such as injection drug users, patients with valvular heart disease, or patients with pacemaker endocarditis. For work published in several reports and/or languages that involved the same patient population, we included the report that had the most complete data. Surveys originating from the same population were included in the review part, and data for different time periods were extracted for the trend analysis.

Data Collection

A data collection form was developed and used to retrieve information on relevant clinical features and results of pertinent studies. Two reviewers (I.M.T. and A.A.L.) independently extracted data. Data included the following items: variables on the

anatomy of the survey and different IE characteristics (sample size, demographics, incidence, proportions with underlying heart disease and injection drug users, proportions of different microorganisms, and outcome).

Assessment of Study Quality

Two reviewers (I.M.T. and A.A.L.) 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.

We deemed the population definition to be inadequate if the residency status of all IE patients was not ascertained. Optimal sampling techniques include complete enumeration or random-sampling techniques. For the purpose of our study, we did not consider a specific case definition to be superior because case definitions have changed over time with the advent of echocardiography and improvement in blood culture techniques. Adequacy of case ascertainment was assessed on the basis of 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. On the basis of 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.

Statistical Analysis

We supplemented our systematic review with metaregression analyses to test the hypothesis that there are global temporal trends in IE characteristics by using weighted linear regression (metaregression) models. We included only the 15 best-quality studies in our analysis. The study by Nolsoe et al⁴ did not contribute results because it did not include data on all IE characteristics. Long-term studies were grouped in 5-year periods, when data were available, in order to better define the rates in each time frame (data available on request). For all studies, the time point used in the metaregression analysis and plots was taken as the midpoint of the study time interval or subinterval for the long-term studies. For example, if the time interval for a study was from 1980 to 1985, the time point used was 1982. Binomial SEs were calculated for each time period, and the reciprocals of these SEs were used as weights in the regression analysis. The analyses attempted to remove confounding of time period and country. This was done for each characteristic by assuming similar time trends across countries, but allowing the intercept to vary for each country. Therefore, country was included as a fixed effect in each regression model, and country-specific intercepts for the baseline year in the analysis, 1970, are reported. Because similar time trends are assumed for each country, the intercept gives the relative position of each country in the analysis. F tests were used to determine the overall significance of country effects in these metaregression analyses. Bubble plots are shown in Figures 2, 3. In these plots, only studies from countries with multiple time points, and therefore contributing to the estimated slope in the adjusted analysis, are shown. Bubble sizes in these plots are proportional to weights used in the analysis, and the regression lines presented have an intercept that is calculated as the average across individual countries. Analyses were performed using statistical software (SAS version 8.2; SAS Institute; Cary, NC).

RESULTS

Eligible Studies

Our search identified 466 studies. Figure 1 outlines the selection process of eligible studies. Ultimately, 15 population-based investigations from seven different countries (Denmark, France, Italy, the Netherlands, Sweden, United Kingdom, and United States) were selected for inclusion. Table 1 summarizes the characteristics of identified studies, including population characteristics and study design.

Different procedures were used to capture all IE cases, including census of existing diagnoses, record-linkage system, and direct contact survey or a combination of these. Census of existing diagnoses was performed by searching one or more of the following: hospital diagnostic codes, autopsy registries, death certificates, national or county registries of discharge diagnoses, and records of specialized units. A record-linkage system that linked all diagnoses for the population it serves was only available in Olmsted County, MN. Sixteen studies used a direct contact survey design and involved sending a questionnaire to physicians and/or microbiologists that asked them to report relevant information on any confirmed and suspected IE case. Surveillance systems were applied in three surveys in which they actively recruited any suspected IE patient in participating hospitals.

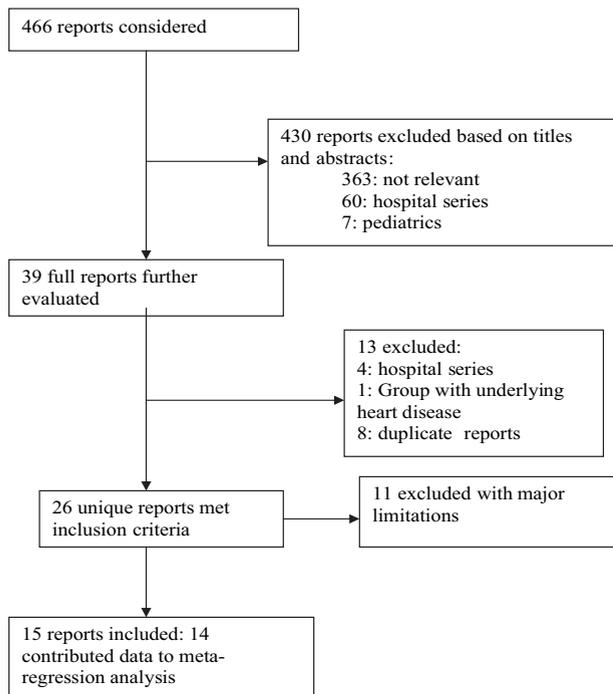


FIGURE 1. Flow diagram of eligible studies.

Quality Assessment

Eleven studies were excluded. Ten of these studies^{19–28} had considerable shortfall in reporting or inadequate/unclear case-finding procedures. Nine of the 11 studies used the direct contact survey that led to inadequate case ascertainment. The other studies that used direct contact survey were more successful because they either supplemented it with active search for cases or they recruited more specialties to participate in the study and used active follow-up visits or reminders during the study period. One study²⁹ used discharge codes and did not validate the diagnoses or checked for duplicates.

IE Characteristics and Temporal Trends

Table 2 summarizes the incidence, demographics, and characteristics of IE in different surveys.

Individual Studies That Examined Temporal Trends: The only study¹⁸ designed to examine temporal trends of IE incidence and characteristics was the one conducted in Olmsted County, MN. The results of another survey¹⁰ from France restricted to the regions of Ile de France, Lorraine, and Rhone-Alpes were compared to an earlier survey⁹ from 1990 of the same regions. Table 3 summarizes the main findings of these two studies.

Metaregression: Table 4 summarizes the results of different metaregression analyses based on 14 of the 15 included studies (Table 1); the study by Nolsoe et al⁴ was omitted from the analysis because it did not include data on all IE characteristics. Because country effects were considered to be important to control for, all analyses are presented as both unadjusted and after adjusting for country.

In the unadjusted regression analysis, there was an overall decline in the proportion of IE patients with underlying RHD and an increase in the proportion of patients undergoing valve surgery, the point estimates being a decrease of 12% (95% CI, – 21 to – 3%; $p = 0.01$) and an increase of 9% (95% CI, 3 to 16%) per decade, respectively.

There was significant country effect for the rheumatic heart disease variable (p value for F test = 0.05). This country effect refers to the estimated intercept (the proportion in 1970) for the each country and indicates where each country lies relative to the others. After adjusting for country, the decline in IE patients with underlying RHD became nonsignificant, but the proportions of IE patients undergoing valve surgery and those with underlying prosthetic valves both showed both a 7%-per-decade increase (95% CI, – 4 to 14%; $p = 0.06$; and 95% CI, – 1 to 16%; $p = 0.07$,

Table 1—Study and Population Characteristics of Eligible Studies

Source	Geographic Boundaries				Population			Sampling Definition (Intended Sample: Nonrandom vs Complete Enumeration)	Case Definition (Diagnostic Criteria; Levels of Diagnostic Certainty)	Case Ascertainment		
	Country	Location	Residency Ascertained	Population Size, /million	Source of Estimate	Temporal Boundaries, yr	Other			Case Finding Procedure	Source List	
											Case Finding Procedure	Source List
Nolsoe et al ⁴	Denmark	Herlev County	Unknown	0.195552	Unknown	1981–1983	Complete enumeration	Other	Census of existing diagnoses	County registry, postmortem diagnosis, diagnostic codes		
Nissen et al ⁵	Denmark	Counties: Fynen, Southern Jutland, and Ribe	Unknown	0.93	Unknown	1980–1989	Complete enumeration	Other D/P	Census of existing diagnoses	Twenty-five hospital diagnostic codes and death certificates		
Benn et al ⁶	Denmark	Viborg County	Unknown	0.23	Unknown	1984–1993	Complete enumeration	Von Reyn et al ³⁰ D/P/P	Census of existing diagnoses	Hospital diagnostic codes, death certificates, and autopsy reports		
Foghsgaard et al ⁷ and Pedersen et al ⁸	Denmark	Frederiksberg County	Unknown	Unknown	Unknown	1990–2000	Complete enumeration	Dukef D/P	Census of existing diagnoses	County registry, diagnostic codes, positive blood cultures		
Delahaye et al ⁹	France	Ile de France, Lorraine, Rhone-Alpes	Yes	18.5	Census	1990–91	Complete enumeration	Modified from Von Reyn et al ³⁰ D/P/P	Direct contact survey	All cardiologists, CTS, ID, intensivists, internal medicine, and microbiologists		
Hoen et al ¹⁰	France	Ile de France, Lorraine, Rhone-Alpes, Franche-Comte, Marne, and New Caledonia	Yes	16	Census	1999	Complete enumeration	Dukef D	Direct contact survey	All physicians		
Rossi et al ¹¹	Italy	Veneto	Yes	4.0 (average)	Census	1975–1984	Nonrandom	Other	Census of existing diagnoses	Hospital diagnostic codes		
van der Meer et al ¹²	the Netherlands	Nationwide	N/A	14.5	Unknown	1986–1988	Complete enumeration	Von Reyn et al ³⁰ D/P/P	Direct contact survey	All clinical microbiologist		
Hogevik et al ¹³	Sweden	City of Goteborg	Yes	0.428	Statistical Yearbook	1984–1988	Complete enumeration	Modified Von Reyn et al ³⁰ D/P/P	Direct contact survey; census of existing diagnoses	Active recruitment at University of Goteborg; diagnostic codes of other hospitals		
Skelhan et al ¹⁴	United Kingdom	Northeast Thames region	Yes but included all cases in analysis	3.375	Census	1982–1984	Complete enumeration	Other	Direct contact survey; census of existing diagnoses	To all physicians; diagnostic codes and autopsy search		

Table 1—Continued

Source	Population				Case Definition (Diagnostic Criteria; Levels of Diagnostic Certainty)	Case Finding Procedure	Case Ascertainment			
	Geographic Boundaries		Sampling (Intended Sample: Nonrandom vs Complete Enumeration)	Case Ascertainment						
	Country	Location						Residency Ascertained	Population Size, /million	Source of Estimate
Whitby et al ¹⁵	United Kingdom	Glasgow	No	1.5	Unknown	1976–1981	Complete enumeration	Von Reyn et al ³⁰ D/P/P/R (likely)	Census of existing diagnoses; direct contact survey	Diagnostic codes and autopsy; Scottish home and health department; consultants who may have treated IE
Smith et al ¹⁶	United Kingdom	Southeast Area of Scotland	Unknown	1.2	Unknown	1969–1972	Complete enumeration	Other	Census of existing diagnoses; direct contact survey	Diagnostic codes, autopsy, and medical records of specialized units; consultants
Griffin et al ¹⁷	United States	Olmsted County, MN	Yes	0.0482–0.091	Census	1950–1981	Complete enumeration	Von Reyn et al ³⁰ D/P/P	Records-linkage system	Rochester Epidemiology Project-Linkage system (diagnostic codes and autopsy)
Steckelberg et al ³	United States	Olmsted County, MN	Yes		Census	1970–1987	Complete enumeration	Modified from Von Reyn et al ³⁰	Records-linkage system	Rochester Epidemiology Project-Linkage system
Tleyjeh et al ¹⁸	United States	Olmsted County, MN	Yes	0.051–0.09	Census	1970–2000	Complete enumeration	Modified Duke† D/P	Records-linkage system	Rochester Epidemiology Project-Linkage system

*N/A = not applicable; D = definite; D/P = definite/probable; D/P/P = definite/probable/possible/rejected; CTS = cardiothoracic surgeons; ID = infectious diseases physicians.

†Duraek et al.³¹

‡Li et al.³²

Table 2—Demographics and Clinical Characteristics of Eligible Studies*

Source	No.	Crude Incidence, /100,000	Demographics		Risk Factors and Underlying Heart Disease, %				Causative Organisms, %			Outcome		
			Age Range, yr (Mean or Median)	Male/Female Ratio	None	RHD	Congenital Heart Disease	Mitral Valve Prolapse	Prosthetic Valve	IVDA	Viridans streptococci	S aureus	Valve Surgery, %	Mortality Definition
Nolsoe et al ⁴	33	1.8	> 15	12/21	58	1.5	4.5	0	3.0	21.6	27.6	14		33
Nissen et al ⁵	132	1.4	Men (59); women (70)	1.2/1										
Benn et al ⁶	62	1.7/3.6†	14–83 (55.4)	1.4/1	34	9.7	11.3	14.5	4.8	21	33.9	32.3	1 yr	35.5
Foghsgaard et al ⁷ and Pedersen et al ⁸	135	3.5	0–87	2/1	69	2	6	16	5	34	16	21		14
Delahaye et al ⁹	415	2.2	0–91 (56)		34		3.1	22	4.8	27	18	30	In-hospital	21
Hoen et al ¹⁰	390	3.0	16–95 (59.5)	2.5/1	47		1	16	6	17.4	23	49	In-hospital	16
Rossi et al ¹¹	80	1.6	(48)	1.35/1	21	40	7.5	5	2.5	6.8†	12.2†	35	In-hospital	17.5
van der Meer et al ¹²	438	1.5	2–89		2		12	3	7	37.2	18.7		In-hospital	19.7
Hogevik et al ¹³	99	6.2	8–88 (69)	1.2/1	43	18	10	7	7	27	31	15	Short term	23
Skehan et al ¹⁴	185	1.5	(54.5)		10	18		19	6.5	45	14.6	18.4		21
Whitby et al ¹⁵	71		17–87 (51.3)	2/1	20	44	4	18	0	41.5	13	22		45
Smith et al ¹⁶	78	1.6	15–88	1.3/1	24.4	29.5	6.4	16.7	0	26.9	20.5	12.8	60 d	46
Griffin et al ¹⁷	78		1–90 (58)	1.4/1	14	26	14	5.1	0	35	32	18	In-hospital	40
Steckelberg et al ³	68	4.2		2.6/1	25	25	15	24	0.3	40	29	28	In-hospital	19
Tleyjeh et al ¹⁸	107	4.95§	18.8–90.6 (61.5)	2.7/1	32	13	7	17	3	44	33	15	6 mo	26

*IVDA = IV drug abuse.

†Data on 74 of 80 subjects.

‡1.7 in the first 5 years and 3.6 the next 5 years.

§Average incidence.

||Male/female gender, No.

Table 3—Individual Studies That Examined Temporal Trends*

Source	Incidence	Causative Organisms	Underlying Valvular Heart Disease	Surgery and Outcome
Tleyjeh et al ¹⁸	The age- and sex-adjusted incidence of IE ranged from 5.0 to 7.0 cases per 100,000 person-yr (p = 0.42 for trend). The adjusted annual incidence was 5.4 per 100,000 with 95% CI, 3.7 to 7.2 for the period 1970–1984, and 6.5 per 100,000 with 95% CI, 5.0 to 8.1 for the period 1985–2000 (p = 0.29).	Viridans group streptococcal IE was the most common organism-specific IE subgroup between 1970 and 2000, accounting for 33 to 50% of IE cases, with an annual adjusted incidence of 1.7 to 3.5 cases per 100,000 person-yr. <i>S aureus</i> IE was the second most common subgroup, accounting for 20 to 38% of IE cases, with an annual adjusted incidence of 1.0 to 2.2 cases per 100,000. No time trend was detected for either pathogen group (p = 0.63 and p = 0.66, respectively).	The majority of IE cases occurred in patients with no known underlying heart disease, accounting for 56% of the cases in 1995–2000. There was a declining trend over time in the proportion of patients with underlying RHD (p = 0.08). An increasing temporal trend was observed in the proportions of prosthetic valve IE cases (p = 0.09).	6-mo mortality rates ranged from 14 to 33%. Valve surgery was performed in 0 to 23% of IE patients over different 5-yr time periods. There was no significant time trend in rates of valve surgery or in 6-mo mortality (p = 0.97 and p = 0.59, respectively).
Delehay et al ⁹ and Hoen et al ¹⁰	The annual age- and sex-standardized incidence was 3.1 (95% CI, 2.8 to 3.5) cases per 100,000, not including the region of New Caledonia, which had 16.1 (95% CI, 117 to 216) cases per 100,000 presumably due to a high rate of injection drug use. A small decrease in the annual incidence of definite IE from was observed: 3.1 (95% CI, 2.8 to 3.5) cases per 100,000 in 1991, to 2.6 (95% CI, 2.4 to 3.0) cases per 100,000 in 1999.	There was a decreased incidence of oral streptococcal IE (7.8 cases per million vs 5.1 cases per million; p < 0.001) and no significant change in the incidence of IE due to group D streptococci (5.3 cases per million vs 6.2 cases per million; p = 0.67) or <i>S aureus</i> IE (4.9 cases per million vs 5.7 cases per million; p = 0.97)	The proportion of IE patients without previously known cardiac disease increased from 34% in 1991 to 47% in 1999. The incidence of prosthetic valve IE decreased (from 6.9 cases per million in 1991 to 4.7 cases per million in 1999; p < 0.001), and the incidence of IE in patients with known UHD decreased (from 20.6 cases per million to 15.1 cases per million; p < 0.001).	The rate of surgical treatment has significantly increased from 31.2 to 79.7%, and the mortality rate tended to decrease from 21.6 to 16.6% from 1991 to 1999.

*UHD = underlying heart disease.

respectively). There were no significant temporal trends in the proportion of IE cases due to viridans group streptococci or with underlying mitral valve prolapse. There did appear to be weak-to-moderate evidence of country effects when examining the temporal trends among most characteristics of IE. Distribution of proportions across countries and results of metaregression analyses for temporal trends in the proportions of viridans group streptococci and *S aureus* are shown in Figures 2, 3.

DISCUSSION

Our systematic review highlights several important aspects of IE epidemiology in the general population

and the different limitations that have distorted the findings of available IE population-based surveys. It reveals significant variability and between-country heterogeneity in IE characteristics. Furthermore, it does not support the current belief that IE is undergoing a metamorphosis.

First, although all identified studies attempted to describe the epidemiology of IE in a given population, many failed to ascertain the residency status of all cases; failure to do so can lead to inclusion of referral cases. Second, the majority of identified studies intended complete enumeration of all IE cases in the population to avoid selection bias; however, many had considerable shortfall in case identification. Third, failure to use a validated case definition by several studies may have

Table 4—Results of Metaregression Analyses for Temporal Trends of IE Characteristics*

Parameters	Change in Proportion per Decade						
	Culture Positive	<i>S aureus</i>	Viridans streptococci	Mitral Valve Prolapse	Prosthetic Valve	RHD	Surgery
Overall change per decade	0.03 (− 0.03 to 0.08); p = 0.32	0.01 (− 0.04 to 0.05); p = 0.77	− 0.03 (− 0.12 to 0.05); p = 0.40	− 0.003 (− 0.07 to 0.06); p = 0.93	0.04 (− 0.02 to 0.11); p = 0.16	− 0.12 (− 0.21 to − 0.03); p = 0.01	0.09 (0.03 to 0.16); p = 0.01
Overall change per decade, adjusted for country	0.02 (− 0.02 to 0.07); p = 0.27	− 0.03 (− 0.09 to 0.04); p = 0.40	0.02 (− 0.07 to 0.11); p = 0.65	0.04 (− 0.06 to 0.14); p = 0.39	0.07 (− 0.01 to 0.16); p = 0.07	− 0.03 (− 0.12 to 0.06); p = 0.40	0.07 (− 0.004 to 0.14); p = 0.06
Denmark	0.83 (0.72 to 0.93)	0.31 (0.17 to 0.46)	0.25 (0.05 to 0.45)	− 0.06 (− 0.28 to 0.16)	− 0.08 (− 0.23 to 0.08)	0.09 (− 0.09 to 0.27)	0.08 (− 0.09 to 0.24)
France	0.86 (0.74 to 0.98)	0.28 (0.11 to 0.46)	0.19 (− 0.06 to 0.43)	− 0.05 (− 0.28 to 0.19)	0.005 (− 0.22 to 0.23)	NA	0.22 (0.02 to 0.42)
Italy	0.68 (0.52 to 0.84)	0.18 (0.03 to 0.33)	0.07 (− 0.11 to 0.26)	0.02 (− 0.20 to 0.23)	0.18 (− 0.05 to 0.42)	0.43 (0.19 to 0.67)	0.29 (0.08 to 0.50)
the Netherlands	0.94 (0.85 to 1.03)	0.23 (0.09 to 0.33)	0.35 (0.14 to 0.55)	− 0.03 (− 0.24 to 0.17)	0.09 (− 0.11 to 0.29)	NA	NA
Sweden	0.84 (0.70 to 0.98)	0.40 (0.22 to 0.57)	0.28 (0.04 to 0.52)	0.01 (− 0.25 to 0.27)	0.03 (− 0.20 to 0.27)	0.24 (0.00 to 0.47)	0.04 (− 0.16 to 0.24)
United Kingdom	0.85 (0.77 to 0.93)	0.20 (0.11 to 0.29)	0.43 (0.30 to 0.57)	0.05 (− 0.18 to 0.28)	0.08 (− 0.05 to 0.20)	0.37 (0.21 to 0.54)	0.12 (0.01 to 0.24)
United States	0.96 (0.87 to 1.04)	0.30 (0.17 to 0.43)	0.41 (0.22 to 0.60)	0.05 (− 0.13 to 0.23)	0.05 (− 0.09 to 0.19)	0.15 (− 0.04 to 0.34)	0.02 (− 0.11 to 0.15)
p Value for country (F test)	0.01	0.20	0.02	0.70	0.16	0.05	0.06

*Data are presented as change in proportion (95% CI). NA = data not available.

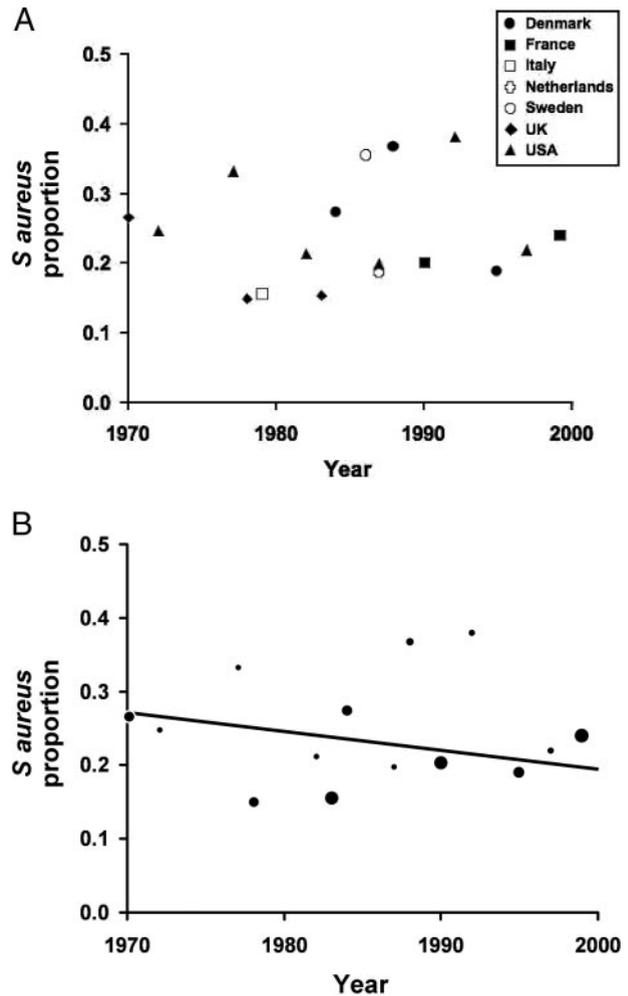


FIGURE 2. *Top, A:* Distribution of proportions of *S aureus* IE among culture-positive IE cases across different countries: X-axis (year), Y-axis (proportion of viridans streptococcal IE among culture-positive IE cases). Each country is represented by a different shape and color. *Bottom, B:* Metaregression analyses: overall temporal trends in *S aureus* IE among culture-positive IE cases: X-axis (year), Y-axis (proportion of *S aureus* IE among culture-positive IE cases). Only studies from countries with multiple time points, and therefore contributing to the estimated slope in the adjusted analysis, are shown. Bubble sizes in these plots are proportional to weights used in the analysis, and the regression lines presented have an intercept that is calculated as the average across individual countries.

contributed to disease misclassification by including false-positive cases and excluding false-negative cases. Fourth, case ascertainment was inadequate in several studies.

There are advantages and disadvantages of different study designs. The direct contact survey design has some advantages over searching of existing diagnoses because it can cover a larger population and include a larger sample size. Nevertheless, this design is prone to underreporting and selection bias because of the voluntary nature of participation. The extent of underreporting is difficult to assess unless investigators com-

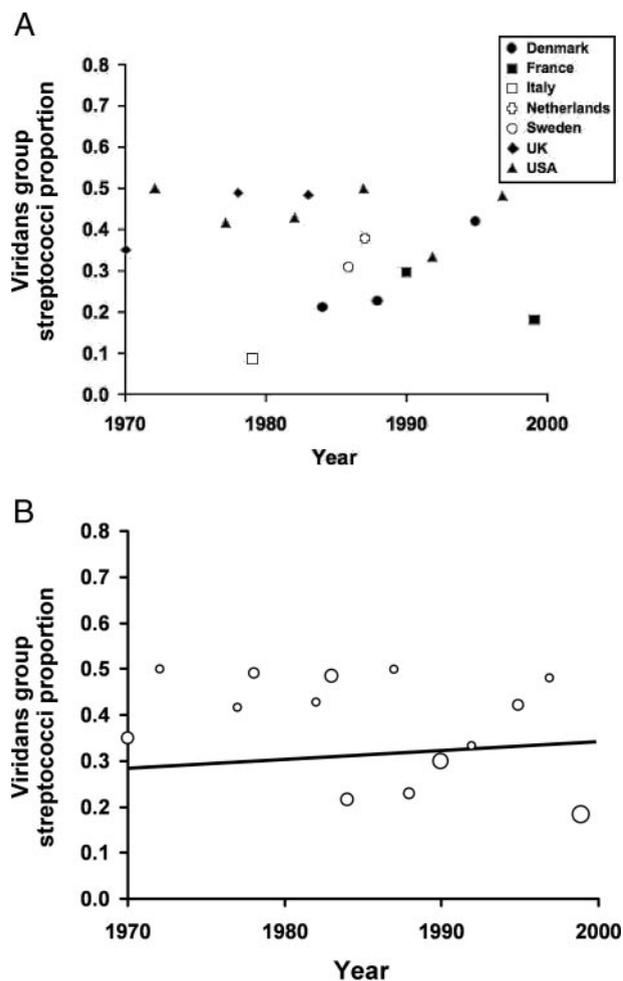


FIGURE 3. *Top, A:* Distribution of proportions of viridans streptococcal IE among culture-positive IE cases across different countries: X-axis (year), Y-axis (proportion of viridans streptococcal IE among culture-positive IE cases). Each country is represented by a different shape. *Bottom, B:* Metaregression analyses: overall temporal trends in viridans streptococcal IE among culture-positive IE cases: X-axis (year), Y-axis (proportion of viridans streptococcal IE among culture-positive IE cases). Only studies from countries with multiple time points, and therefore contributing to the estimated slope in the adjusted analysis, are shown. Bubble sizes in these plots are proportional to weights used in the analysis and the regression lines presented have an intercept which is calculated as the average across individual countries.

pare survey results to those from searching existing diagnoses in the same population at the same time. Moreover, survey design may fail to include culture-negative IE cases or cases diagnosed on postmortem examination. Census of existing diagnoses, if performed in a comprehensive manner, is more reliable in capturing all cases; however, it is also prone to underestimation of the true number of cases if diagnostic coding procedures are not complete. Given the seriousness of IE, it is less likely that cases are not reported in discharge codes. Census of existing diagnoses relies on abstracting data retrospectively from medical records

and is prone to missing or inaccurate information and lack of standard definitions, especially when describing underlying heart disease. In addition, this procedure is most often used in a small population and is limited by the small sample size and limited generalizability of the results. Record-linkage systems provide a unique opportunity to study IE epidemiology because they are more reliable in capturing all cases; however, they are of limited availability worldwide and can be affected by small sample size, information bias, and limited generalizability.

We observed significant between-country heterogeneity in IE characteristics as manifested by the wide variability in the proportions of IE cases with a specific underlying heart disease or caused by a specific organism. There was also an important country effect on the results of the adjusted metaregression analysis. This between-country heterogeneity may be related to different study design, case definition and ascertainment, and different populations at risk, and thus it precludes a definitive interpretation of the metaregression analyses to study global temporal trends in IE. This type of analysis is prone to bias because it compares different populations at different times. There was also a spread of studies across different countries, and there were limited observations to detect a significant effect with metaregression while controlling for country. Nevertheless, the directions of temporal trends obtained from these analyses are clinically plausible.

Results of the metaregression analyses and one individual temporal trend study¹⁵ suggest an increase in IE cases with underlying prosthetic valve, a nonsignificant increase in cases with underlying mitral valve prolapse and a nonsignificant decrease in IE cases with underlying RHD, in developed countries. Although these trends did not reach statistical significance due to the limited number of studies in the meta-regression analyses, the direction of the trends are plausible. The decline in RHD likely accounts for the decline in the proportion of IE cases with this as a predisposing cardiac condition. The apparent increase in IE cases with mitral valve prolapse could be due to detection bias with the more frequent use of echocardiography.

Although the results of the metaregression analyses suggest no overall temporal trends in *S aureus* or viridans group streptococcal IE, a heterogeneous pattern of temporal change in IE-causative organisms exists across different countries. The direction of the overall trend was an increase in viridans group streptococcal IE and a decrease in *S aureus*. The proportions of *S aureus* and viridans group streptococcal IE ranged from 12.2 to 33.9% and 6.8 to 45% among 15 studies with no major limitations.

Our review provides the first summary of IE population-based studies based on findings from

different geographic and temporal investigations. We performed a comprehensive search and included studies published in any language to capture surveys from different countries. Moreover, we critically appraised the quality of included studies to make our assessment and to help guide the future development of well-designed studies to investigate global characteristics of IE.

Despite the thoroughness of this systematic review, limitations to our understanding of global IE epidemiology remain. First, all population-based studies are prone to incomplete case ascertainment or disease misclassification. Second, different IE case definitions used over time and across different studies limit our ability to examine temporal trends or geographic patterns of IE. Third, many regions in the world are underrepresented in the IE literature. Several IE studies addressing IE epidemiology have been published from different countries, but only very few were population based. All 15 well-designed studies were from developed countries. Fourth, even within one country, few regions are represented. For example, in the United States, the only IE population-based study was from Olmsted County, MN. The relative uniformity of the racial and ethnic composition of Olmsted County potentially limits the ability to generalize the findings of the study to groups underrepresented in the population within and outside the United States. Finally, the country adjustment in the metaregression analysis lessens the power to detect trends; nevertheless, given the fact that we have different countries represented at different time points, it is important to take these country effects into account. This emphasizes the need for additional, large, and well-executed studies to further define these issues. Coordinated multinational studies covering the same time span and using the same methodology are particularly useful.

CONCLUSION

Our review provides the first summary of IE population-based studies from different geographic and temporal investigations. Evidence from well-planned representative epidemiologic surveys is scarce in many countries. The available evidence does not support the contention that IE epidemiology is undergoing major changes. More appropriately designed studies from different countries are needed to expand our understanding of the global epidemiology of IE.

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