Global and Regional Burden of Infective Endocarditis, 1990–2010

A Systematic Review of the Literature

Aref A. Bin Abdulhak*, Larry M. Baddour†, Patricia J. Erwin‡, Bruno Hoen§, Vivian H. Chu||, George A. Mensah¶, Imad M. Tleyjeh†,#,**,††

Kansas City, MO, USA; Rochester, MN, USA; Cedex, France; Durham, NC, USA; Bethesda, MD, USA; and Riyadh, Saudi Arabia

ABSTRACT

Infective endocarditis (IE) is a life-threatening disease associated with serious complications. The GBD 2010 (Global Burden of Disease, Injuries, and Risk Factors) study IE expert group conducted a systematic review of IE epidemiology literature to inform estimates of the burden on IE in 21 world regions in 1990 and 2010. The disease model of IE for the GBD 2010 study included IE death and 2 sequelae: stroke and valve surgery. Several medical and science databases were searched for IE epidemiology studies in GBD high-, low-, and middle-income regions published between 1980 and 2008. The epidemiologic parameters of interest were IE incidence, proportions of IE patients who developed stroke or underwent valve surgery, and case fatality. Literature searches yielded 1,975 unique papers, of which 115 published in 10 languages were included in the systematic review. Eligible studies were population-based (17%), multicenter hospital-based (11%), and single-center hospital-based studies (71%). Population-based studies were reported from only 6 world regions. Data were missing or sparse in many low- and middle-income regions. The crude incidence of IE ranged between 1.5 and 11.6 cases per 100,000 people and was reported from 10 countries. The overall mean proportion of IE patients that developed stroke was 0.158 ± 0.091, and the mean proportion of patients that underwent valve surgery was 0.324 ± 0.188. The mean case fatality risk was 0.211 ± 0.104. A systematic review for the GBD 2010 study provided IE epidemiology estimates for many world regions, but highlighted the lack of information about IE in low- and middle-income regions. More complete knowledge of the global burden of IE will require improved IE surveillance in all world regions.

Infective endocarditis (IE) is a serious life-threatening disease, with up to 22% in-hospital and 40% 5-year mortality rates [1–3]. IE is also associated with significant complications among survivors, including heart failure, usually because of severe valvular insufficiency, and embolic stroke. Valve surgery may be life-saving and has been shown to reduce embolic risk [4]. The magnitude of global health loss due to IE is largely unknown as it was not specifically included in the previous iterations of the GBD (Global Burden of Disease, Injuries, and Risk Factors) study [5,6]. A previous report indicated a scarcity of representative IE epidemiologic surveys from many countries [7]. Furthermore, no comprehensive assessments of the incidence, mortality, burden, and sequelae of IE have been undertaken previously for most areas of the world.

The GBD study is a systematic, scientific effort to quantify the comparative magnitude of health loss due to diseases, injuries, and risk factors by age, sex, and geography for specific points in time [8]. The GBD study was initiated by World Bank in 1991 and used standard methods to provide a comprehensive assessment of the mortality and disability burden of major diseases, injuries, and risk factors for the year 1990 [5,6,9]. However, IE was not included among major diseases in the 1990 study. The GBD 2010 study aimed to improve and update GBD methods and analyze the burden of diseases, risk factors, and injuries for the years 1990, 2005, and 2010 in 21 world regions for 291 diseases and risk factors and 1,161 sequelae among 20 age groups for each sex separately [8]. The GBD 2010 study's hierarchical causes list included IE among the 291 diseases.

Here, we summarize the methodology of the comprehensive systematic review used to estimate the global burden of IE and provide summary data about the crude incidence and sequelae of IE.

METHODS

GBD 2010 study definitions related to infective endocarditis

IE was defined by any of the following criteria: Pelletier and Petersdorf [10], Von Reyn or modified Von Reyn [11], Duke or modified Duke [12,13] criteria. A simplified disease model for the systematic review of IE was employed (Fig. 1). Stroke was defined as a neurological deficit that lasts >24 h and of presumed vascular origin [14]. Valve surgery included either valve replacement or repair.

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The views expressed in this article are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services, or any other government entity.

From the *Department of Medicine, School of Medicine, University of Missouri—Kansas City, Kansas City, MO, USA; †Division of Infectious Diseases, Mayo Clinic, Rochester, MN, USA; ‡Mayo Medical Library, Mayo Clinic, Rochester, MN, USA; §Department of Infectious Diseases, Dermatology, and Internal Medicine, University Medical Center of Guadeloupe, Cedex, France; ||Division of Infectious Diseases, Department of Medicine, Duke University Medical Center, Durham, NC, USA; ¶Center for Translation Research and Implementation Science (CTRIS), National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, USA; #Division of Epidemiology, Mayo Clinic, Rochester, MN, USA; **Department of Medicine, Infectious Diseases Section, King Fahad Medical City, Riyadh, Saudi Arabia; and the ††College of Medicine, Al Faisal University, Riyadh, Saudi Arabia. Correspondence: I. M. Tleyjeh (itlaygeh@gmail.com).

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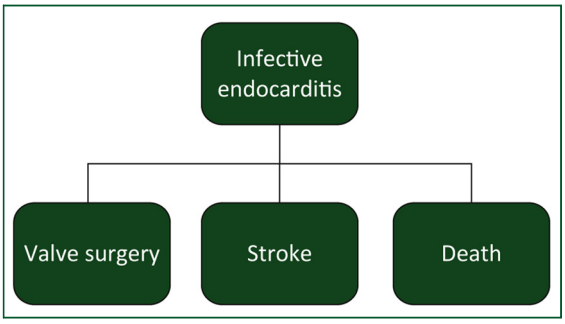

FIGURE 1. Infective endocarditis disease model. Simplified disease model for systematic review.

The GBD 2010 study divided the world into 21 world regions on the basis of epidemiology, homogeneity, and geographical contiguity (Fig. 2).

Search strategy

Ovid Medline, Ovid Embase, Global Health Library, AMED (Allied and Complementary Medicine Database), EXTRAMed, Scopus, Web of Science, SciELO (Scientific Electronic Library Online), and the Ovid Cochrane databases were searched for relevant publications dating from January 1, 1980 through December 31, 2008. The search strategies used both subject headings and text words for the epidemiology of IE, such as "endocarditis," "bacterial/epidemiology," "ethnology," and "mortality," as well as text words "bacterial endocarditis," "infectious/infective endocarditis," and "epidemiologic," "ethnic," "incidence," and "prevalence." The strategy was tailored to each database to allow for the variations in structure and terminology. Bibliographies of full-text papers identified in the electronic search were also manually reviewed for additional eligible studies. All results were downloaded into EndNote 7.0 (Thompson ISI Research Soft, Philadelphia, PA, USA), a bibliographic database manager, and duplicate citations were identified and removed.

Study selection

Any study that reported an incidence or sequelae of IE was eligible for inclusion. Population-based studies would only be considered if they included 4 methodological components (defined general population, use of IE diagnostic criteria, adequate sampling techniques, and case ascertainment) [7]. There were no language or age restrictions. Non-English language studies were translated by a group of heath researchers/translators assigned by the GBD 2010 study.

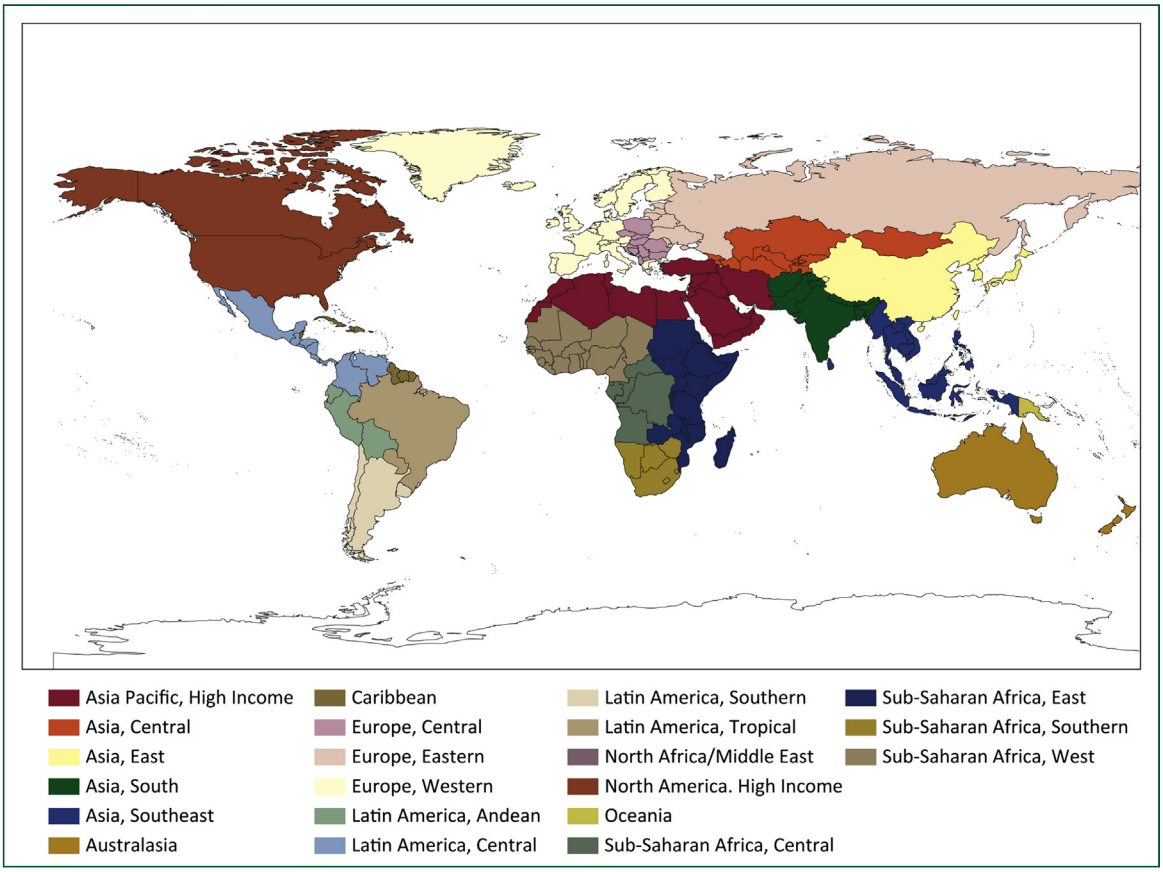

FIGURE 2. The 21 world regions of Global Burden of Disease, Risk Factors, and Injuries 2010 study.

Data extraction

Two reviewers (A.B. and I.T.) independently extracted data into a pre-designed data collection form. Final study inclusion was only considered if both reviewers were in agreement and any inconsistency was discussed with IE expert group. Data was extracted from selected studies regarding the study's definition of IE, sampling method, case finding procedures, country of origin, type of the study (population-based, multicenter hospital-based, and single-center hospital-based), study period, method of calculating estimates, size and age and sex composition of the sample, incidence of IE, frequency of valve surgeries, incidence of stroke, mortality definitions, and short- and long-term mortality among IE patients.

Statistical analysis

Summary estimates of the incidence of stroke or valve surgery and case fatality risk estimated from the systematic review study data are presented as mean ± SD and median (interquartile range [IQR]), respectively. The crude incidence was reported as number of patients per 100,000 people. Incidence of stroke and valve surgeries and case fatality risks among IE patients were stratified on type of patient cohorts for comparison. Evidence of differences in rates by study type were tested using the Kruskal-Wallis test and a p value of <0.05 was indicative of a significant difference.

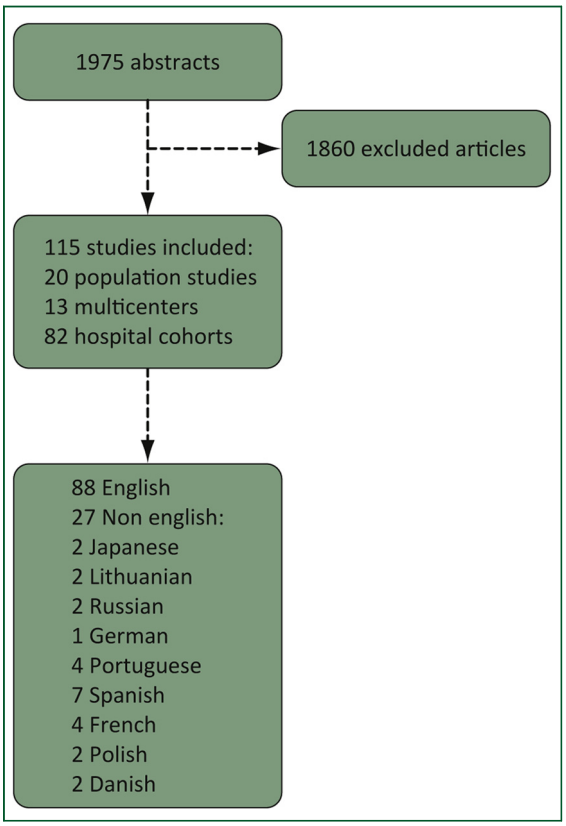

FIGURE 3. Flow diagram of the included studies.

RESULTS

Yield of search strategy

The initial search strategy yielded 1,975 publications, and 1,860 studies were excluded after careful review of full-text publications. One hundred fifteen citations [15–129] were included that were published in 10 languages. Tleyjeh et al. [117] reported on 4 different periods and thus accounted for 4 results from this 1 study. Figure 3 summarizes the results of the systematic review.

Descriptive overview of the included studies

Of 115 eligible studies, 20 (17%) were population-based, 13 (11%) were multicenter hospital-based, and 82 (71%) were single-center hospital-based studies. Population-based studies were reported from only 6 (29%) of 21 world regions (High Income North America, Western Europe, Eastern Europe, North Africa/Middle East, Australasia, and Southern Latin America) and multicenter studies from 5 (24%) of the world regions (Western Europe, Eastern Europe, High Income Asian Pacific, North Africa/Middle East, Southern Latin America). Duke criteria was used in 8 of the population-based studies followed by modified Duke (4 studies) and Von Reyn (4 studies) and modified Von Reyn (3 studies). Eligible studies covered only 16 (76%) of the world regions; no studies were found from Central Asia, the Caribbean, Andean Latin America, Oceania, or Eastern Sub-Saharan Africa. The included studies reported data on both sexes with a wide range of ages from 0 to 106 years. Table 1 summarizes general characteristics of the included studies. The incidence and outcomes reported in the included studies are summarized in Table 2.

Crude incidence of IE

IE incidence was reported in 17 of 20 population-based studies from only 4 world regions (High Income North America, Western Europe, North Africa/Middle East, Australasia). These broad geographic regions were represented by only 10 countries: Australia, Denmark, France, Greece, Italy, the Netherlands, Sweden, Tunisia, the United States, and the United Kingdom. In these studies, the crude incidence of IE was in the range of 1.5 to 11.6 cases per 100,000 people. The highest incidence was reported from the United States (11.6 cases per 100,000 people) and the lowest from the Netherlands (1.5. cases per 100,000 people). However, IE incidence varied greatly, including within the same country (Fig. 4).

Sequelae of IE

Stroke. The overall mean proportion of IE patients who developed stroke reported from all studies was 0.158 ± 0.091; the median was 0.136 (IQR: 0.099). The median proportions of IE patients that developed stroke from

TABLE 1. Characteristics of included studies

Reference	First Author	Sex	Country Code	Country	Geographic Region	Minimum Age, yrs	Maximum Age, yrs	Study Starting Year	Study Ending Year	Study Type
15	Ako J	Both	JPN	Japan	Asia Pacific, High Income	6	82	1980	1999	Hospital cohort
16	Aksoy O	Both	USA	United States	North America, High Income	6	11	1996	2002	Hospital cohort
17	Alshammary A	Both	CAN	Canada	North America, High Income	0	16	1985	2004	Hospital cohort
18	Anavekar NS	Both	USA	United States	North America, High Income	18	100	1980	1998	Hospital cohort
19	Arzanauskiene R	Both	LTU	Lithuania	Europe, Eastern	18	82	1999	2001	Hospital cohort
20	Ashkenazi S	Both	ISR	Israel	North Africa/Middle East	0	16	1980	1991	Hospital cohort
21	Assef MA	Both	BRA	Brazil	Latin America, Tropical	2	76	1980	1987	Hospital cohort
22	Ben HK	Both	TUN	Tunisia	North Africa/Middle East	5	67	1982	2000	Hospital cohort
23	Ben-Ami R	Both	ISR	Israel	North Africa/Middle East	38	104	1995	1998	Hospital cohort
24	Benn M	Both	DNK	Denmark	Europe, Western	14	84	1984	1993	Population
25	Bennis A	Both	MAR	Morocco	North Africa/Middle East	11	65	1983	1994	Hospital cohort
26	Berkowitz FE	Both	ZFA	South Africa	Sub-Saharan Africa, Southern	0	9	1986	1988	Hospital cohort
27	Berlin JA	Both	USA	United States	North America, High Income	18	100	1988	1990	Population
28	Bhat AW	Both	IND	India	Asia, South	0	15	1983	1993	Hospital cohort
29	Bishara J	Both	ISR	Israel	North Africa/Middle East	18	93	1987	1996	Hospital cohort
30	Blackett K	Both	CMR	Cameroon	Sub-Saharan Africa, West	8	70	1984	1980	Hospital cohort
31	Blumberg EA	Both	USA	United States	North America, High Income	14	81	1985	1990	Hospital cohort
32	Borer A	Both	ISR	Israel	North Africa/Middle East	16	84	1980	1994	Hospital cohort
33	Bouza E	Both	ESP	Spain	Europe, Western	19	89	1994	1996	Hospital cohort
34	Braun S	Both	CHL	Chile	Latin America, Southern	0	100	1980	1999	Hospital cohort
35	Buchholtz K	Both	DNK	Denmark	Europe, Western	31	91	2002	2003	Multicenter
36	Carceller A	Both	CAN	Canada	North America, High Income	0	18	1986	2000	Hospital cohort
37	Cecchi E	Both	ITA	Italy	Europe, Western	15	89	2000	2001	Multicenter
38	Chao TH	Both	TWN	Taiwan	Asia, East	17	100	1990	1997	Hospital cohort
39	Cheng A	Both	AUS	Australia	Australasia	20	94	1994	1999	Population
40	Choudhury R	Both	IND	India	Asia, South	2	75	1981	1991	Hospital cohort
41	Chu J	Both	NZL	New Zealand	Australasia	7	89	1997	2002	Hospital cohort
42	Chu VH	Both	USA	United States	North America, High Income	26	90	1996	2001	Hospital cohort
43	Cicalini S	Both	ITA	Italy	Europe, Western	9	68	1980	2003	Hospital cohort
44	Costa MA	Both	BRA	Brazil	Latin America, Tropical	7	70	1988	1998	Hospital cohort
45	Coward K	Both	USA	United States	North America, High Income	0	28	1990	2002	Hospital cohort
46	Delahaye F	Both	FRA	France	Europe, Western	0	91	1990	1991	Population
47	Dhawan A	Both	IND	India	Asia, South	2	16	1984	1990	Hospital cohort
48	Di Salvo G	Both	ITA/FRA	Italy/France	Europe, Western	17	88	1993	2002	Multicenter
49	Dyson C	Both	GBR	United Kingdom	Europe, Western	0	89	1987	1996	Hospital cohort
50	Ejima K	Both	JPN	Japan	Asia Pacific, High Income	0	85	1984	2003	Hospital cohort
51	Fedorova TA	Both	RUS	Russian Federation	Europe, Eastern	16	81	2000	2007	Hospital cohort
52	Ferreiros E	Both	ARG	Argentina	Latin America, Southern	24	93	2002	2002	Multicenter
53	Foghsgaard J	Both	DNK	Denmark	Europe, Western	0	100	1990	2000	Population
54	Fonager K	Both	DNK	Denmark	Europe, Western	15	100	1980	97	Population
55	Garg N	Both	IND	India	Asia, South	4	68	1992	2001	Hospital cohort
56	Giannitsioti E	Both	GRC	Greece	Europe, Western	53	73	2000	2004	Population
57	Gotsman I	Both	ISR	Israel	North Africa/Middle East	1	97	1991	2000	Hospital cohort
58	Goulet V	Both	FRA	France	Europe, Western	1	89	1982	1983	Population

(continued)

TABLE 1. Continued

Reference	First Author	Sex	Country Code	Country	Geographic Region	Minimum Age, yrs	Maximum Age, yrs	Study Starting Year	Study Ending Year	Study Type
59	Heiro M	Both	FIN	Finland	Europe, Western	20	89	1980	2004	Hospital cohort
60	Hermida Ameijeinas A	Both	ESP	Spain	Europe, Western	19	84	1989	2003	Hospital cohort
61	Hill EE	Both	BEL	Belgium	Europe, Western	54	73	2000	2004	Hospital cohort
62	Hoen B	Both	FRA	France	Europe, Western	16	95	1999	1999	Population
63	Hogevik H	Both	SWE	Sweden	Europe, Western	8	88	1984	1988	Population
64	Hricak V	Both	SVK	Slovakia (Slovak Republic)	Europe, Eastern	0	100	1984	2006	Multicenter
65	Hsu CN	Both	TWN	Taiwan	Asia, East	0	92	1995	2003	Hospital cohort
66	Hwang JJ	Both	TWN	Taiwan	Asia, East	14	75	1989	1991	Hospital cohort
67	Hwang JJ	Both	TWN	Taiwan	Asia, East	17	75	1989	1992	Hospital cohort
68	Ifere OA	Both	NGA	Nigeria	Sub-Saharan Africa, West	0	15	1982	1989	Hospital cohort
69	Jaffe WM	Both	USA	United States	North America, High Income	15	88	1983	1988	Hospital cohort
70	Jain V	Both	USA	United States	North America, High Income	18	100	1993	2003	Hospital cohort
71	Janion M	Both	POL	Poland	Europe, Central	0	100	2001	2005	Hospital cohort
72	Jorge Sdo C	Both	BRA	Brazil	Latin America, Tropical	0	76	1985	1990	Hospital cohort
73	Jung HO	Both	KOR	Korea, Republic of (South Korea)	Asia Pacific, High Income	11	73	1983	1993	Multicenter
74	Kanafani ZA	Both	LBN	Lebanon	North Africa/Middle East	13	87	1986	2001	Hospital cohort
75	King J	Both	USA	United States	North America, High Income	15	90	1985	1986	Population
76	Knyshov GV	Both	UKR	Ukraine	Europe, Eastern	1	75	1982	200	Hospital cohort
77	Koegelenberg CF	Both	ZAF	South Africa	Sub-Saharan Africa, Southern	7	69	1997	2000	Hospital cohort
78	Krcmery V	NA	SVK	Slovakia (Slovak Republic)	Europe, Eastern	NA	NA	1991	2001	Population
79	Leblebicioglu H	Both	TUR	Turkey	North Africa/Middle East	18	100	2002	2004	Multicenter
80	Letaief A	Both	TUN	Tunisia	North Africa/Middle East	0	66	1991	2000	Population
81	Lewena S	Both	AUS	Australia	Australasia	0	17	1985	2001	Hospital cohort
82	López-Dupla M	Both	ESP	Spain	Europe, Western	15	86	1990	2004	Hospital cohort
83	Loupa C	Both	GRC	Greece	Europe, Western	17	86	1997	2000	Multicenter
84	Manford M	Both	GBR	United Kingdom	Europe, Western	23	85	1983	1989	Incidence
85	Milovsky V	Both	SVK	Slovakia (Slovak Republic)	Europe, Eastern	3	18	1990	1997	Multicenter
86	Mouly S	Both	FRA	France	Europe, Western	23	90	1997	1998	Hospital cohort
87	Moura L	Both	ESP	Spain	Europe, Western	26	86	1989	2001	Hospital cohort
88	Mourvillier B	Both	FRA	France	Europe, Western	18	84	1993	2000	Hospital cohort
89	Nadji G	Both	FRA	France	Europe, Western	30	90	1990	2003	Hospital cohort
90	Nashmi A	Both	SAU	Saudi Arabia	North Africa/Middle East	0	78	1993	2003	Hospital cohort
91	Netzer ROM	Both	CHE	Switzerland	Europe, Eastern	17	90	1980	1995	Hospital cohort
92	Nkoua JL	Both	COR	Congo, Republic of (Brazzaville)	Sub-Saharan Africa, Central	1	53	1985	1990	Hospital cohort
93	Nolsøe C	Both	DNK	Denmark	Europe, Western	0	100	1981	1983	Population
94	Expósito Ordóñez E	Both	ESP	Spain	Europe, Western	11	86	1992	1996	Hospital cohort
95	Ostrowski S	Both	POL	Poland	Europe, Central	19	70	1986	1994	Hospital cohort
96	Oyonarte M	Both	CHE	Chile	Latin America, Southern	12	86	1998	2002	Population
97	Pachirat O	Both	THA	Thailand	Asia, Southeast	15	75	1990	1999	Hospital cohort
98	Pachirat O	Both	THA	Thailand	Asia, Southeast	4	74	1990	2002	Hospital cohort
99	Paganini H	Both	ARG	Argentina	Latin America, Southern	2	14	1988	2000	Hospital cohort
100	Pedersen SA	Both	DNK	Denmark	Europe, Western	0	100	1990	2000	Population
101	Pereira CA	Female	BRA	Brazil	Latin America, Tropical	0	13	1993	2001	Hospital cohort
102	Pergola V	Both	FRA	France	Europe, Western	27	87	1993	2001	Hospital cohort
103	Roca B	Both	ESP	Spain	Europe, Western	22	84	1999	2004	Hospital cohort
104	Rozwodowska M	Both	POL	Poland	Europe, Central	18	78	1998	2000	Hospital cohort
105	Ruiz Júnior E	Both	BRA	Brazil	Latin America, Tropical	0	106	1992	1997	Hospital cohort
106	Sadiq M	Both	PAK	Pakistan	Asia, South	0	16	1997	2000	Hospital cohort

(continued)

TABLE 1. Continued

Reference	First Author	Sex	Country Code	Country	Geographic Region	Minimum Age, yrs	Maximum Age, yrs	Study Starting Year	Study Ending Year	Study Type
107	Sekido M	Both	JPN	Japan	Asia Pacific, High Income	18	68	1986	1996	Hospital cohort
108	Skehan JD	Both	GBR	United Kingdom	Europe, Western	19	91	1982	1984	Population
109	Smith JM	Both	USA	United States	North America, High Income	18	100	1993	2004	Hospital cohort
110	Souto Meiriño CA	Both	MEX	Mexico	Latin America, Central	0	100	1990	1994	Hospital cohort
111	Tariq M	Both	PAK	Pakistan	Asia, South	0	72	1997	2001	Hospital cohort
112	Teixeira F	Both	PRT	Portugal	Europe, Western	1	15	1993	1997	Hospital cohort
113	Thalme A	Both	SWE	Sweden	Europe, Western	40	72	1995	2000	Hospital cohort
114	Thuny F	Both	FRA	France	Europe, Western	17	96	1990	2005	Multicenter
115	Thuny F	Both	FRA/ITA	France/Italy	Europe, Western	16	94	1993	2003	Multicenter
116	Tiurin VP	Both	RUS	Russian Federation	Europe, Eastern	17	78	1980	1996	Hospital cohort
117	Tleyjeh IM	Both	USA	United States	North America, High Income	34	89	1995	2000	Population
117	Tleyjeh IM	Both	USA	United States	North America, High Income	28	84	1990	1994	Population
117	Tleyjeh IM	Both	USA	United States	North America, High Income	24	81	1985	1989	Population
117	Tleyjeh IM	Both	USA	United States	North America, High Income	19	90	1980	1984	Population
118	Tornos P	Both		Europe (international)	Europe	25	89	2001	2001	Multicenter
119	Tran CT	Both	DNK	Denmark	Europe, Western	19	83	1998	2000	Hospital cohort
120	Van der Meer JT	Both	NLD	Netherlands	Europe, Western	2	89	1986	1988	Population
121	Venkatesan C	Both	USA	United States	North America, High Income	0	16	1990	2007	Hospital cohort
122	Vlessis AA	Both	USA	United States	North America, High Income	11	90	1982	1992	Hospital cohort
123	Wallace SM	Both	GBR	United Kingdom	Europe, Western	0	100	1981	1999	Hospital cohort
124	Walpot J	Both	NLD	Netherlands	Europe, Western	36	81	2002	2004	Population
125	Werner M	Both	SWE	Sweden	Europe, Western	14	100	1995	2005	Multicenter
126	Zacherl S	Both	AUS	Australia	Australasia	0	18	1983	1993	Hospital cohort
127	Zaliaduonyte-Peksiene D	Both	LTU	Lithuania	Europe, Eastern	24	85	2002	2005	Hospital cohort
128	Zamorano J	Both	ESP	Spain	Europe, Western	0	100	1991	1991	Hospital cohort
129	Zarzur J	Both	MAR	Morocco	North Africa/Middle East	0	100	1995	2001	Hospital cohort

NA, not available.

population-based, multicenter hospital-based, and single-center hospital-based studies were 0.152 (IQR: 0.039), 0.145 (IQR: 0.069), and 0.122 (IQR: 0.119), respectively.

Southern Latin America recorded the highest stroke proportion (0.19) followed by North Africa/Middle East (0.18), Eastern Europe (0.166), Sub-Saharan Africa Southern (0.166), South Asia (0.160), Western Europe (0.143), Tropical Latin America (0.138), North America (0.123), Southern Asia (0.118), Australia (0.087), Central Europe (0.083), and East Asia (0.066). No data about stroke were available for other world regions.

Valve surgery. The overall mean proportion of IE patients that underwent valve surgery was 0.324 ± 0.188, whereas the median was 0.267 (IQR: 0.286). The median proportions of IE patients that underwent valve surgery from population-based, multicenter hospital-based, and single-center hospital-based studies were 0.229 (IQR: 0.138), 0.523 (IQR: 0.00), and 0.277 (IQR: 0.286), respectively.

Eastern Europe has the highest proportion of valve surgeries (0.75) followed by Southeast Asia (0.47), Asia Pacific (0.46), Latin America (0.413), Central Europe (0.410), Latin America (0.39), Southern Sub-Saharan Africa (0.383), North Africa/Middle East (0.380), Western Europe (0.37), North America (0.31), East Asia (0.28), Australia (0.24), and South Asia (0.124).

Overall mortality. Mortality information was reported from only 8 world regions. No mortality time element was reported from a majority of the studies. Southern Latin America followed by Eastern Europe and then East Asia have reported the highest case fatality risk from IE with a mean overall risk from all included studies of 0.211 ± 0.104, and the median was 0.200 (IQR: 0.126). The median case fatality risks from population-based, multicenter hospital-based, and single-center hospital-based studies were 0.200 (IQR: 0.112), 0.150 (IQR: 0.127), and 0.200 (IQR: 0.132), respectively.

Comparison of sequelae risks by study design. There were no statistically significant differences in the

TABLE 2. Outcomes of included studies

Reference	Principle Author	Incidence per 100,000 People	Valve Surgery Proportion	Stroke Proportion	Mortality Proportion	Sample Size
15	Ako J	NR	0.659	NR	0.154	194
16	Aksoy O	NR	0.286	0.173	0.169	426
17	Alshammary A	NR	0.2	NR	0.05	40
18	Anavekar NS	NR	NR	0.116	0.471	600
19	Arzanauskiene R	NR	NR	NR	0.246	138
20	Ashkenazi S	NR	NR	NR	0.04	25
21	Assef MA	NR	NR	NR	0.397	83
22	Ben HK	NR	0.547	0.293	0.301	126
23	Ben-Ami R	NR	NR	NR	0.241	87
24	Benn M	2.7	0.322	0.435	0.354	62
25	Bennis A	NR	0.101	0.101	0.286	157
26	Berkowitz FE	NR	0.2	0.4	0.6	10
27	Berlin JA	NR	NR	NR	NR	670
28	Bhat AW	NR	0	NR	0.25	28
29	Bishara J	NR	0.173	NR	0.272	213
30	Blackett K	NR	0.25	NR	0.35	20
31	Blumberg EA	NR	NR	NR	0.254	51
32	Borer A	NR	0.154	0.084	0.169	71
33	Bouza E	NR	0.229	0.119	0.256	109
34	Braun S	NR	0.523	0.192	0.16	261
35	Buchholtz K	NR	0.545	NR	0.138	231
36	Carceller A	NR	0.107	0.196	0.125	56
37	Cecchi E	3.6	0.306	0.136	0.19	147
38	Chao TH	NR	0.284	NR	0.25	88
39	Cheng A	3	0.31	NR	0.172	58
40	Choudhury R	NR	0.005	0.163	0.247	190
41	Chu J	NR	0.184	0.076	0.2	65
42	Chu VH	NR	0.265	0.202	0.187	267
43	Cicalini S		0.116	0.109	0.14	283
44	Costa MA	NR	0.639	NR	0.263	186
45	Coward K	NR	0.298	NR	0.122	57
46	Delahaye F	2.2	0.244	0.036	0.21	415
47	Dhawan A	NR	NR	0.135	0.432	37
48	Di Salvo G	NR	0.482	0.139	0.107	315
49	Dyson C	NR	NR	NR	0.172	122
50	Ejima K	NR	0.266	NR	0.266	75
51	Fedorova TA	NR	NR	0.258	0.258	112
52	Ferreiros E	NR	0.261	0.205	0.246	390
53	Foghsgaard J	3.5	NR	NR	NR	135
54	Fonager K	3.7 F 5.1 M	NR	NR	0.234	3,351
55	Garg N	NR	0.164	0.121	0.21	198
56	Giannitsioti E	2.1	0.271	NR	0.2	195
57	Gotsman I	NR	0.25	NR	0.08	100
58	Goulet V	1.8	0.28	NR	0.211	288
59	Heiro M	NR	0.279	0.101	0.131	326
60	Hermida Ameijeinas A	NR	0.252	0.045	0.08	87
61	Hill EE	NR	0.632	0.227	0.217	193
62	Hoen B	3	0.489	0.164	0.158	390
63	Hogevik H	6.2	0.151	0.121	0.131	99

(continued)

TABLE 2. Continued

Reference	Principle Author	Incidence per 100,000 People	Valve Surgery Proportion	Stroke Proportion	Mortality Proportion	Sample Size
64	Hricak V	NR	0.425	NR	0.15	606
65	Hsu CN	NR	NR	0.066	0.215	315
66	Hwang JJ	NR	0.325	NR	0.093	43
67	Hwang JJ	NR	0.5	0.08	0.12	50
68	Ifere OA	NR	NR	0.151	0.4848	33
69	Jaffe WM	NR	0.514	0.271	0.1	70
70	Jain V	NR	NR	0.06	0.149	247
71	Janion M	NR	0.543	NR	0.122	57
72	Jorge Sdo C	NR	0.326	NR	0.231	263
73	Jung HO	NR	NR	0.325	0.262	80
74	Kanafani ZA	NR	0.241	0.12	0.175	91
75	King J	1.7	0.333	0.1333	0.12	75
76	Knyshov GV	NR	0.754	NR	NR	1,128
77	Koegelenberg CF	NR	0.383	0.166	0.283	60
78	Krcmery V	NR				
79	Leblebicioglu H	NR	0.133	NR	0.285	112
80	Letaief A	5.5	0.506	0.163	0.204	440
81	Lewena S	NR	0.304	0.26	0.086	23
82	López-Dupla M	NR	0.2	NR	0.191	120
83	Loupa C	NR	0.445	NR	0.158	101
84	Manford M	NR	0.333	0.151	0.242	33
85	Milovsky V	NR	0.3	NR	0.2	20
86	Mouly S	NR	0.555	0.2	0.2	90
87	Moura L	NR	0.413	NR	NR	150
88	Mourvillier B	NR	0.456	0.298	0.447	228
89	Nadji G	NR	0.377	NR	0.248	310
90	Nashmi A	NR	0.446	0.234	0.085	47
91	Netzer ROM	NR	0.382	NR	0.24	212
92	Nkoua JL	NR	0.487	NR	0.512	39
93	Nolsøe C	1.8	NR	NR	NR	33
94	Expósito Ordóñez E	NR	0.223	0.035	0.094	85
95	Ostrowski S	NR	0.95	NR	0.191	120
96	Oyonarte M	NR	0.352	NR	0.271	321
97	Pachirat O	NR	0.45	0.118	0.25	160
98	Pachirat O	NR	0.49	NR	0.225	200
99	Paganini H	NR	0.244	0.197	0.127	86
100	Pedersen SA	NR	0.422	NR	0.14	135
101	Pereira CA	NR	NR	NR	0.035	28
102	Pergola V	NR	0.577	0.169	0.092	206
102	Roca B	NR	0.092	NR	0.27	54
104	Rozwodowska M	NR	0.25	0.083	0.196	56
105	Ruiz Júnior E	NR	0.211	0.138	0.405	180
106	Sadiq M	NR	0.088	0.066	0.133	45
107	Sekido M	NR	0.605	0.078	0.157	38
108	Skehan JD	2.3	0.183	NR	0.21	185
109	Smith JM	NR	0.505	NR	0.114	87
110	Souto Meiriño CA	NR	NR	NR	0.274	131
111	Tariq M	NR	0.09	0.212	0.272	66
112	Teixeira F	NR	0.428	NR	0.142	7
113	Thalme A	NR	0.187	NR	0.088	192

(continued)

TABLE 2. Continued

Reference	Principle Author	Incidence per 100,000 People	Valve Surgery Proportion	Stroke Proportion	Mortality Proportion	Sample Size
114	Thuny F	NR	0.596	0.125	0.118	496
115	Thuny F	NR	0.523	0.161	0.205	384
116	Tiurin VP	NR	NR	0.406	NR	172
117	Tleyjeh IM	6.3	0.148	NR	0.296	27
117	Tleyjeh IM	6.5	0.095	NR	0.333	21
117	Tleyjeh IM	7	0.2	NR	0.2	20
117	Tleyjeh IM	5	0.214	NR	0.142	14
118	Tornos P	NR	0.484	0.15	0.125	159
119	Tran CT	NR	0.386	NR	0.147	163
120	Van der Meer JT	1.5	NR	NR	0.197	438
121	Venkatesan C	NR	NR	0.06	NR	115
122	Vlessis AA	NR	0.407	0.042	0.371	140
123	Wallace SM	NR	0.514	0.1	0.269	208
124	Walpot J	9.6	0.37	0.125	0.343	32
125	Werner M	NR	0.202	NR	0.106	2,509
126	Zacherl S	NR	0.312	NR	0.062	16
127	Zaliaduonyte-Peksiene D	NR	NR	0.043	NR	116
128	Zamorano J	NR	0.495	NR	0.135	103
129	Zarzur J	NR	NR	0.121	NR	82

F, female; M, male; NR, not reported.

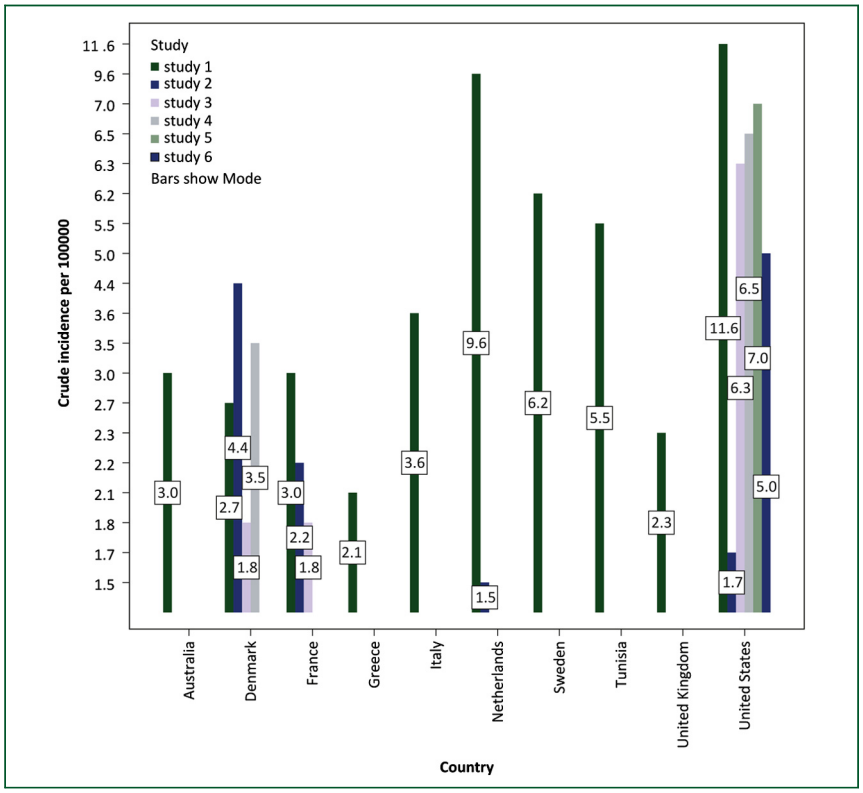

FIGURE 4. Incidence of infective endocarditis among different countries.

TABLE 3. Comparison of infective endocarditis sequelae among study designs

Variable	Single-Center Hospital-Based	Multicenter Hospital-Based	Population-Based	Significance, Kruskal-Wallis Test
Median valve surgery	0.277 (0.286)	0.523 (0.00)	0.229 (0.138)	$X^2 = 3.411$, $p = 0.1817$
Median stroke	0.122 (0.119)	0.145 (0.069)	0.152 (0.039)	$X^2 = 1.554$, $p = 0.4599$
Median mortality	0.200 (0.132)	0.150 (0.127)	0.200 (0.112)	$X^2 = 2.123$, $p = 0.3460$

Values are proportions (interquartile ranges).

occurrence of IE-related sequelae (stroke, valve surgery, and mortality) among different types of study designs (Table 3).

DISCUSSION

A comprehensive systematic review of the literature in 21 world regions revealed that IE, though an uncommon disease in the general population, is associated with significant morbidity and mortality. Additionally, the majority of the epidemiological findings are primarily from single hospital-based cohorts, with no data reported from Central Asia, Caribbean, Andean Latin America, Oceania, and Eastern Sub-Saharan Africa regions that constitute 24% (5 of 21) of the world's regions.

Ideally, the epidemiology of IE should be derived from population-based studies, due to the influence of a well-recognized referral bias on the observed profile of IE [130]. However, population-based studies represent only 17% of the current literature of IE, representing only 6 world regions, and even these regions were represented by studies of only 10 countries. Nevertheless, no statistically significant differences were observed among IE sequelae incidence among population-based studies, multicenter hospital-based studies, and single-center hospital-based cohorts. However, sampling from different populations, and referral bias may explain the absence of difference in the sequelae incidence among different study designs. Nonetheless, multicenter or single-center hospital-based cohorts could be used to estimate the global burden of IE in areas of the world that have not been characterized by population-based studies.

Based on these limited data, IE incidence appears to be generally low. IE incidence appears to vary greatly among different populations even within the same country. In the United States, for example, the incidence varied from 1.7 to 11.6 cases per 100,000 people. Multiple factors could have led to variability in IE incidence, including referral and case ascertainment biases, disease misclassification, differences in populations at risk, study designs, and use of different case definitions [7]. Moreover, IE can be associated with devastating outcomes. Almost 1 in 4 cases of IE will not survive.

Although our review was very comprehensive and aimed to globally estimate the IE burden, there are certain challenges that include incompleteness and nonrepresentative biases, missing data from several countries, inability to access unpublished data, and effect of referral bias that make our goals difficult.

Despite searching multiple library databases and the inclusion of studies published in several languages, few IE epidemiology studies were identified in our systematic review. Incidence of IE is largely unknown in most parts of the world due to scarcity of population-based studies from several world regions. Efforts should be made to report the incidence of IE using a standard case definition and to assist health planners and policy makers with setting the appropriate strategies to decrease the burden of this often fatal or disabling disease.

SUMMARY

Our study represents the first comprehensive effort to estimate the global burden of IE in 21 world regions for the years 1990 and 2010. IE literature covered 76% of the world regions, and it primarily included hospital-based cohorts with substantially fewer population-based studies. Although IE is an uncommon disease, it is associated with significant morbidity and mortality. High-quality population-based studies are urgently needed and may permit a better estimate of the global burden of IE.

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