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Global, Regional, and National Burden of Rheumatic Heart Disease, 1990–2015

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ABSTRACT

BACKGROUND

Rheumatic heart disease remains an important preventable cause of cardiovascular death and disability, particularly in low-income and middle-income countries. We estimated global, regional, and national trends in the prevalence of and mortality due to rheumatic heart disease as part of the 2015 Global Burden of Disease study.

METHODS

We systematically reviewed data on fatal and nonfatal rheumatic heart disease for the period from 1990 through 2015. Two Global Burden of Disease analytic tools, the Cause of Death Ensemble model and DisMod-MR 2.1, were used to produce estimates of mortality and prevalence, including estimates of uncertainty.

RESULTS

We estimated that there were 319,400 (95% uncertainty interval, 297,300 to 337,300) deaths due to rheumatic heart disease in 2015. Global age-standardized mortality due to rheumatic heart disease decreased by 47.8% (95% uncertainty interval, 44.7 to 50.9) from 1990 to 2015, but large differences were observed across regions. In 2015, the highest age-standardized mortality due to and prevalence of rheumatic heart disease were observed in Oceania, South Asia, and central sub-Saharan Africa. We estimated that in 2015 there were 33.4 million (95% uncertainty interval, 29.7 million to 43.1 million) cases of rheumatic heart disease and 10.5 million (95% uncertainty interval, 9.6 million to 11.5 million) disability-adjusted life-years due to rheumatic heart disease globally.

CONCLUSIONS

We estimated the global disease prevalence of and mortality due to rheumatic heart disease over a 25-year period. The health-related burden of rheumatic heart disease has declined worldwide, but high rates of disease persist in some of the poorest regions in the world. (Funded by the Bill and Melinda Gates Foundation and the Medtronic Foundation.)

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Rheumatic heart disease is a sequela of acute rheumatic fever,[1] which is usually a disease of poverty associated with overcrowding, poor sanitation, and other social determinants of poor health.[2,3] The near elimination of acute rheumatic fever and reduction in the rates of rheumatic heart disease in high-income countries during the late 20th century was attributed in part to improvements in socioeconomic conditions and the widespread use of penicillin G benzathine to treat streptococcal pharyngitis.[4,5] The remaining burden of rheumatic heart disease is found mostly in low-income and middle-income countries and among immigrants and older adults in high-income countries.[6,7]

Guidelines for the prevention and treatment of acute rheumatic fever and rheumatic heart disease were originally released by the World Health Organization (WHO) more than 60 years ago.[8] Many countries have had striking reductions in mortality related to acute rheumatic fever and rheumatic heart disease; these reductions can be credited to the implementation of control programs and improvements to health systems.[9,10] Despite these improvements, high prevalences of and mortality due to rheumatic heart disease continue to be reported in many regions, including Africa, South Asia, and the Pacific Islands.[7,11-13]

There is increasing interest in the burden of rheumatic heart disease, driven in part by the availability of echocardiography-based screening in areas in which the condition is endemic and a growing need to meet benchmarks in cardiovascular health.[14,15] The WHO and World Heart Federation have called for a 25% reduction in mortality due to cardiovascular causes, including rheumatic heart disease, by the year 2025.[16,17] As part of the 2015 Global Burden of Disease study (GBD 2015), we estimated the global, regional, and national burden of rheumatic heart disease for the years 1990 through 2015.

Methods

Strategy for Estimating Mortality Due to Rheumatic Heart Disease

The overall objectives, methods, and organization of GBD 2015 have been reported previously.[18-20] Methods relevant to rheumatic heart disease are described briefly in this section and in detail in the Supplementary Appendix, available with the full text of this article at NEJM.org.

We identified rheumatic heart disease–specific deaths from vital registration systems using codes from the *International Classification of Diseases, 9th Revision* (ICD-9) and *10th Revision* (ICD-10) (Table S1 in the Supplementary Appendix). In total, 10,049 site-years of vital registration data from 132 countries were used. Deaths attributed to ill-defined or nonspecific causes (e.g., "heart disease, unspecified" [ICD-10 code I51.9]) or intermediate causes (i.e., causes, such as "heart failure" [ICD-10 code I50], that are not the underlying disease that initiated the chain of events leading to death) were reassigned to accepted causes of death, including rheumatic heart disease, with the use of algorithms developed for GBD 2015.[20] We performed a sensitivity analysis in which we evaluated uncertainty in the reassignment to rheumatic heart disease of deaths that had originally been coded to left heart failure, the ICD-10 code most commonly reassigned to rheumatic heart disease.

The GBD 2015 Cause of Death Ensemble model was used to produce estimates of the fraction of deaths caused by rheumatic heart disease according to age, sex, and location for each year from 1980 through 2015. Separate Ensemble models were run for each sex and for two levels of data availability. Country-level covariates associated with rheumatic heart disease were included to inform the models. These covariates were the proportion of the population under 30 years of age, years of education per capita, income per capita, the proportion of children under 5 years of age with low body weight for age (i.e., >2 standard deviations below the WHO standard weight-for-age curve), access to health care (a summary variable based on principal-component analysis of several health services indicators), the proportion of the population with access to improved water sources (as defined by the WHO–UNICEF Joint Monitoring Program for Water Supply and Sanitation [JMP]), the proportion of the population with access to improved sanitation (as defined by the JMP), sociodemographic index (a summary indicator derived from measures of income per capita, educational attainment, and fertility), and a summary exposure variable for rheumatic heart disease (a measure of risk-weighted prevalence of exposure).

The results obtained with the ensemble models were then adjusted to account for secular trends in mortality due to human immunodeficiency

virus–acquired immunodeficiency syndrome (HIV–AIDS), which biases death estimates in countries with a high HIV–AIDS burden. Finally, the model results were adjusted by scaling them within the fraction of deaths due to all cardiovascular diseases and all deaths. Age-standardized mortality was calculated with the use of the direct method and a 2015 world reference population based on United Nations Population Division data updated for GBD 2015. Years of life lost were calculated by multiplying the number of deaths due to rheumatic heart disease in each age group by the global standard remaining life expectancy at the mean age at death for persons who die in each age group.[18]

STRATEGY FOR ESTIMATING THE PREVALENCE OF RHEUMATIC HEART DISEASE

We performed a systematic literature review for data on rheumatic heart disease incidence, prevalence, and case fatality rate. Data were identified primarily from community-based cross-sectional and cohort studies and nationally representative hospital administrative data sets. Our case definition was rheumatic heart disease identified by a clinician, with or without echocardiographic confirmation, that would require antibiotic prophylaxis or medical or surgical treatment.[21] We excluded studies that reported only the results of echocardiographic screening without clinical confirmation or expert interpretation. We did not use estimates of rates of "borderline" rheumatic heart disease (i.e., minor abnormalities revealed by echocardiography that could represent normal variation in the structure of the aortic or mitral valve).[22]

We considered countries to have one of two patterns of rheumatic heart disease: endemic, with high mortality and prevalence among children, and nonendemic, with low mortality and prevalence among children and predominance at older ages, when the delayed sequelae of rheumatic heart disease occur (Fig. 1). Because of the differences between these disease patterns, countries with each pattern were modeled separately. Endemicity was defined on the basis of estimates of mortality due to rheumatic heart disease from GBD 2015, with a threshold of 0.15 deaths per 100,000 population among children 5 to 9 years of age in 2015. After expert review of country assignments, Kenya and Nicaragua were reclassified as having an endemic pattern of disease on the basis of studies that showed a high prevalence of childhood rheumatic heart disease in these countries. Estimates of prevalence on a global level were based on a combination of the endemic and nonendemic models, under the assumption that very few cases of asymptomatic rheumatic heart disease exist among young people in countries with a nonendemic pattern.

We separately modeled the prevalence of symptomatic heart failure due to rheumatic heart disease. We estimated the prevalence of heart failure due to any cause for each location, age, sex, and year, then assigned cases to 20 specific causes, relying on published and administrative data on the causes of heart failure and rates of mortality due to these causes. Heart failure was estimated as mild, moderate, or severe with the use of Medical Expenditure Panel Survey data on patient-reported quality of life among persons with heart failure.[19]

All data were analyzed with the use of a Bayesian mixed-effects meta-regression tool (designated DisMod-MR 2.1) that was developed for the GBD study.[19] DisMod-MR 2.1 is a compartmental model that consists of three states — susceptible, diseased, and dead — with state transitions determined by the rates of incidence, remission, excess mortality, and other-cause mortality.[23] Differential equations with appropriate boundary conditions ensure consistency among all disease parameters in the model. The tool uses an offset log-normal model with fixed effects for study characteristics (i.e., design factors) that deviate from a predetermined reference and for location-specific covariates (income and the summary exposure variable).

To make predictions for all countries, estimates were made in an analytical cascade from the world to 7 super-regions, then to 21 world regions, and then to 195 countries and territories. This cascade took advantage of the assumption that geographic proximity influences patterns of disease prevalence for rheumatic heart disease. Information from higher levels in the cascade were used as prior distributions at the next level. Uncertainty intervals were taken as the 2.5th and 97.5th percentiles of the posterior distribution.

Years lived with disability were estimated by multiplying the number of cases by disability weights developed for the GBD studies.[19] For

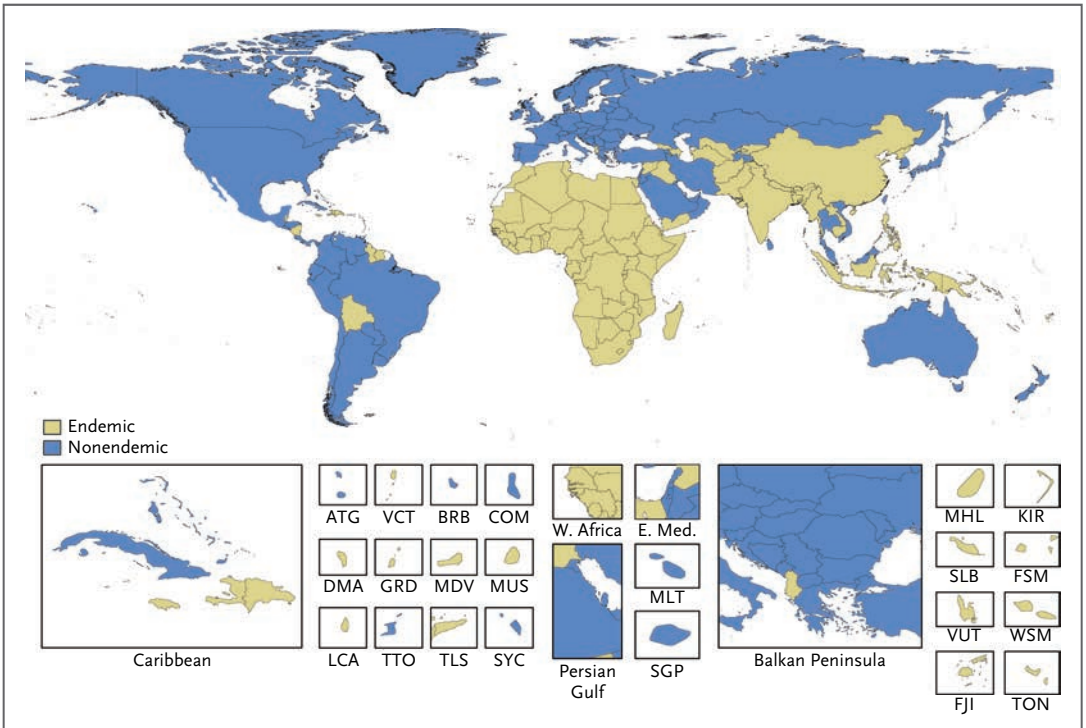


Figure 1. Classification of Countries as Having an Endemic or Nonendemic Pattern of Rheumatic Heart Disease.

A country was classified as having an endemic pattern of disease if its estimated childhood mortality due to rheumatic heart disease was greater than 0.15 deaths per 100,000 population among children 5 to 9 years of age. ATG denotes Antigua and Barbuda, BRB Barbados, COM Comoros, DMA Dominica, E. Med. eastern Mediterranean region, FJI Fiji, FSM Federated States of Micronesia, GRD Grenada, KIR Kiribati, LCA Saint Lucia, MDV Maldives, MHL Marshall Islands, MLT Malta, MUS Mauritius, SGP Singapore, SLB Solomon Islands, SYC Seychelles, TLS Timor-Leste, TON Tonga, TTO Trinidad and Tobago, VCT Saint Vincent and the Grenadines, VUT Vanuatu, W. Africa West Africa, and WSM Samoa.

asymptomatic rheumatic heart disease, we used a disability weight that represented a healthy person with the need for long-term medication use (prophylactic antibiotic therapy). For heart failure, we used disability weights representing New York Heart Association class II, III, or IV symptoms. Years of life lost and years lived with disability were summed to obtain the number of disability-adjusted life-years due to rheumatic heart disease.[18]

DATA AVAILABILITY

The availability of data on fatal and nonfatal cases of rheumatic heart disease varied widely across countries and regions. Figure 2 shows the types of data (on fatal cases, nonfatal cases, or both) available according to country. Figure S2 in the Supplementary Appendix shows the amount of available data for both modeling processes according to region and year. Data on fatal or nonfatal cases were available from most countries. For sub-Saharan Africa, data were available from only 14 countries. We also relied on country-specific covariates from all countries and geospatial modeling, as described above, to develop estimates of prevalence and mortality for countries without data on rheumatic heart disease.

RESULTS

MORTALITY DUE TO RHEUMATIC HEART DISEASE

Figure 3 shows the raw numbers of global deaths that were coded to rheumatic heart disease and to indeterminate or intermediate cause-of-death codes that were reassigned to rheumatic heart disease, according to year. The increase in the number of deaths in 2008 is due to the addition of data from the China Mortality Registration and Reporting System.

The cause-of-death codes that were most com-

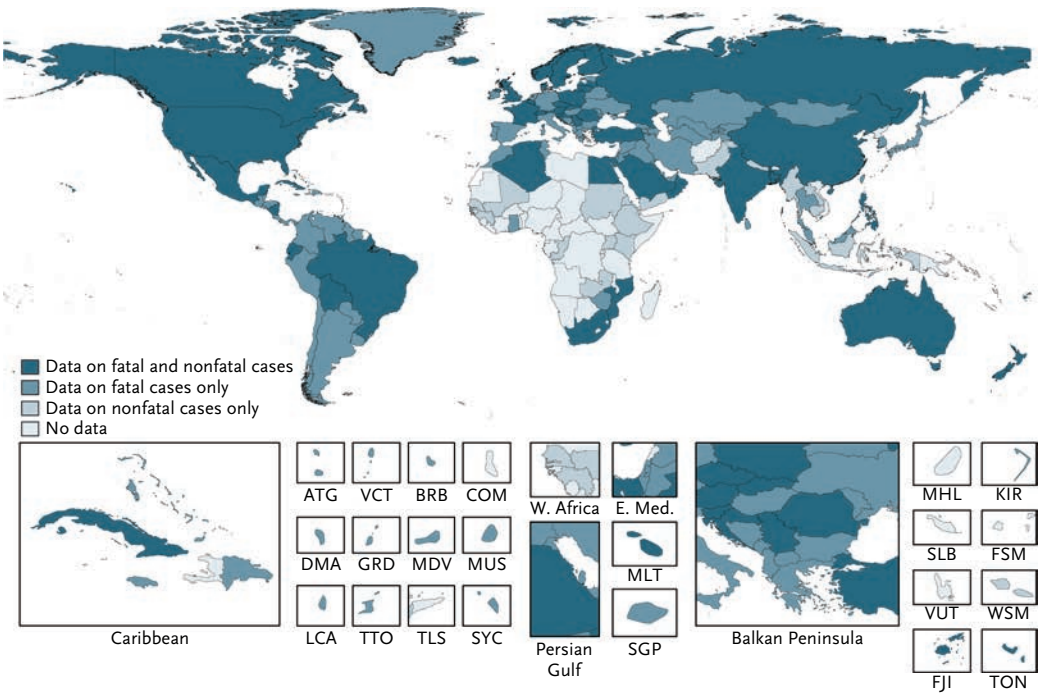


Figure 2. Classification of Countries According to the Availability of Data on Fatal and Nonfatal Cases of Rheumatic Heart Disease.

monly reassigned to rheumatic heart disease were left heart failure and right heart failure, which accounted for 25.5% and 5.3%, respectively, of deaths from rheumatic heart disease after reassignments had been made. Detailed results of the sensitivity analyses performed to assess the uncertainty in reassignment of deaths due to left heart failure are provided in the Supplementary Appendix.

On the basis of results derived from the ensemble models, we estimated that there were 347,500 deaths (95% uncertainty interval, 328,300 to 367,100) from rheumatic heart disease in 1990 and 319,400 deaths (95% uncertainty interval, 297,300 to 337,300) in 2015, a decrease of 8.1% (95% uncertainty interval, 2.7 to 13.5). Global age-standardized mortality from rheumatic heart disease decreased from 9.2 deaths per 100,000 population (95% uncertainty interval, 8.7 to 9.7) in 1990 to 4.8 deaths per 100,000 population (95% uncertainty interval, 4.4 to 5.1) in 2015, a decrease of 47.8% (95% uncertainty interval, 44.7 to 50.9). An estimated 77% and 82% of the deaths in 1990 and 2015, respectively, occurred in locations with an endemic disease pattern.

Patterns of mortality due to rheumatic heart disease varied significantly according to world region in 2015. The largest number of deaths occurred in East Asia and South Asia. The highest age-standardized death rates occurred in Oceania, South Asia, and central sub-Saharan Africa, the only regions where the 95% uncertainty intervals in 1990 and 2015 overlap (Fig. 4A).

In 2015, the countries with the highest estimated numbers of deaths due to rheumatic heart disease were India (119,100 deaths), China (72,600), and Pakistan (18,900). The highest estimated age-standardized death rates — more than 10 deaths per 100,000 population — were in the Solomon Islands, Pakistan, Papua New Guinea, Kiribati, Vanuatu, Fiji, India, Federated States of Micronesia, Marshall Islands, Central African Republic, and Lesotho.

PREVALENCE OF RHEUMATIC HEART DISEASE

We estimated that in 2015 a total of 33,194,900 cases (95% uncertainty interval, 29,466,400 to 42,905,600) of rheumatic heart disease occurred in countries with an endemic pattern of disease and 221,600 cases (95% uncertainty interval,

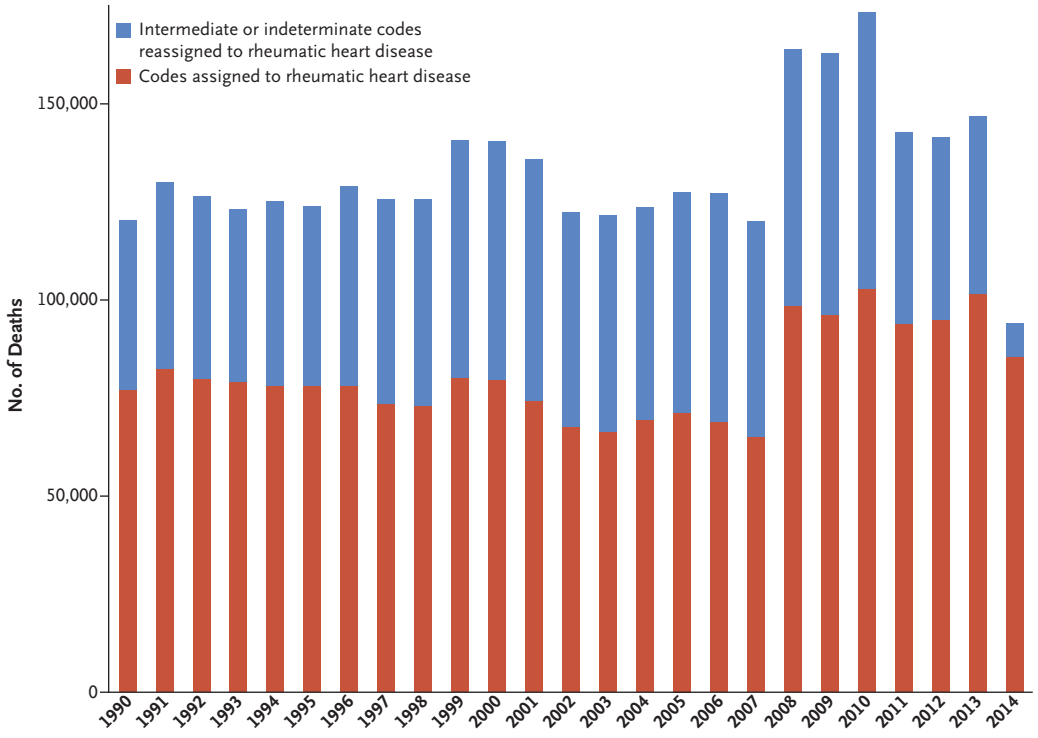


Figure 3. Total Reported Deaths Assigned to Rheumatic Heart Disease and Intermediate or Nonspecific Causes of Death Reassigned to Rheumatic Heart Disease, 1990–2014.

Rheumatic heart disease–specific deaths were identified from vital registration systems with the use of codes from the *International Classification of Diseases, 9th Revision* (ICD-9) and *10th Revision* (ICD-10) (Table S1 in the Supplementary Appendix). Deaths attributed to ill-defined or nonspecific causes (e.g., "heart disease, unspecified" [ICD-10 code I51.9]) or intermediate causes (e.g., "heart failure" [ICD-10 code I50]) were reassigned to accepted causes of death, including rheumatic heart disease, with the use of algorithms developed for the Global Burden of Disease study for 2015. The increase in the number of deaths in 2008 is due to the inclusion of the China Mortality Registration and Reporting System starting in 2008. The decrease in intermediate or indeterminate coded deaths in 2014 is due to a delay in the receipt of data from vital registration data systems that had higher proportions of indeterminate or intermediate death codes.

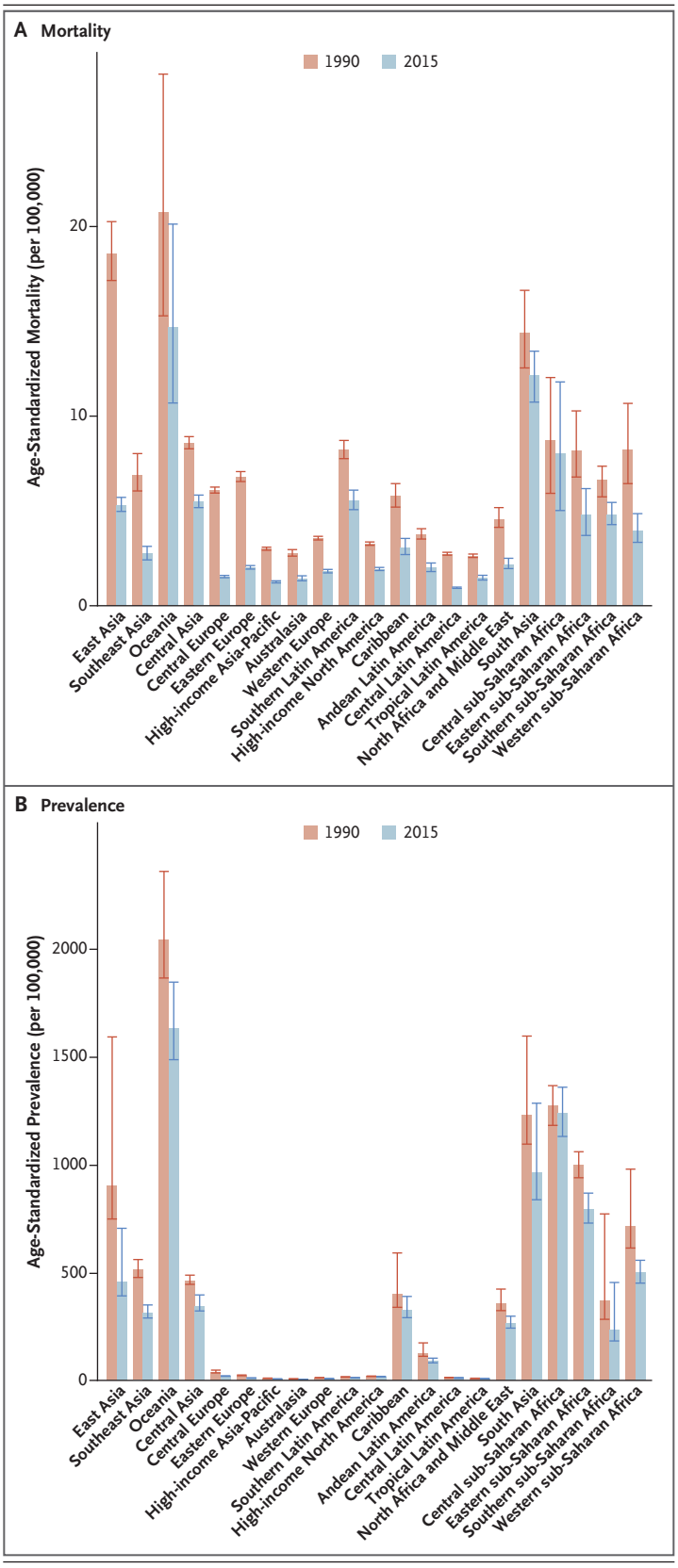
205,800 to 238,300) occurred in countries with a nonendemic pattern. The estimated age-standardized prevalence of rheumatic heart disease in 2015 was 444 cases per 100,000 population for countries with an endemic pattern and 3.4 cases per 100,000 population for countries with a nonendemic pattern. Between 1990 and 2015, the age-standardized prevalence declined significantly in several regions (Fig. 4B). In 2015, the age-standardized prevalence remained highest in Oceania, followed by central sub-Saharan Africa and South Asia. In 2015, the countries with the largest estimated numbers of cases of rheumatic heart disease were India (13.17 million cases), China (7.07 million), Pakistan (2.25 million), Indonesia (1.18 million), and the Democratic Republic of the Congo (805,000), together accounting for 73% of global cases. Twenty countries with an endemic pattern of disease had an age-standardized prevalence exceeding 1%.

NUMBER OF CASES OF HEART FAILURE AMONG CASES OF RHEUMATIC HEART DISEASE

We estimated that there were 156,900 cases (95% uncertainty interval, 103,400 to 212,500) of mild heart failure, 129,500 cases (95% uncertainty interval, 93,700 to 170,300) of moderate heart failure, and 352,400 cases (95% uncertainty interval, 302,300 to 405,300) of severe heart failure due to rheumatic heart disease in 1990. For 2015, our estimates were 295,300 cases (95% uncertainty interval, 194,100 to 401,400) of mild

Figure 4. Age-Standardized Mortality Due to and Prevalence of Rheumatic Heart Disease According to World Region in 1990 and 2015.

I bars represent 95% uncertainty intervals.



heart failure, 243,700 cases (95% uncertainty interval, 176,600 to 320,900) of moderate heart failure, and 663,000 cases (95% uncertainty interval, 566,800 to 763,900) of severe heart failure, which represents an 88% increase in the number of cases overall.

SUMMARY MEASURES OF HEALTH

The number of disability-adjusted life-years due to rheumatic heart disease in 2015 was 10,513,200 (95% uncertainty interval, 9,611,000 to 11,514,500), accounting for 0.43% of global disability-adjusted life-years due to any cause. The global rate of disability-adjusted life-years due to rheumatic heart disease in 2015 was 142.6 per 100,000 population (95% uncertainty interval, 130.4 to 156.2). The highest age-standardized rates were found in Oceania, South Asia, and Africa (Fig. 5). Most disability-adjusted life-years due to rheumatic heart disease were the result of years of life lost (84.9%), which indicated that premature death was a larger driver of total health loss from rheumatic heart disease than was years of life lived with disability.

DISCUSSION

We used multiple sources of data and epidemiologic modeling techniques to estimate the global prevalence of and mortality due to rheumatic heart disease over a 25-year period. Over this interval, the health-related burden of rheumatic heart disease declined in most countries, but the condition persisted in some of the poorest regions in the world. We estimate that 10 persons per 1000 population living in South Asia and central sub-Saharan Africa and 15 persons per 1000 population in Oceania were living with rheumatic heart disease in the year 2015.

Rheumatic heart disease is a consequence of untreated streptococcal pharyngitis, and its major antecedents are the factors that influence the transmission of this infection, including access to high-quality health care and social determinants of health.[2,3] At the national level, progress — or lack thereof — in addressing social deter-

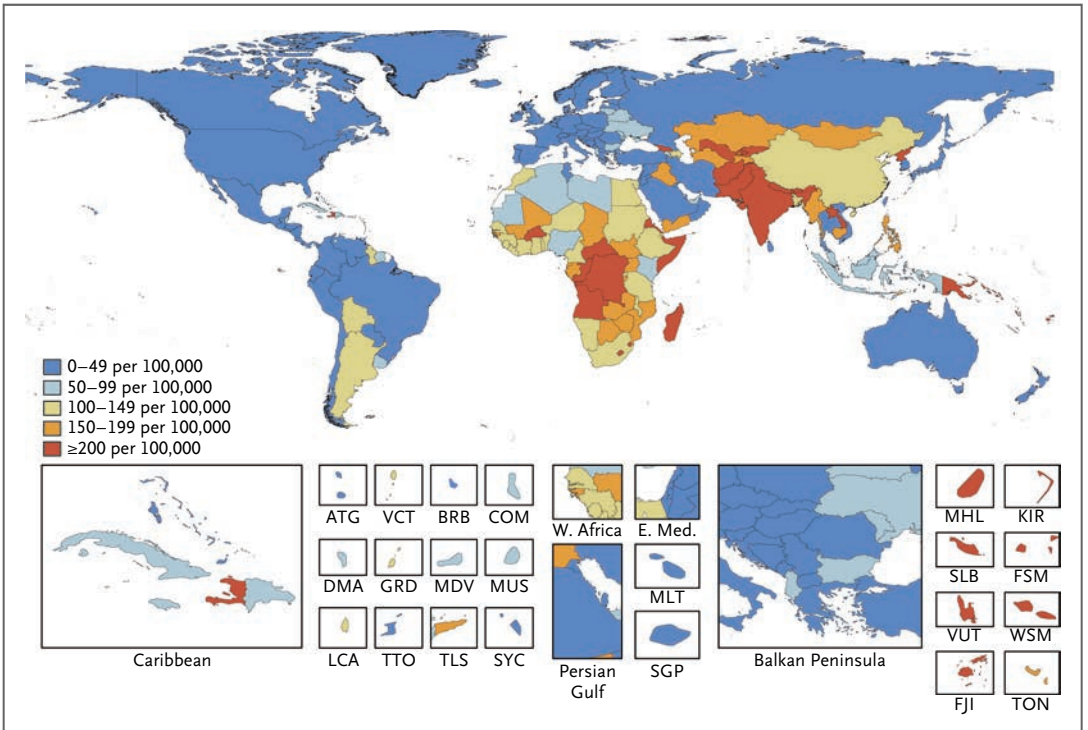


Figure 5. Age-Standardized Disability-Adjusted Life-Years Due to Rheumatic Heart Disease per 100,000 Population, 2015.

minants such as education and income has tracked closely with mortality due to rheumatic heart disease.[24]

In addition to impeding the effective prevention of acute rheumatic fever, social and economic factors may also make the management of chronic rheumatic heart disease more difficult. Lifelong treatment options for rheumatic heart disease, although effective, place large demands on health systems.[25] Major shortfalls in medical and surgical care for rheumatic heart disease have been documented in countries where the condition is endemic, even at tertiary centers.[26]

We adjusted our mortality input data by reassigning codes for intermediate or indeterminate causes of death, including heart failure, and this adjustment substantially increased the estimates of the number of deaths due to rheumatic heart disease. Advances in methods for handling cause-of-death codes are an important component of improved estimates of mortality due to rheumatic heart disease. At the same time, it is likely that some deaths from stroke and endocarditis are miscoded, so we cannot estimate how many of the 6.3 million cases of stroke and 85,000 deaths from endocarditis that were estimated for 2015 were actually the result of underlying rheumatic heart disease.[20]

Our estimates of disease prevalence are similar to those in a recent meta-analysis of screening studies in which the overall prevalence of rheumatic heart disease in low-income and middle-income countries was shown to range from 2.7 cases per 1000 population (for "clinically manifest" disease) to 21.1 cases per 1000 population (for "clinically silent" disease).[7] Among subclinical cases of rheumatic heart disease that are detected through echocardiographic screening (termed "borderline" rheumatic heart disease), some may progress to definite rheumatic heart disease, whereas others may regress. To date, only a few small prospective studies have evaluated the progression of borderline disease.[27,28] Our prevalence estimates would have been higher if we had included borderline cases in our model; however, current data do not support this approach, because it is unclear how this condition should be managed clinically.[29]

It is possible that our estimates for some locations were biased upward by the use of studies of prevalence that were conducted in subnational areas with an endemic pattern of disease.

Yet most of these studies focus on schoolchildren, among whom rheumatic heart disease might be less common than in the total population.[30] To clarify these issues, future prevalence studies should sample more broadly and screen persons beyond school-aged children. It is also possible that some middle-income countries (e.g., in Latin America, where our estimates are comparatively low) will have subpopulations that differ from the national average in their patterns of disease (i.e., endemic vs. nonendemic).[31] Future work on disease burden at the state or provincial level will be required to address this discrepancy. Finally, our analysis was limited to English-language studies.

Better data for low-income and middle-income countries are needed to guide policies for the control of rheumatic heart disease. In our analysis, we used epidemiologic modeling techniques to provide estimates for countries for which data were insufficient. However, further improvements in estimates of the burden of rheumatic heart disease will require new research in three areas: the extent of misclassification in death certification, prevalence among adults in low-income and middle-income countries, and rates of nonfatal outcomes and excess mortality in longitudinal studies involving persons with rheumatic heart disease. Improvements in the measurement of the burden of rheumatic heart disease will assist in planning for its control and will help identify countries where further investments are needed.

In summary, we estimated the global disease prevalence of and mortality due to rheumatic heart disease over a 25-year period. The health-related burden of rheumatic heart disease has declined worldwide, but the condition persists in some of the poorest regions in the world.

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

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APPENDIX

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