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Title: The Economic Impact of Rheumatic Heart Disease in Low- and Middle-Income Countries

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1. Introduction

Rheumatic heart disease (RHD) is an important cause of cardiovascular death and disability among children and working-age adults in low- and middle-income countries (LMICs).[1] RHD is the consequence of untreated streptococcal pharyngitis, which in susceptible individuals leads to repeated attacks of acute rheumatic fever (ARF) that over time cause progressive heart valve damage, resulting in sequelae such as heart failure, atrial fibrillation/stroke, and premature death. The condition is highly preventable with prompt antibiotic treatment of acute pharyngitis ("primary prevention") or regular prophylactic antibiotic use among individuals who have a history of ARF ("secondary prevention"). Surgical repair or replacement of damaged heart valves is also a last-resort option in many cases.[2]

ARF disappeared from many wealthier countries during the latter half of the 20th century.[3] In most cases its decline was attributed to comprehensive control programs that simultaneously rolled out primary and secondary prevention services, although the contribution of improved living conditions and reduced exposure to bacterial pharyngitis continues to be debated.[2,4] Unfortunately, although mortality from RHD globally has declined since 1990, progress has been uneven, with many parts of sub-Saharan Africa, South Asia, and Oceania experiencing no significant reduction in mortality rates.[1]

Over the past decade there has been a renewed interest in RHD among clinicians and researchers in LMICs, stimulated in part by echocardiography-based screening studies showing a persistently high prevalence of asymptomatic RHD in schoolchildren.[5,6] Yet despite this growing interest, RHD continues to be neglected in the global health and global noncommunicable disease (NCD) policy agendas.[7,8] One potential contributing factor to this neglect is a lack of appreciation for the disproportionate economic impact that RHD might have in LMICs as compared with other NCDs.

There are good reasons to suspect that, relatively speaking, RHD carries a higher economic cost than the more common and widely recognized NCDs of aging such as ischemic heart disease and cancer. For one, it strikes younger, working-age populations at much higher rates, leading to greater losses in productivity and reduced consumption due to high health expenditure, e.g., on heart surgery. At the same time, because RHD is almost completely preventable, the "counterfactual" burden of disease could be much smaller than for many other NCDs, making the preventable burden worth relatively more in economic terms.[9]

While these reasons may be compelling in principle, the extant literature from the past 20 years contains only a handful of studies that have addressed the economic impact of RHD, and none have been conducted using methods that are fully consistent with economic theory.[10-14] In the present study, we seek to fill a critical knowledge gap by estimating the global economic impact of RHD in 2015. We take a macroeconomic, welfare-based approach that allows for comparisons across world regions.

2. Methods

Our analysis involved four major steps. First, we selected a method for valuing health benefits; second, we estimated the counterfactual health impact of RHD; third, we assigned monetary values to the difference between measured and counterfactual estimates of burden (i.e., avertable mortality); fourth, we conducted sensitivity analyses on the key assumptions in our model.

2.1 Selecting a method for valuing health benefits

Health directly influences individual utility and social welfare, and it is also instrumental to economic activity. Several methods can be used to assess the economic impact of ill health, depending on the level of analysis (i.e., micro- vs. macroeconomic) and whether the quantity of interest includes (non-health) market losses, non-market losses, or both – i.e., total economic welfare.15 The "cost-of-illness" approach, although popular and intuitive from a medical standpoint, has been criticised by economists, in part because the direct and indirect costs in these studies measure different underlying quantities of interest and when aggregated do not truly reflect total societal welfare.16 Further, most households affected by RHD are very poor and chronically unemployed, which calls into question the validity of assumptions underlying the human capital approach.17

By contrast, using a welfare-based approach, such as the "full income" approach described below, to estimate the economic impact of RHD is attractive for two major reasons. First, welfare-based approaches come closer to capturing the total amount of societal economic losses due to disease, which has a clear interpretation that is consistent with economic theory. Second, by contrast to other approaches (the extreme case being computable general equilibrium models), such an approach is relatively straightforward to implement and has modest data requirements, which is appealing for a condition like RHD where epidemiological data are limited.

2.2 Estimating the counterfactual health impact of RHD

In order to estimate economic impact, we first defined a counterfactual health burden of RHD based on the age- and sex-specific patterns of mortality observed in high-income countries in 2015. In general, high-income countries (HIC) can be viewed as having near full penetration of RHD-related prevention and treatment interventions, including advanced medical and surgical care. Hence this is the most feasible pattern of mortality reduction that could be achieved in LMICs using current medical technologies.

We took estimates of RHD-specific mortality, all-cause mortality, and population size from the Global Burden of Disease 2015 study.[1,18] For simplicity, we used aggregate estimates for seven world regions, with HICs (defined by the World Bank according to level of gross national income per capita in 2015) serving as the counterfactual and hence being excluded from the analysis. We conducted separate analyses for males and females in light of the well-documented disparity in prevalence and mortality by sex.[2]

Using the HIC counterfactual, we next constructed a series of associated single-decrement life tables using mortality and population data by world region and sex.19 These life tables allowed us to assess gradients in mortality by age and sex to produce more nuanced economic estimates, described below. We also estimated the total number of preventable deaths and the potential increase in population life expectancy by world region and sex.

2.3 Monetizing avertable mortality

In order to quantify and monetize the impact of premature, avoidable mortality from RHD, we implemented the full income approach, described in great detail by Jamison and colleagues in the *Lancet Commission on Investing in Health* (CIH).[20] In brief, our unit of valuation was a "standardised mortality unit (SMU)," defined as a 10^{-4} reduction in risk of death over a short period. This small level of risk is empirically significant because most VSL estimates are extrapolated from wage differential studies that assess mortality risks of this order. Incidentally, age-standardised mortality rates from RHD in LMICs are of a similar magnitude.[1]

We estimated the aggregate number of SMUs by age and sex that were avoidable in each world region and multiplied this by the region- and sex-specific estimated economic value of an SMU. The CIH had previously estimated the willingness-to-pay (WTP) to avoid one SMU at age 35 to be approximately 1·8% of gross domestic product (GDP) per capita in the United States in the year 2000, or $660 in 2015 US dollars. Based on a follow-on analysis of the CIH approach by Chang and colleagues, we used $900 as our base WTP value.[21] These WTP values were adjusted downward based on average GDP per capita in each region assuming an income elasticity of one. We also weighted the value of SMUs more heavily if they occurred in populations younger than 35 and less heavily if they occurred in populations older than 35, using the ratio of remaining life expectancy in each age group to remaining life expectancy at age 35 by world region and sex.

Finally, we aggregated the estimated value of all SMUs by age and presented the total economic impact of RHD by sex and world region in 2015. Because the time horizon of our analysis was one year, with any given individual in the population only experiencing a small risk of death from RHD in 2015, discounting was not required. All monetary values are reported in 2015 US dollars.

2.4 Sensitivity Analysis

There are several fundamental uncertainties in applying VSL estimates that have been derived from predominately HIC settings to LMICs. To explore the influence of these uncertainties, we performed a sensitivity analysis that included five scenarios that were variants on two model parameters.

First, as described above, in the base case we assumed that the income elasticity of WTP was one. In other words, we assumed that the VSL changes in proportion to the change in real income. A recent meta-analysis of VSL estimates found that a reasonable starting value would be around 0·6, which would imply smaller proportional decrease in WTP for LMICs when transferring VSL from HICs.[22] A more conservative assumption would be higher relative WTP in HICs, so we assessed the effect of changing income elasticity to 0·6 and 1·5, respectively.[23]

Second, in the base case we anchored the SMU value at age 35 and remaining life expectancy of 45 years, a typical age for VSL estimates derived from revealed preference studies. Since populations in different regions face different life expectancies, we explored the effect of changing the anchoring age to the age in which remaining life expectancy is approximately 45 years. Finally, we explored the joint effect of different anchoring age combined with the higher and lower estimates of income elasticity.

3. Results

3.1 Health Impact of RHD

In 2015 there were an estimated 320,000 deaths from RHD globally, with about 250,000 deaths in LMICs. Applying HIC age- and sex-specific mortality rates to the six LMIC regions would avert about 180,000 deaths, corresponding to a 72% reduction in deaths. The corresponding increase in life expectancy at birth by sex and region is given in Table 1.

We estimated that the largest gains in life expectancy at birth would occur in South Asia, averaging between one and two months, with larger gains among females than males. Southeast Asia, East Asia, Oceania, and sub-Saharan Africa would all experience health gains of about two to three weeks in life expectancy at birth. The lowest incremental gains would be in the Latin

America and Caribbean region, where it is widely accepted than the burden of RHD has declined dramatically in recent decades.[4,24]

Table 1. Increase in life Expectancy at Birth Achievable by Eliminating RHD from LMICs

Region	**Females**	**Males**
South Asia	49 days	38 days
Southeast Asia, East Asia, and Oceania	23 days	14 days
Sub-Saharan Africa	23 days	18 days
Central Europe, Eastern Europe, and Central Asia	14 days	12 days
North Africa and Middle East	11 days	7 days
Latin America and Caribbean	6 days	2 days

3.2 Economic Impact of RHD

We estimated the total global economic impact of avoidable RHD mortality in 2015 to be US$ 35·3 billion among females and US$ 29·5 billion among males, or US$ 64·8 billion in total. There were significant differences in impact by region and sex (Table 2). When compared to health impact (Table 1), differences in economic impact were mostly driven by differences in population size and higher WTP values in regions with more middle-income countries. For instance, relative to health impact, the economic impact was higher in Southeast Asia, East Asia, and Oceania (mostly driven by China) and lower in Sub-Saharan Africa.

Table 2. Economic Impact of Avoidable RHD Mortality by World Region and Sex in 2015, Billions of 2015 US Dollars.

Region	Females	Males	Both
South Asia	$8·2	$8·1	$16·3
Southeast Asia, East Asia, and Oceania	$17·6	$13·2	$30·7
Sub-Saharan Africa	$2·3	$2·1	$4·4
Central Europe, Eastern Europe, and Central Asia	$3·2	$3·5	$6·7
North Africa and Middle East	$2·3	$1·8	$4·1
Latin America and Caribbean	$1·6	$0·8	$2·4

3.3 Results of Sensitivity Analysis

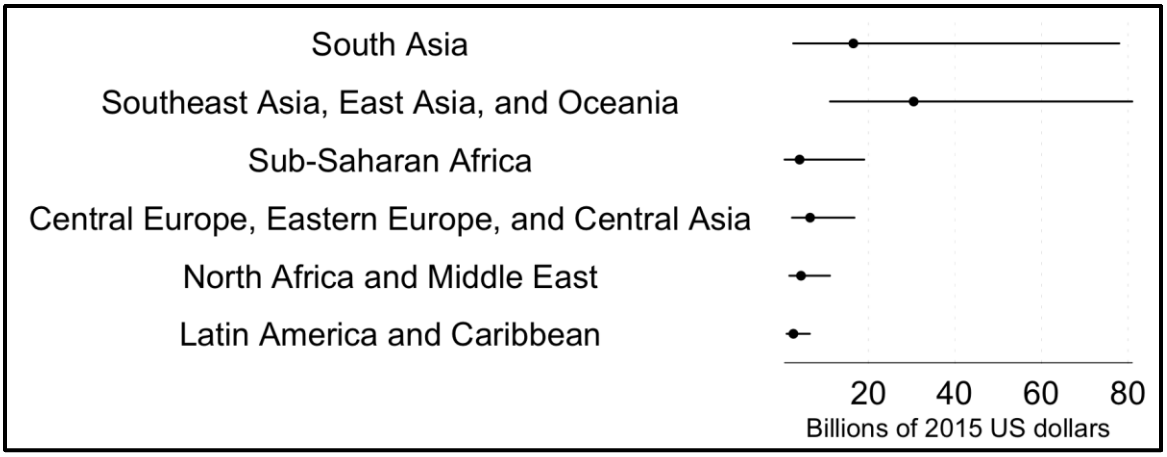
Alternative assumptions altered our estimates of impact by about a factor of ten. The scenario where income elasticity was 1·5 and the anchoring age was 45 decreased our base case estimate to US$ 19·5 billion. By contrast, the scenario where income elasticity was 0·6 and anchoring age remained 35 increased our base case estimate to US$ 213 billion. Detailed variations by world region and scenario are provided in Table 3. The Figure provides a visualization of the uncertainty range by world region.

Table 3. Sensitivity Analysis of Economic Impact Estimates by World Region (both sexes) in 2015, Billions of 2015 US Dollars

Region	Scen 1	Scen 2	Scen 3	Scen 4	Scen 5
South Asia	$3·0	$77·5	$13·9	$2·6	$65·8
Southeast Asia, East Asia, and Oceania	$11·8	$81·4	$29·4	$11·3	$77·8
Sub-Saharan Africa	$0·8	$19·8	$3·4	$0·7	$15·5
Central Europe, Eastern Europe, and Central Asia	$2·7	$17·1	$6·1	$2·5	$15·4
North Africa and Middle East	$1·6	$10·7	$3·9	$1·6	$10·2
Latin America and Caribbean	$1·0	$6·2	$2·4	$1·0	$6·0

See text for details. Scen 1 = increase income elasticity to 1·5; Scen 2 = decrease income elasticity to 0·6; Scen 3 = changing SMU anchoring age to the age with remaining life expectancy of 45 years; Scen 4 = increase income elasticity to 1·5 and increase SMU anchoring age to 45 years; Scen 5 = decrease income elasticity to 0·6 and increase SMU anchoring age to 45 years.

Figure 1. Range of estimates for economic impact of RHD found in the sensitivity analysis. See text for details.



4. Discussion

RHD continues to be an important cause of cardiovascular mortality in LMICs. We estimated that about 180,000 preventable deaths occurred in LMICs in 2015, with a disproportionate impact on females. We also estimated the total economic impact of these deaths to be about US$ 64·8 billion, or an average of US$ 360,000 per preventable death in LMICs.

To date, all studies of the economic impact of RHD have employed some variant of the "cost-of-illness" approach. An older study in Brazil and a newer study in South Korea attempted to quantify both direct and indirect costs from a societal perspective. Recent studies in China and New Zealand focused exclusively on direct medical costs to the health system, emphasizing inpatient medical costs as a major driver of economic burden.[12,13] A recent study in Fiji, focused primarily on quantifying attributable mortality, also reported indirect costs using the human capital method.[11] As discussed earlier, studies using cost-of-illness methods have a limited interpretability and can only provide a partial snapshot of impact, particularly when reporting macroeconomic impact.[16]

By contrast, we attempt to estimate the full impact of preventable RHD mortality on social welfare. Our estimates of the economic value of mortality reduction are much larger than would be expected, e.g., using the human capital approach, which is more commonly used in health economics.[11] On the other hand, the full income approach has been used extensively in other sectors such as environment, transportation, and agriculture.[16] One implication of our work is that the costs and benefits of reduced RHD mortality can be directly compared to costs and benefits of interventions within health and across other sectors. Wider use of full income methods in health evaluations may facilitate intersectoral comparisons and make a stronger case for expanding healthcare budgets to provide a broader range of very powerful, cost-effective interventions.[20]

The high economic impact of RHD stands in contrast to the relatively modest cost of prevention. For example, a recent evaluation of a comprehensive ARF/RHD program in Cuba estimated that about US$ 0·07 per at-risk child per year was required to deliver necessary primary and secondary prevention measures.[25] While not all existing RHD can be prevented, we found a significant per-capita benefit that, when compared to these relatively low costs, suggests RHD interventions can provide a large return on investment. The findings of this study will be of immediate use in conducting benefit-cost analysis of more controversial aspects of RHD care, compared to other competing interventions such as cardiac surgery and vaccine development.

There are a number of important limitations to this study. On the health side, the limitations of the mortality data have been previously described.[1] It is quite possible that the total number of deaths from RHD in LMICs is higher than current estimates, which would increase the total economic impact. An additional limitation is the use of cross-sectional demographic methods (including period life expectancy), which would need to be converted into a dynamic model of mortality trends over time in order to be used in a formal benefit-cost analysis.

On the economic side, the full income method as implemented by the CIH has a variety of limitations and sources of uncertainty that are summarized by Chang and colleagues.[21] We tried to address these limitations by conducting a variety of sensitivity analyses on the results. We note that the range of possible values varied by a factor of five to twenty across regions (Table 3), which further underscores the need for further empirical research to inform fundamental model assumptions and parameters.

5. Conclusions

We estimated that the economic impact of RHD in LMICs in 2015 was about US$ 65 billion, ranging US$ 20-220 billion in a variety of sensitivity analyses. In all scenarios, there was a disproportionate impact among females and in the populations of South Asia, Southeast Asia, East Asia, Oceania, and sub-Saharan Africa. These estimates represent the global cost of business as usual and, alternatively, the potential economic benefits of increasing access to evidence-based, cost-effective RHD prevention and treatment services in LMICs.

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