Estimates of the Global Burden of Rheumatic Heart Disease

Liesl J. Zühlke*,†, Andrew C. Steer‡,§,||

Cape Town, South Africa; and Melbourne, Victoria, Australia

ABSTRACT

In this review, we make the case that currently available figures used to define the global burden of acute rheumatic fever and rheumatic heart disease, although crucial to control efforts, are imperfect. Data have been hindered by methodological differences between studies, by patchy coverage within countries and across regions, and by an incomplete understanding of the relationship between echocardiographic detection of asymptomatic mild disease and progression to symptomatic disease. We argue that in order to advocate effectively for patients with rheumatic heart disease now and into the future, true burden of disease estimates on local, national, and international levels are urgently required. We critically review previous burden of disease estimates and outline the issues in defining the "true" burden of rheumatic heart disease, and we propose a new model for rheumatic heart disease epidemiologic studies. This is of particular relevance in 2012 with an ever-increasing burden of cardiovascular disease globally.

Acute rheumatic fever (ARF) and its sequel rheumatic heart disease (RHD) continue to cause significant morbidity and mortality in developing countries and have been under-recognized as a global health problem for decades. There are a number of reasons for this under-recognition: the competing heavy burden of infectious disease mortality in young children due to the human immunodeficiency virus, malaria, tuberculosis, diarrheal disease and pneumonia; the impressive decline in the incidence of ARF in industrialized countries over the second half of the last century such that ARF/RHD are uncommon in these countries today and no longer priority diseases; and the paucity of good quality, widely collected epidemiologic data from developing countries [1]. However, more recently, there is increasing awareness of RHD because of prioritization of control of the disease by a number of individual countries with high disease burdens, reinvigorated regional initiatives directed at control of RHD, particularly in the Pacific and Africa, and advocacy efforts led by international bodies such as the World Heart Federation. Central to this increased awareness have been updated and persuasive global morbidity and mortality figures [2–4]. Recent directives from the World Health Organization and the World Heart Federation have pledged to decrease the number of deaths due to noncommunicable diseases by 25% by 2025 [5]. RHD is a disease where this may be achievable because there are relatively inexpensive, proven, and effective control strategies that can lead to reductions in deaths, especially in young people [6].

BURDEN OF DISEASE ESTIMATES: POPULATION-BASED STUDIES

World Health Organization's global burden of group A streptococcal disease study

In 2005, a summary report on the global burden of group A streptococcal disease, commissioned by the World Health Organization, was released that encapsulated population-based data relating to ARF and RHD published between 1985 and 2005 [4]. This study calculated prevalence of RHD, incidence of ARF, and incidence of new cases of RHD cases across multiple geopolitical regions. In determining prevalence, the investigators used population-based data only, extrapolating from cross-sectional studies conducted in school-aged children and compiling final regional prevalence estimates from studies where prevalence was confirmed using echocardiography as opposed to auscultation. This study found an overall global burden of 471,000 annual cases of ARF, with the incidence of ARF in children ages 5 to 15 years ranging from 10 cases per 100,000 in industrialized countries to 374 cases per 100,000 in the Pacific region. The overall burden of RHD was estimated to be 15.6 million prevalent cases with 282,000 new cases and over 233,000 deaths per year. As the investigators noted in their publication [4], there are some important caveats in these estimates relating to the number of available studies, extrapolations made to reach all-ages estimates and global mortality estimates, and the significance of echocardiographic detection of RHD in screening studies. All of these issues are discussed here.

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From the *Department of Paediatrics, Red Cross War Memorial Children's Hospital and University of Cape Town, Cape Town, South Africa; †Department of Medicine, Groote Schuur Hospital Cape Town, South Africa; ‡Centre for International Child Health, University of Melbourne, Melbourne, Victoria, Australia; §Department of General Medicine, Royal Children's Hospital, Melbourne, Victoria, Australia; ||Murdoch Children's Research Institute, Melbourne, Victoria, Australia. Correspondence: A. Steer (andrew.steer@rch.org.au).

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Subsequent reviews of global burden of disease

Three groups subsequently reviewed the global burden of ARF and RHD; 2 reports were published in 2011 [2,3], and a third, as part of the Global Burden of Disease 2010 Study, was published in 2013 [7].

The first study added several new datasets, used a clearly defined systematic review design, included only studies in which RHD was diagnosed by echocardiogram [8], and incorporated vital registration data from the World Health Organization. Mortality rates were calculated using the most recent population data in the World Health Organization database, but countries were included only if completeness of death reporting was more than 90% of the total deaths occurring in the country. The study concluded that there is considerable global variation in ARF incidence and RHD prevalence with the sub-Saharan African and Asian-Pacific regions identified as high disease burden areas. The study noted several limitations including that data were unavailable from several parts of the world and that there were very few data regarding RHD mortality. Key estimates that were not addressed included the burden caused by the distal sequelae of RHD (congestive cardiac failure, infective endocarditis, atrial fibrillation, and stroke), average duration of disability for incident cases, average duration to death, and relative risk of patients with RHD dying from all causes relative to those without RHD.

The second study [3] observed that the overall global prevalence of RHD appears to be increasing while the incidence of ARF is decreasing in many parts of the world, including in Africa. The investigators explained this apparent discrepancy by reporting bias; that is, that systematic reporting of ARF in many countries has decreased at the same time that RHD case ascertainment has increased because of RHD screening studies. The investigators also suggested that longer survival of patients with RHD may have contributed to this discrepancy, but there are few data to support this assertion [9].

The recently published Global Burden of Disease Study reports that the number of years lived with disability due to RHD was estimated in 2010 at 1,430 (944 to 2,067) worldwide, a figure that represents up to one-fourth of all neoplasms [10]. Lozano et al. [11] reported 345,100 deaths due to RHD in 2010, which represents a 25.4% reduction from 1990, with ages-standardized death rate of 5.2 per 100,000, which was a 53.1% reduction from 1990. These figures should be viewed with caution, however, particularly because the modeling method adopted in the analysis of the data uses a different age-related profile of RHD than that used in the previous reviews of the global burden of the disease. Further analysis of these data is currently underway (J. Carapetis, personal communication, June, 2013).

Uncertainty around estimates of rheumatic heart disease: inadequate data

The 2005 study included 57 studies of RHD from multiple geographic regions of the world [4]. Even though the publication of these data filled an important gap in the literature, there were some significant limitations. The major limitation was the poor-quality data from some of the most affected regions, especially relating to mortality, with only a single publication available from some regions of importance, including Eastern Europe and China. Because of the paucity of data, prevalence figures from a small number of studies in a limited number of countries were extrapolated to whole regions, thereby ignoring the considerable differences in disease burden that are likely to exist between countries and, indeed, between states and districts within many of the larger countries. For example, many prevalence studies of RHD cited in this study were conducted in urban and peri-urban populations, although it is known that the prevalence of RHD is often higher in rural areas [12,13].

Uncertainty around estimate of rheumatic heart disease: extrapolation of data

Screening for RHD at a population level has been most consistently carried out in children ages 5 to 15 years. RHD is a cumulative disease such that there are more people over 15 years old with the disease than under 15 years. To extrapolate to all-ages estimates of RHD, the investigators of both the 2005 and the first of the 2011 studies used a multiplication factor of between 5.5 and 7.2 on the basis of published data from 2 studies [14,15]. Although care was taken to err on the side of underestimation rather than overestimation, these extrapolated figures are clearly subject to error. The burden of RHD mortality was derived from the overall prevalence of RHD by applying an annual case-fatality rate per year of 1.5%; this extrapolation was based upon limited data, including data from industrialized countries where quality of care is higher. Therefore, the annual number of global deaths due to RHD estimated in these studies is likely to be an underestimate of the true situation in endemic regions; for example, in Pakistan and Ethiopia, the mortality rate has been reported as high as 6.8% and 12.1%, respectively [2,16]. Ideally local mortality rates should be applied to local RHD prevalence figures to compile overall mortality.

Uncertainty around estimates: progression of echocardiographic changes detected as part of screening

The methodology used for detecting RHD in screening studies of asymptomatic children has progressively changed over the past 2 decades from auscultation for a murmur, to auscultation with second-line echocardiographic confirmation of suspected cases, to first-line echocardiography without auscultation. The first study that used echocardiographic diagnosis as first-line screening for RHD in asymptomatic school children was published in 1996 [17]. This study went largely unrecognized until just over 10 years later, when a new era of prevalence studies in asymptomatic school children in affected countries commenced [18–24].

These studies focused the world's attention on the seemingly submerged iceberg of asymptomatic RHD because the number of cases detected by echocardiography compared with those detected by auscultation differed by a factor of up to 10 [18]. The specter of subclinical carditis in the context of ARF is well recognized [25,26], and the concept of instituting early prophylaxis in asymptomatic RHD in high prevalence areas to retard progress to RHD is very attractive. However, application of prevalence figures determined by studies that used first-line echocardiography diagnosis to regional estimates of RHD leads to a considerably higher burden of disease than has previously been estimated [23]. There are several critical issues regarding echocardiographic diagnosis of RHD in asymptomatic patients, and these are discussed in detail herein.

WHAT IS SUBCLINICAL RHEUMATIC HEART DISEASE?

Subclinical RHD has not been formally defined in the literature, although subclinical carditis has been defined as part of the presentation of ARF. A patient with subclinical RHD is asymptomatic, has no clinically detectable pathologic murmur, but has findings of RHD on echocardiogram (Table 1). There is a spectrum of findings of RHD on echocardiogram suggestive of subclinical RHD. The establishment of World Heart Federation standardized criteria for the diagnosis of RHD on echocardiogram has been an extremely important advance and has helped to refine these findings into "definite" RHD and "borderline" RHD on the basis of available evidence and expert consensus opinion (Table 2) [27].

However, there remain a number of troubling aspects to subclinical findings suggestive of RHD on echocardiogram, with few data available to guide both the clinician deciding upon a course of action for an individual patient and the epidemiologist trying to determine whether patients with these subclinical findings should be added to the total number of RHD cases. This is especially true of borderline RHD; it has been unclear whether borderline RHD is at the very mild end of the spectrum of RHD, or whether it is simply a normal physiologic variant.

Does subclinical carditis occur in rheumatic fever?

The Jones criteria for the diagnosis of ARF were last updated in 1992, and at that time, echocardiographic diagnosis was not included in the definition of the major manifestation of carditis [28]. However, many clinicians use echocardiography in both the assessment and diagnosis of carditis in patients with ARF. In Australia and New Zealand, echocardiographic findings without clinical signs (that is, subclinical carditis) is accepted as fulfilling the criteria for carditis [29].

Figueroa et al. [30] were the first to examine the natural history of subclinical carditis in the context of ARF. Of 25 patients with carditis at presentation of ARF, 15 had clinical and echocardiographic evidence of carditis and 10 had echocardiographic evidence only; in both groups, valvular changes persisted in over 40% of cases at 1- and 5-year follow-up. Three further studies focused specifically on the long-term follow-up and evaluation of subclinical carditis [26,31,32]. Taken together, the available data suggest that subclinical carditis occurs in 15% to 20% of cases of ARF and that 30% to 50% of patients with subclinical carditis develop RHD [33]. Karaaslan et al. [32] concluded that subclinical lesions represent true, albeit mild, carditis and that patients require secondary prophylaxis and follow-up. They also concluded that the use of strict criteria for the echocardiographic diagnosis of carditis could increase the sensitivity for the diagnosis of ARF, especially in patients with atypical disease such as monoarthritis without leading to overdiagnosis. Stricter criteria have subsequently been developed [25,34,35].

What is known about the progression of subclinical rheumatic heart disease over time?

There have been 3 studies in the modern era that have reported on short-term progress of subclinical RHD in asymptomatic populations [22,23,36,37]. The first study assessed the outcome of mitral regurgitation found at screening after 2 years of follow-up. The investigators reported that significant mitral regurgitation coexisting with morphological abnormalities was more likely to persist on follow-up examination. Of 15 children with both regurgitation and morphologic changes, 1 child had worsening of echocardiographic findings, 10 had persisting changes, and 4 children had regression of regurgitation, although they still had residual morphological changes. In contrast, 39% of screened children with isolated regurgitation without morphologic changes were shown on follow-up to have completely regressed with no residual pathological

TABLE 1. Spectrum of rheumatic heart disease and correlation to echocardiographic findings

	Clinical Symptoms	Clinical Signs	Echocardiographic Findings
Symptomatic rheumatic heart disease	Yes	Yes	Moderate to severe definite rheumatic heart disease
Asymptomatic clinical rheumatic heart disease	No	Yes (murmur)	Mild (to moderate) definite rheumatic heart disease
Asymptomatic subclinical rheumatic heart disease	No	No	Mild definite rheumatic heart disease or borderline rheumatic heart disease

TABLE 2. Summarized 2012 World Heart Federation criteria for the echocardiographic diagnosis of rheumatic heart disease [27]

Echocardiographic Criteria for Individuals Aged ≤20 Years	
Definite RHD (A, B, C, or D)	
A. Pathological MR and at least 2 morphological features of RHD of the MV	
B. MS mean gradient ≥4 mm Hg	
C. Pathological AR and at least 2 morphological features of RHD of the AV	
D. Borderline disease of both the AV and the MV	
Borderline RHD (A, B, or C)	
A. At least 2 morphological features of RHD of the MV without pathological MR or MS	
B. Pathological MR	
C. Pathological AR	
Criteria for Pathological Regurgitation	
Pathological mitral regurgitation	Pathological aortic regurgitation
(All 4 Doppler echocardiographic criteria must be met)	
Seen in 2 views	Seen in 2 views
In at least 1 view, jet length ≥2 cm	In at least 1 view, jet length ≥1 cm
Velocity ≥3 m/s for 1 complete envelope	Velocity ≥3 m/s in early diastole
Pan-systolic jet in at least 1 envelope	Pan-diastolic jet in at least 1 envelope
Morphological Features of RHD	
Features in MV	Features in AV
AMVL thickening ≥3 mm (age-specific)	Irregular or focal thickening
Chordal thickening	Coaptation defect
Restricted leaflet motion	Restricted leaflet motion
Excessive leaflet tip motion during systole	Prolapse

These have been summarized for the purposes of this review. Please see the full referenced article for important explanatory notes and caveats. AMVL, anterior mitral valve leaflet; AR, aortic regurgitation; AV, aortic valve; MR, mitral regurgitation; MS, mitral stenosis; MV, mitral valve; RHD, rheumatic heart disease. Adapted, with permission, from Remenyi et al. [27].

regurgitation on echocardiography, and none of these children were found to have worsening of echocardiographic findings. On short- to medium-term follow-up (range 3 to 27 months) in the RHEUMATIC (Rheumatic Heart Echo Utilisation and Monitoring Actuarial Trends in Indian Children) study [22], the severity of "subclinical RHD" was nonprogressive in 68% of children, whereas it worsened in 4% and regressed in 28%. In a follow-up study of patients detected with RHD by echocardiographic screening in Nicaragua, 9% of the cohort developed progression of anatomic changes or worsening mitral regurgitation over the 4-to-12-month follow-up period [23]. These studies represent the first indication that the natural history of subclinical lesions in asymptomatic populations follows that seen in ARF and that definite disease does have the potential to worsen.

Supporting the echocardiographic follow-up studies, clinical studies prior to the echocardiographic era also showed similar results. In a 4- year follow-up study of patients with abnormalities detected on auscultation, patients with short systolic murmurs and nonejection clicks (most likely corresponding to borderline disease using today's definitions) were most likely to regress or persist with very few progressing to overt RHD [38]. In comparison, patients with bona fide murmurs were found to have persistent clinical findings with a small percentage requiring tertiary follow-up or intervention [39].

Does the prevalence of subclinical rheumatic heart disease differ between endemic and nonendemic populations?

An alternate epidemiologic method to determine the true meaning of subclinical findings of RHD on echocardiogram is to assess the prevalence of these findings in endemic and nonendemic populations. Two studies have made these direct comparisons; however, data are not yet available from either study.

How can the meaning of subclinical rheumatic heart disease best be determined?

Well-designed, longitudinal, observational studies of patients identified with subclinical disease will be important in expanding our understanding of subclinical RHD. A potential confounder in these studies that will need to be accounted for in the analysis will be secondary prophylaxis; that is, if patients are started on secondary prophylaxis, this could modify their disease progression and eventual outcome. Comparison of the progression of echocardiographic changes and incidence of ARF in patients with subclinical RHD to people with normal echocardiogram findings will complement these follow-up studies. Finally, a randomized controlled study of a known effective intervention for RHD (i.e., antibiotic prophylaxis) in patients with subclinical RHD may provide the ultimate evidence for

defining the meaning of subclinical RHD; however, this study would require clinical equipoise, which may not exist if the results from the simpler observational studies are unequivocal.

How should rheumatic heart disease prevalence determined by echocardiographic screening be incorporated into global burden of disease estimates? Toward a new model of rheumatic heart disease

The use of echocardiography as a screening tool no doubt has a major role to play in disease control as well as for advocacy and awareness of RHD [40]. However, using these numbers in computing overall disease figures carries the potential for an inaccurate description of the burden of disease.

It is perhaps time to change the way that we think about RHD and attempt to describe the disease burden with greater subtlety that takes into account our increasing understanding of the disease. Such a revised model might include an assessment of RHD burden in 2 categories: 1) symptomatic disease, which could also be called active disease; and 2) asymptomatic disease, which could also be called latent disease (Fig. 1). This approach has some similarities (but also obvious differences) to the model of disease applied to other latent diseases including infection with *Mycobacterium tuberculosis*.

BURDEN OF DISEASE ESTIMATES: THE VALUE OF ESTIMATING THE BURDEN OF RHEUMATIC HEART DISEASE CAUSING SYMPTOMATIC DISEASE

As noted, the prevalence of RHD detected in screening studies largely indicates the burden of asymptomatic RHD, as well as some cases of symptomatic disease that have previously been undetected. There are a number of other

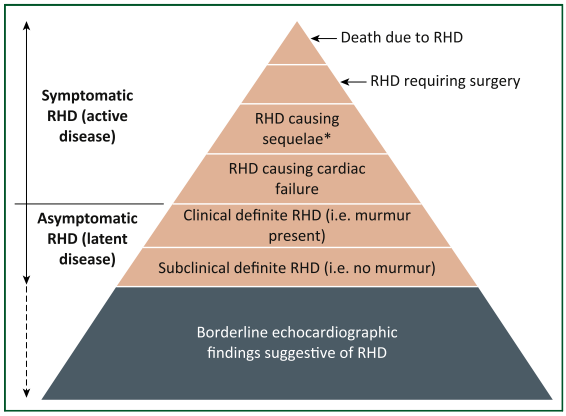

FIGURE 1. A new model for assessing and reporting the burden of rheumatic heart disease that incorporates asymptomatic and symptomatic disease. *Sequelae include atrial fibrillation, infective endocarditis, and stroke. RHD, rheumatic heart disease.

key data sources that provide important information regarding symptomatic patients; these include RHD registry data, hospital admission data including RHD in pregnant women, and RHD surgical data. We believe that these data have been underestimated and an assessment of the link between asymptomatic and symptomatic disease has been neglected.

The clinical characterization of cases on RHD registers and the incidence of cases presenting to the hospital have been described in very few centers. A study arising from a clinical registry in Soweto, South Africa, estimated the annual incidence of new cases of RHD in the region to be 23.5 cases per 100,000 people over 14 years of age [41]. This study highlighted the severity of disease in patients presenting for the first time with symptomatic RHD; the majority of patients presented with impaired systolic function, elevated right ventricular systolic pressure >35 mm Hg and atrial fibrillation, and surgery was necessary in 22%. The study also highlighted the relevance of the complications of RHD; 26% were admitted within 30 months of initial diagnosis for suspected infective endocarditis.

RHD as a cause of fetal and maternal morbidity and mortality has been underestimated. In a study of pregnant women with RHD in Senegal, the maternal mortality rate was 34%, peaking at 54% for women with mitral stenosis [42]. In South Africa, 0.6% of pregnant women have pre-existing cardiac abnormalities, with RHD being the commonest cardiac problem [43]. In the Pacific, RHD is a leading cause of maternal mortality, and in a study from Fiji, the prevalence of RHD in pregnant women was 0.2% [44].

Significant challenges exist in the provision of cardiac surgery regions where RHD is endemic [45–47]. Cardiac surgery is expensive and a lack of infrastructure, human resources, and equipment makes it almost impossible to provide timely and appropriate surgery. The collaboration between nongovernmental agencies as well as humanitarian missions has been essential in providing a cardiac service in many parts of the developing world [48]. Surgery for RHD is challenging, with the complication of prosthetic valves, anticoagulation, and failed repairs, being an ever-present issue. Results differ among units and relate largely to experience, the time of presentation, timing of surgery, and presence of comorbidities [49,50]. Comprehensive data regarding all aspects of cardiac surgery for RHD, including needs, costs, outcomes, and complications are urgently needed, especially for countries with a high burden of RHD attempting to establish cardiac surgical programs [51].

Rheumatic fever incidence, subclinical rheumatic heart disease, and symptomatic rheumatic heart disease: Do the numbers add up?

There are very few populations worldwide that have been sufficiently studied to allow modeling and linking of RHD prevalence (definite and borderline), ARF incidence, RHD incidence (symptomatic cases), RHD surgery, and RHD mortality. A modeling exercise such as this could

allow for a better understanding of progression rates of borderline RHD, as well as the ability to use a single marker of disease burden (such as the number of definite cases detected through screening programs) to extrapolate to multiple downstream measures of disease. It is important to note that the number of definite cases of RHD has been shown to remain relatively consistent in recent studies in multiple diverse populations at a prevalence of 3 to 8 per 1,000. Populations in the Pacific (Australia, New Zealand, and Fiji) as well as in South Africa are currently in the best position with high-quality data to allow this type of modeling to be performed, although many other countries are developing improved disease surveillance systems.

FUTURE EFFORTS TO BETTER DEFINE THE TRUE BURDEN OF DISEASE DUE TO RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE

Moving forward, it will be critical to generate high-quality and comprehensive data regarding all aspects of the burden of ARF and RHD to better inform national, regional, and global control strategies [52]. Although there are increasing data on RHD prevalence from screening studies in school-aged children, there is considerable value in non-prevalence data. New studies are underway in several high-prevalence sentinel areas in diverse geographic locations to address the need for contemporary data [53]. Particular emphasis must be given to comprehensive, prospective cohort studies of long-term outcome particularly related to progression of disease to the distal sequelae of RHD, such as stroke, atrial fibrillation, and infective endocarditis, as well as duration of disability, mortality rates, and economic impact. Medium- and long-term data that chart the course of patients with subclinical disease detected by echocardiography is necessary to delineate the natural history of subclinical carditis and to inform future control strategies. These data will provide vital information in order to advocate even more strongly for directed funding and public health interventions to control ARF and RHD.

REFERENCES

1. Tibazarwa KB, Volmink JA, Mayosi BM. Incidence of acute rheumatic fever in the world: a systematic review of population-based studies. Heart 2008;94:1534–40.
2. Jackson SJ, Steer AC, Campbell H. Systematic review: estimation of global burden of non-suppurative sequelae of upper respiratory tract infection: rheumatic fever and post-streptococcal glomerulonephritis. Trop Med Int Health 2011;16:2–11.
3. Seckeler MD, Hoke TR. The worldwide epidemiology of acute rheumatic fever and rheumatic heart disease. Clin Epidemiol 2011;3: 67–84.
4. Carapetis JR, Steer AC, Mulholland EK, Weber M. The global burden of group A streptococcal diseases. Lancet Infect Dis 2005;5:685–94.
5. Smith SC Jr, Collins A, Ferrari R, et al. Our time: a call to save preventable death from cardiovascular disease (heart disease and stroke). Circulation 2012;126:2769–75.
6. Ralston J. New global target on non-communicable diseases: a call to action for the global cardiovascular disease community. Cardiovasc J Afr 2012;23:241–2.
7. Murray CJ, Ezzati M, Flaxman AD, et al. GBD 2010: design, definitions, and metrics. Lancet 2012;380:2063–6.
8. Jaffe WM, Roche AH, Coverdale HA, McAlister HF, Ormiston JA, Greene ER. Clinical evaluation versus Doppler echocardiography in the quantitative assessment of valvular heart disease. Circulation 1988;78:267–75.
9. Nkgudi B, Robertson KA, Volmink J, Mayosi BM. Notification of rheumatic fever in South Africa—evidence for underreporting by health care professionals and administrators. S Afr Med J 2006;96: 206–8.
10. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990—2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2163–96.
11. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2095–128.
12. Tantchou Tchoumi JC, Butera G. Rheumatic valvulopathies occurence, pattern and follow-up in rural area: the experience of the Shisong Hospital, Cameroon. Bull Soc Pathol Exot 2009;102:155–8.
13. Longo-Mbenza B, Bayekula M, Ngiyulu R, et al. Survey of rheumatic heart disease in school children of Kinshasa town. Int J Cardiol 1998; 63:287–94.
14. Agarwal AK, Yunus M, Ahmad J, Khan A. Rheumatic heart disease in India. J R Soc Health 1995;115:303–4, 309.
15. Carapetis JR, Currie BJ, Mathews JD. Cumulative incidence of rheumatic fever in an endemic region: a guide to the susceptibility of the population? Epidemiol Infect 2000;124:239–44.
16. Günther G, Asmera J, Parry E. Death from rheumatic heart disease in rural Ethiopia. Lancet 2006;367:391.
17. Anabwani GM, Bonhoeffer P. Prevalence of heart disease in school children in rural Kenya using colour-flow echocardiography. East Afr Med J 1996;73:215–7.
18. Marijon E, Ou P, Celermajer DS, et al. Prevalence of rheumatic heart disease detected by echocardiographic screening. N Engl J Med 2007; 357:470–6.
19. Steer AC, Jenney AW, Kado J, et al. High burden of impetigo and scabies in a tropical country. PLoS Negl Trop Dis 2009;3:e467.
20. Beaton A, Okello E, Lwabi P, Mondo C, McCarter R, Sable C. Echocardiography screening for rheumatic heart disease in Ugandan schoolchildren. Circulation 2012;125:3127–32.
21. Webb RH, Wilson NJ, Lennon DR, et al. Optimising echocardiographic screening for rheumatic heart disease in New Zealand: not all valve disease is rheumatic. Cardiol Young 2011;21:436–43.
22. Saxena A, Ramakrishnan S, Roy A, et al. Prevalence and outcome of subclinical rheumatic heart disease in India: the RHEUMATIC (Rheumatic Heart Echo Utilisation and Monitoring Actuarial Trends in Indian Children) study. Heart 2011;97:2018–22.
23. Paar JA, Berrios NM, Rose JD, et al. Prevalence of rheumatic heart disease in children and young adults in Nicaragua. Am J Cardiol 2010; 105:1809–14.
24. Carapetis JR, Hardy M, Fakakovikaetau T, et al. Evaluation of a screening protocol using auscultation and portable echocardiography to detect asymptomatic rheumatic heart disease in Tongan schoolchildren. Nat Clin Pract Cardiovasc Med 2008;5:411–7.
25. Wilson N. Echocardiography and subclinical carditis: guidelines that increase sensitivity for acute rheumatic fever. Cardiol Young 2008;18: 565–8.
26. Ozkutlu S, Hallioglu O, Ayabakan C. Evaluation of subclinical valvar disease in patients with rheumatic fever. Cardiol Young 2003;13:495–9.
27. Remenyi B, Wilson N, Steer A, et al. World Heart Federation criteria for echocardiographic diagnosis of rheumatic heart disease-an evidence-based guideline. Nat Rev Cardiol 2012;9:297–309.
28. Special Writing Group of the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young of the American Heart Association. Guidelines for the diagnosis of rheumatic fever. Jones Criteria, 1992 update. JAMA 1992;268:2069–73.

29. RHDAustralia (ARF/RHD writing group). The Australian Guideline for Prevention, Diagnosis and Management of Acute Rheumatic Fever and Rheumatic Heart Disease. 2nd edition. Auckland, Australia: National Heart Foundation of Australia and New Zealand; 2012.

30. Figueroa FE, Fernandez MS, Valdes P, et al. Prospective comparison of clinical and echocardiographic diagnosis of rheumatic carditis: long term follow up of patients with subclinical disease. Heart 2001;85:407–10.

31. Lanna CC, Tonelli E, Barros MV, Goulart EM, Mota CC. Subclinical rheumatic valvitis: a long-term follow-up. Cardiol Young 2003;13: 431–8.

32. Karaaslan S, Demiroren S, Oran B, Baysal T, Baspinar O, Ucar C. Criteria for judging the improvement in subclinical rheumatic valvitis. Cardiol Young 2003;13:500–5.

33. Tubridy-Clark M, Carapetis JR. Subclinical carditis in rheumatic fever: a systematic review. Int J Cardiol 2007;119:54–8.

34. Caldas AM, Terreri MT, Moises VA, Silva CM, Carvalho AC, Hilario MO. The case for utilizing more strict quantitative Doppler echocardiographic criterions for diagnosis of subclinical rheumatic carditis. Cardiol Young 2007;17:42–7.

35. Vijayalakshmi IB, Vishnuprabhu RO, Chitra N, Rajasri R, Anuradha TV. The efficacy of echocardiographic criterions for the diagnosis of carditis in acute rheumatic fever. Cardiol Young 2008;18:586–92.

36. Bhaya M, Panwar S, Beniwal R, Panwar RB. High prevalence of rheumatic heart disease detected by echocardiography in school children. Echocardiography 2010;27:448–53.

37. Bhaya M, Beniwal R, Panwar S, Panwar RB. Two years of follow-up validates the echocardiographic criteria for the diagnosis and screening of rheumatic heart disease in asymptomatic populations. Echocardiography 2011;28:929–33.

38. Cohen M, Pocock WA, Lakier JB, McLaren MJ, Lachman AS, Barlow JB. Four year follow-up of black schoolchildren with non-ejection systolic clicks and mitral systolic murmurs. Am Heart J 1978;95:697–701.

39. McLaren MJ, Hawkins DM, Koornhof HJ, et al. Epidemiology of rheumatic heart disease in black schoolchildren of Soweto, Johannesburg. Br Med J 1975;3:474–8.

40. Zühlke L, Mayosi BM. Echocardiographic screening for subclinical rheumatic heart disease remains a research tool pending studies of impact on prognosis. Curr Cardiol Rep 2013;15:343.

41. Sliwa K, Carrington M, Mayosi BM, Zigiriadis E, Mvungi R, Stewart S. Incidence and characteristics of newly diagnosed rheumatic heart disease in Urban African adults: insights from the Heart of Soweto Study. Eur Heart J 2010;31:719–27.

42. Diao M, Kane A, Ndiaye MB, et al. Pregnancy in women with heart disease in sub-Saharan Africa. Arch Cardiovasc Dis 2011;104: 370–4.

43. Watkins DA, Sebitloane M, Engel ME, Mayosi BM. The burden of antenatal heart disease in South Africa: a systematic review. BMC Cardiovasc Disord 2012;12:23.

44. Steer AC, Kado J, Jenney AW, et al. Acute rheumatic fever and rheumatic heart disease in Fiji: prospective surveillance, 2005—2007. Med J Aust 2009;190:133–5.

45. Mocumbi AO. The challenges of cardiac surgery for African children. Cardiovasc J Afr 2012;23:165–7.

46. Hoosen EG, Cilliers AM, Hugo-Hamman CT, et al. Paediatric cardiac services in South Africa. S Afr Med J 2011;101:106–7.

47. Hewitson J, Brink J, Zilla P. The challenge of pediatric cardiac services in the developing world. Semin Thorac Cardiovasc Surg 2002;14: 340–5.

48. Dearani JA, Neirotti R, Kohnke EJ, et al. Improving pediatric cardiac surgical care in developing countries: matching resources to needs. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 2010;13: 35–43.

49. Yankah CA, Siniawski H, Detschades C, Stein J, Hetzer R. Rheumatic mitral valve repair: 22-year clinical results. J Heart Valve Dis 2011;20: 257–64.

50. Agneta Geldenhuys JJK, Human PA, Mtwale JF, Brink JG, Zilla P. A retrospective review of rheumatic mitral valve repair in a threshold country. S A Heart 2011;8:235.

51. Severino ES, Petrucci O, Vilarinho KA, et al. Late outcomes of mitral repair in rheumatic patients. Rev Bras Cir Cardiovasc 2011;26: 559–64.

52. Carapetis JR, Zühlke LJ. Global research priorities in rheumatic fever and rheumatic heart disease. Ann Pediatr Cardiol 2011;4:4–12.

53. Karthikeyan G, Zühlke L, Engel M, et al. Rationale and design of a Global Rheumatic Heart Disease Registry: the REMEDY study. Am Heart J 2012;163:535–540.e1.