White Paper: Research Agenda for Measuring the Global Burden of RHD

First report of the Global Burden of RHD Working Group

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Background

Rheumatic heart disease (RHD) remains the most important cause of acquired cardiovascular disease in children and young adults globally. A recent assessment from the Global Burden of Disease 2015 Study systematically reviewed available datasets on fatal and non-fatal RHD from 1990 to 2014.[1] While research output on the epidemiology of RHD has increased dramatically over the past decade, there remain a number of important data gaps that pose challenges for tracking progress on RHD, especially in low- and middle-income countries, and advocating for more resources devoted to its prevention and treatment.

The concept of a Global Burden of RHD Working Group was initiated by RhEACH[2] in February 2017 to identify research priorities, develop scientific norms, raise awareness among decision-makers, and mobilize research funding in the area of descriptive epidemiology related to RHD. An inaugural meeting of the Working Group was held in conjunction with the 20th Lancefield International Symposium on Streptococci and Streptococcal Diseases in Fiji on 16 October 2017 (Annex 1). The objectives of that meeting were (1) to review the current state of the literature on the burden of Group A streptococci and its sequelae (including RHD, the focus of this report) and (2) to identify research priorities and potential collaborations.[3] This report summarizes the discussion and recommendations of the October 2017 meeting and situates those recommendations within the broader context of recent research on RHD epidemiology.

Topics discussed at first Working Group meeting

Dr. Watkins opened the meeting with a brief presentation on data gaps and needs. The point was made that the term "burden of disease," as used by this group, would largely refer to descriptive epidemiology studies rather than analytic epidemiology studies or other designs. A counterpoint was made that, from an advocacy standpoint, this group might also be interested

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[1] Watkins DA, Johnson CO, Colquhoun SM, et al. Global, regional, and national burden of rheumatic heart disease, 1990-2015. N Engl J Med 2017; 377:713-722.

[2] RhEACH (http://www.rheach.org/) provides technical support and participates in policy translation activities in order to boost RHD control efforts at the local, national, regional, and global levels.

[3] This pre-Lancefield meeting was also attended by experts on the burden of Group A strep diseases. Priorities for Group A strep research are summarized in a separate white paper.

in the economic burden of RHD – i.e., the costs associated with disability or early death and with receiving healthcare.

Dr. Watkins showed data from Pubmed on publication trends, noting that the number of new epidemiology studies on RHD has tripled since 1990, especially following a landmark study on echocardiographic prevalence of RHD in 2007.[4] (Incidentally, increases were also noted in publications on invasive streptococcal diseases.) The point was stressed, however, that data availability by country vary widely, and even the best-represented countries do not have adequate information along the entire natural history of the disease (i.e., from pharyngitis to acute rheumatic fever to RHD, including rates of sequelae, and to death).[5]

The recommendations of the Global Burden of Disease 2015 report were then presented:

1. Examine the extent of misclassification in RHD-related death certification[6]
2. Obtain more data on prevalence among adults in low- and middle-income countries[7]
3. Quantify non-fatal outcomes and excess mortality in representative, longitudinal studies of individuals with RHD[8]

It was noted that the contributions of the working group to these priority areas could go in three general directions. First, more effort could be made to support the Global Burden of Disease project, including conducting literature reviews on non-heart-failure nonfatal outcomes (such as stroke) and collaborating more closely with modeling experts to incorporate these outcomes into the Global Burden of Disease estimates. Second, the group could develop large-scale, rigorous epidemiological studies, ideally tailored toward the priority areas above, and at new sites. Third, the group could develop pragmatic but less scientifically rigorous rapid assessment methods and tools to get a snapshot of RHD in countries that do not have adequate published data. The pros and cons of these three approaches were noted to include funding constraints, external validity and generalizability of locally-driven tools and datasets, and the fairly rigid analytic structure of the Global Burden of Disease project.

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[4] Marjion E, Ou P, Celermajer DS, et al. Prevalence of rheumatic heart disease detected by echocardiographic screening. New Engl J Med 2007; 357(5):470-476.

[5] Moloi AH, Mall S, Engel ME, et al. The health systems barriers and facilitators for RHD prevalence: an epidemiological meta-analysis from Uganda and Tanzania. Glob Heart 2017; 12(1):5-15.

[6] For an example of the challenges in using vital registration data to measure mortality due to RHD, see: Parks T, Kado J, Miller AE, et al. Rheumatic heart disease-attributable mortality at ages 5-69 years in Fiji: a five-year, national, population-based record-linkage cohort study. PLoS Negl Trop Dis 2015; 9(9):e0004033.

[7] Only two studies included in the Global Burden of Disease 2015 analysis had sought to measure the prevalence of RHD among individuals over the age of 25.

[8] Currently, heart failure attributed to RHD is included in the Global Burden of Disease project, but other sequelae such as stroke and infective endocarditis are not.

Finally, Dr. Watkins presented two pieces of information from the Global Burden of Disease 2015 report: a map of data availability by country (Annex 2) and a list of countries that, as of 2014, did not have any data on fatal or non-fatal RHD (Annex 3). Several populous endemic countries were highlighted on this list as being potentially high-yield locations for future research projects.

In addition, the group noted two additional considerations that may affect the recommendations and priority areas of this Working Group. Firstly, the WHO is considering a resolution on RHD that will be voted on in May 2018. If passed, the WHO resolution would require countries to have a standardized approach to tracking the burden of RHD, ideally with easy-to-use tools and readily available data that could be gathered inexpensively and consistently. Ideally such tools would be developed, reviewed, field-tested, and revised under the supervision of experts, presenting a very practical scope of work for the Working Group.

Secondly, there is a proposal to establish a Global GAS Vaccine Consortium, as a partnership with WHO and supported by funding from the Wellcome Trust. A critical part of the work of this Consortium will be to explore gaps in burden data in critical countries and regions, with a view to understanding the vaccine-preventable disease burden and to develop a global investment case for GAS vaccines.

Summary of deliberations on research priorities

Following the overview session, the Group A strep and RHD Working Groups broke out and considered research priorities for either disease. They were tasked with identifying short- and long-term priorities with a variety of budgetary constraints. They were asked to identify the areas of the world that were overlooked and to propose solutions to engaging new collaborators. Finally, they were asked to comment on how to improve the quality of epidemiological research and to identify the functions that the Working Groups should serve.

Three major themes emerged from the breakout session.

1. Importance of sentinel sites. The group quickly achieved consensus that sentinel sites would be an important approach to gathering data on the burden of RHD. Ideally such sites would span the socioeconomic spectrum and range across a variety of geographies. Fiji and Uganda were immediately identified as countries where excellent epidemiological research has been conducted and could continue. Indonesia and Australia/New Zealand were mentioned as other potential sentinel sites. The importance of strengthening research capabilities in low-income African countries – many of which are highly endemic but have no data – was also highlighted.

2. Practical uses of adult prevalence data. Concern was voiced that conducting echo prevalence studies among adults (a recognized need) may inadvertently undermine the case for RHD. Finding high rates of asymptomatic or mild RHD, it was argued, may lead to confusion about "what to do about this" – in contrast to the clear need to intervention in childhood (i.e., through primary and secondary prevention in high-prevalence settings) and among the subset

of adults with symptomatic disease that is amenable to surgery. A contrasting opinion was offered that prevalence studies might serve an important purpose if they also collect longitudinal data on outcomes and natural history. For instance, "mild" RHD could be more common in rural and remote settings where affected persons might progress rapidly to death before they can access tertiary services. Phenomena like this would be important to measure.

3. Potential short- and long-term projects. A critical need for the first two years was a systematic review of maternal and perinatal prevalence and outcomes, building on and expanding previous reviews.[9] This would be an important paper for linking RHD to the maternal/child health agenda and advocating for more funding. In the longer term (5-7 years, depending on funding), sentinel sites could come on board and provide gold-standard datasets for important endpoints such as mortality, natural history of RHD detected by echo, rates of sequelae (such as heart failure, atrial fibrillation/stroke, and infective endocarditis), maternal/perinatal outcomes, economic burden data, and delivery patterns of secondary prevention. Studies based at antenatal clinics (in countries where coverage of antenatal services is very high) might be ideal locations to measure both prevalence among adults (to a first approximation) and rates of adverse maternal/perinatal outcomes. These sentinel sites would be ideal locations to develop and validate pragmatic and rapid tools that could be used to assess disease burden elsewhere. An important role for the RHD Working Group would be to develop clear case definitions and management protocols for observational studies in these settings, where inevitably a large number of new cases would be identified and would need to be managed clinically.

Recommendations of the Working Group

In light of these discussions and deliberations, the Global Burden of RHD Working Group makes the following preliminary recommendations for RHD descriptive epidemiology research:

A. Funding is urgently needed to **establish a network of sentinel sites** that can serve as centers of research excellence. Potential sites should span Africa, South Asia, and Oceania and include countries of diverse income levels and health system arrangements (such as access to cardiac surgery). Once funding has been identified, the Working Group will advise on the formulation of priority research questions and will be available to vet research protocols and advise on the development of rapid assessment tools.

B. More effort needs to be made to **expand the scope of RHD prevalence studies**. It is likely that significant **gradients** in prevalence exist, inter alia, across age groups, among rural vs. urban populations, and among children in community settings vs. children attending schools. Studies should strive to use methods, such as complex survey sampling, that maximize generalizability of findings to subnational and national

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

populations. Where possible, studies should be resourced to collect **follow-up data** on individuals with borderline or definite RHD to quantify natural history.

C. Absent large, multi-year research funding, there is a need to **conduct a number of global-level systematic reviews** to determine the burden of various **sequelae of RHD**. Some reviews, now dated, have been conducted on the association between RHD and stroke and on complications of RHD in pregnancy, but these need to be updated and expanded to cover all countries.

At the close of the meeting, the working group agreed to meet on an ongoing basis. It was decided that a Global GAS Vaccine Consortium, if established, would be the most appropriate mechanism for convening and supporting future meetings. Hence plans for future meetings will be developed once the plans for a Consortium have become more clear (likely in early- to mid-2018).

Annex 1. List of participants in the first Working Group meeting, 16 Oct 2017, Nadi, Fiji.

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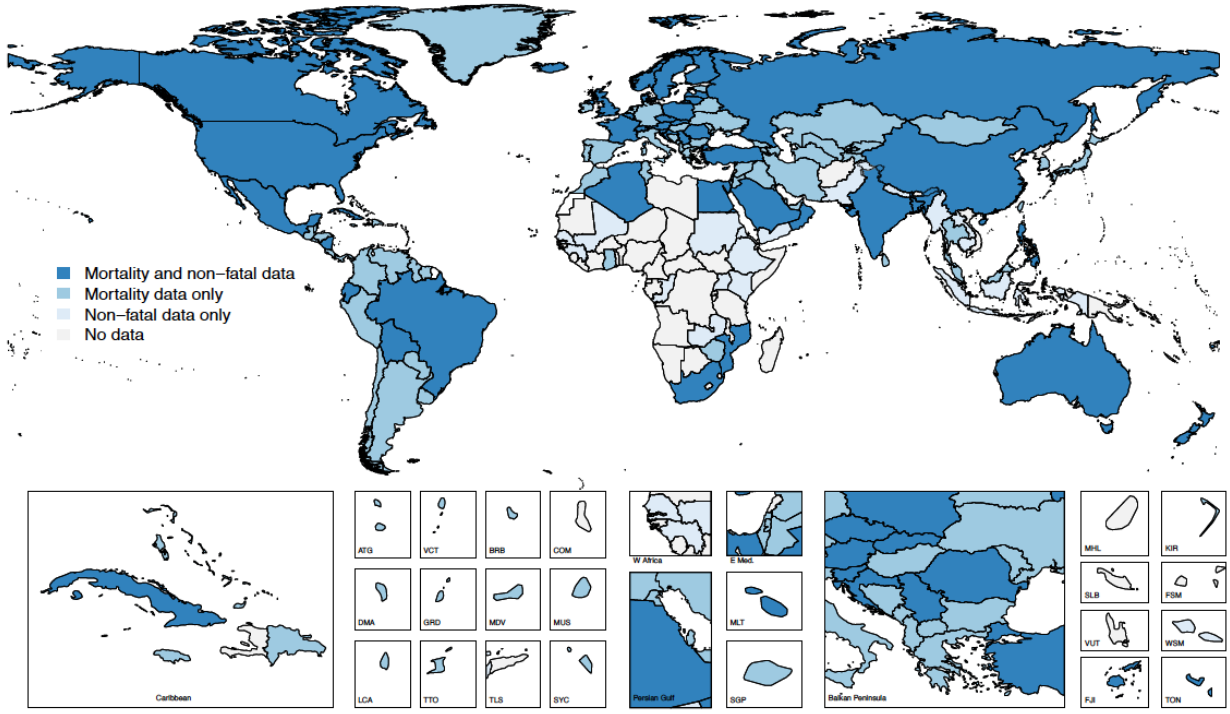
Annex 2. Map of data availability for RHD, 1990-2014.



Reproduced from: Watkins DA, Johnson CO, Colquhoun SM, et al. Global, regional, and national burden of rheumatic heart disease, 1990-2015. N Engl J Med 2017; 377:713-722.

Annex 3. List of countries lacking data on RHD as of 2014.

Afghanistan	Equatorial Guinea	Malawi	Samoa
Albania	Gabon	Maldives	San Marino
Angola	Gambia	Mali	Sao Tome and Principe
Azerbaijan	Georgia	Marshall Islands	Sierra Leone
Belize	Ghana	Mauritania	Solomon Islands
Benin	Grenada	Mauritius	Somalia
Bhutan	Guinea-Bissau	Micronesia	South Sudan

Botswana	Guyana	Morocco	Suriname
Burkina Faso	Haiti	Myanmar	Swaziland
Burundi	Indonesia	Namibia	Syrian Arab Republic
Cameroon	Iraq	Nauru	Timor-Leste
Central Afr. Republic	Jamaica	Niger	Togo
Chad	Kenya	Nigeria	Tunisia
Côte d'Ivoire	Kiribati	Palau	Turkmenistan
North Korea	Kyrgyzstan	Papua New Guinea	Tuvalu
Dem. Rep. Congo	Lesotho	Rwanda	Tanzania
Djibouti	Liberia	Saint Kitts and Nevis	Uzbekistan
Dominica	Libya	Saint Lucia	Vanuatu
Dominican Republic	Madagascar	St. Vincent/Grenadines	Zimbabwe

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