

VIEWPOINT

Gaps, Obstacles, and Opportunities in Rheumatic Heart Disease Research



Where Are We Now?

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Rheumatic heart disease (RHD) is the most common acquired heart disease of childhood resulting from poorly treated group A beta hemolytic streptococcal pharyngitis. Globally, RHD is estimated to affect about 33 million people majority of whom are children and young adult living in some of the poorest regions of the world.¹ From recent estimates, RHD is said to be associated with an attendant 275,000 deaths recorded annually mainly in sub-Saharan Africa, India, Southeast Asia, and some parts of Australia.¹

Multiple factors including poor knowledge of RHD disease process, appropriate treatment of streptococcal pharyngitis, and poorly coordinated health system in these low- and lower middle-income countries (LMICs) contributes to the high burden of RHD. Although evidence-based research has shown the importance of early diagnosis and penicillin prophylaxis especially intramuscular benzathine penicillin in improving the outcomes for patients with RHD, this has not been widely implemented resulting in poor uptake of benzathine penicillin prophylaxis in most RHD care programs, early progression to severe disease and frequent episodes of heart failure, infective endocarditis, and cardiovascular events.^{2,3}

As a disease of social disadvantage, it is endemic in areas where poverty and social inequalities predominate. Currently, very little data exist on the demographics, and factors that inform outcomes for

people with RHD. Until recently, most of the papers that attempt to detail the progression and outcomes of the disease were from high-income countries, where RHD has ceased to be a public health concern. In addition, these studies were more than 50 years old and were conducted before the availability of echocardiography. Very little contemporary evidence exists on the progression and subsequent outcomes associated with RHD globally.

STATUS OF RHD IN GLOBAL RESEARCH

RHD RESEARCH IS NEGLECTED, UNDERFUNDED, AND ABANDONED TO RESEARCHERS FROM LMIC. In the second half of the 20th century, the World Health Organization funded and led research that helped in understanding the drivers and clinical course of RHD.^{4,5} At the turn of the 21st century, commitment to the RHD research waned significantly especially with the increasing significance of HIV morbidity and mortality in developing countries. With the loss of funding from the World Health Organization and its partners, coupled with poor health spendings, RHD almost disappeared from the global health agenda except for the persistent efforts of the Pan-African Society of Cardiology, World Heart Foundation, and its related partners.⁴

Currently, RHD is a neglected research topic in the global research agenda (**Table 1**) even though it contributes significantly to the global burden of cardiovascular diseases especially in children and young adults.⁴ Very few grants and granting agencies target RHD as a disease entity specifically even though it is the most significant acquired heart disease in childhood and young adulthood in most developing countries.^{6,7}

In addition, interest in RHD research waned globally leaving the burden of researching RHD to those in endemic regions of Africa, India, and the aboriginal

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

TABLE 1 Gaps, Opportunities, and Future of RHD Research

Neglected Research Topic/ Subject	Underdiagnosed	Social Inequalities in Disease Presentation and Outcome	Underrepresentation of RHD in Cardiovascular Trials/Research	Almost Nonexistent Population Based Longitudinal Data on the Burden and Outcome of the Disease
Mainly a developing countries problem	Focus is on the severe diseases presenting to the hospital	Mainly affects poor people living in poor areas/ conditions	Most CVD trials target adults and the elderly	Hospital based studies predominate
Mainly a developing country researchers problem	Few community/school-based screening for early/mild disease	Worst outcomes in patients living in LMIC	Young people and children underrepresented in CVD research generally	Novel approach to RHD registry needed
Underfunded and under researched	Potential opportunity for improved diagnosis using Artificial Intelligence	Poor access to care in LMIC	RHD is mainly a disease of children and young adults	Technology driven prevention and control activities needed

CVD = cardiovascular disease; LMIC = low- and lower middle-income country; RHD = rheumatic heart disease.

regions of Australia.^{6,7} Recently, some funded research grants through the efforts of the Wellcome Trust and the Population Health Research Institute in Canada has produced reports on the clinical outcomes and gaps in care as well as genetic information on the possible pathogenesis of the disease.^{8,9} While these efforts are commendable, more needs to be done by the global granting agencies especially those in the rich western hemisphere like the United States in funding RHD research considering it is a disease of poor countries and regions where health research funding is almost always absent.

WHAT CAN THE GLOBAL CARDIOVASCULAR WORKFORCE DO FOR RHD RESEARCH? One of the largest global collaborations on RHD research is the REMEDY (Global Rheumatic Heart Disease Registry) study collaboration, which spans through 42 sites located in 12 African countries, Yemen, and India.^{3,10,11} This multi-country, multisite collaboration showed the significant role researchers, cardiologists, and health workers generally can play in advancing knowledge around an important research topic—RHD by pooling together and sharing resources for a common good.^{3,10,11}

Apart from identifying gaps in care of the patients, this collaboration also demonstrated a low uptake of benzathine penicillin prophylaxis and other evidence-based practices shown to improve the clinical outcomes for patients with RHD suggesting a key need for implementation science research as well as novel approaches to preventing RHD.¹⁰⁻¹² Late presentation with high incidence of severe disease also suggests a need for developing innovative ways for community-wide screening aimed at early diagnosis and timely management.^{11,12} Furthermore, since availability and access to cardiologists and skilled manpower is lacking in most endemic areas, the need for task shifting using technology or artificial

intelligence (AI) may be that missing link that could help lead to early, timely, and accurate diagnosis.

Recently, machine-learning techniques utilizing echocardiography videos from patients with RHD have been developed for possible incorporation in a handheld point of contact ultrasound at the primary care level for ease of diagnosis of RHD.¹³ Preliminary evidence suggests a potential significant role for these innovative applications to the prevention and control of RHD.¹³

In addition to all these, cardiovascular researchers and clinicians managing people living with RHD should begin to advocate the inclusion of patients with RHD in clinical trials involving cardiovascular disease research including those that target women. This will help improve the representation of RHD in global clinical trials as well as helping to advance knowledge about RHD care and management.

HOW CAN ARTIFICIAL INTELLIGENCE IMPROVE RHD PREVENTION AND CONTROL? One of the key drivers of the RHD pandemic is the low utilization of evidence-based technologies and research aimed at improving the detection and outcomes for patients with RHD. Incorporating AI using machine learning or deep learning models can help expand the scope and reach of RHD screening especially in rural areas using lower cadre health staff thereby increasing early detection and thus reducing late presentation with severe disease and its attendant poor outcomes.¹⁴⁻¹⁶

For instance, focused ultrasonography using handheld devices have been used and shown to be effective in the diagnosis of RHD in the field using school children.^{14,15} Most of those screening was done by cardiologist and people trained in echocardiography.^{14,15} AI-enabled point of care devices or tools can help simplify the screening and diagnosis of RHD at the primary care level for use by

non-cardiologists thereby reducing the workload on cardiologists and widening its reach.^{15,16}

These point of care devices have the potential for allowing low-cost identification of patients at higher risk for RHD and other cardiovascular diseases potentially reducing cost of care and avoid late presentation with severe RHD in endemic regions where cardiovascular care is a luxury.¹⁴⁻¹⁶

WHAT SHOULD THE GLOBAL RESEARCH FUNDERS DO? Currently, the most important challenge facing RHD research is funding. Unfortunately, the countries where RHD is endemic either do not have the funds or may be faced with other equally important yet competing demands. This sad reality is what has made research and progress in RHD research difficult, prompting the World Health Assembly to vote to bring back RHD into the global health agenda.

Global research granting agencies should as a matter of priority identify RHD as a neglected yet important disease of public health significance not just in LMICs but as a global cause of cardiovascular disease morbidity and mortality.¹⁶ In addition, these granting agencies especially in the rich countries of the world should as a matter of necessity increase the representation of RHD in their funded research portfolio as what was done for malaria, HIV, and tuberculosis—all diseases of poverty and social neglect.¹⁶

Lastly, there is a need to form diverse and inclusive clinical trial leadership research grants in order to attract young and talented researchers living and working in RHD endemic regions toward investing their time and career in RHD research.¹⁷

FUTURE OF RHD RESEARCH. Apart from leveraging AI for screening, the RHD research agenda in the next few years must primarily revolve around other means of increasing diagnostics accuracy especially in low resource settings and improving preventive measures.

In low resource settings, access to microbiology is often a luxury, making throat culture difficult to impossible to obtain. Thus, there remains an urgent need for low-cost, portable systems for rapid diagnostics of Group A *Streptococcus*.¹⁸

Candidate vaccines, which include cell wall carbohydrate vaccines, M protein vaccines containing conserved C-repeat epitopes, multivalent M protein-based vaccines, and non-M protein multi-component vaccines,¹⁹ are promising but will be facing lack of commercial stakeholder interest once approved considering that countries with high prevalence are low income countries. Furthermore, equitable access will require the right policies in

place to ensure distribution to countries that need it the most.

Genome-wide associated studies is considered by many as the biggest advancement in RHD genetics, investigating the significant heritability of the disease, which is most likely polygenic. Understanding the genetic predisposition behind it may facilitate development of novel therapeutic strategies to address the disease.

Maintaining current registries and establishing new ones is a key to knowing the epidemiology of RHD and its complications. Aside from the burden of the disease, registries can guide policymakers in setting priorities and determining targets for population-based interventions.

CONCLUSIONS

RHD is an important cardiovascular problem not just in children but also among young adults living in many low- and lower middle-income countries. While efforts toward the prevention and control of RHD are commendable, more needs to be done especially in the area of improving early diagnosis in the most vulnerable group in order to reduce the burden and complications associated with late presentation from late diagnosis, as is the case currently. Machine learning models are emerging as potential research areas with promise to address the diagnostic and by extension management gaps currently faced by cardiologists and pediatricians working in the endemic regions. So far, application of AI in echocardiographic diagnosis of cardiovascular disorders is an ongoing experiment with focus on the anatomical changes rather than the functional consequences of the anatomical distortions occasioned by the pathogenic process. While very few if any of the ongoing works target RHD specifically, we see potential for significant improvement in RHD cardiac care especially where human resources for health is inadequate as is seen in most LMIC. In the future, when this technological advancement is applied to RHD, it can potentially close the gap in screening, diagnostics, and early treatment.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS artificial intelligence, LMIC, rheumatic heart disease, technology