

AHA POLICY STATEMENT

The American Heart Association's Call to Action for Reducing the Global Burden of Rheumatic Heart Disease

A Policy Statement From the American Heart Association

ABSTRACT: Rheumatic heart disease (RHD) affects ≈40 million people and claims nearly 300 000 lives each year. The historic passing of a World Health Assembly resolution on RHD in 2018 now mandates a coordinated global response. The American Heart Association is committed to serving as a global champion and leader in RHD care and prevention. Here, we pledge support in 5 key areas: (1) professional healthcare worker education and training, (2) technical support for the implementation of evidence-based strategies for rheumatic fever/RHD prevention, (3) access to essential medications and technologies, (4) research, and (5) advocacy to increase global awareness, resources, and capacity for RHD control. In bolstering the efforts of the American Heart Association to combat RHD, we hope to inspire others to collaborate, communicate, and contribute.

In the early to mid-20th century, rheumatic fever (RF) and its major sequela, rheumatic heart disease (RHD), were highly prevalent in the United States and Western Europe, and patients with these conditions routinely occupied almost 25% of pediatric beds.¹ The American Heart Association (AHA) was established largely to address RF, dubbed childhood's greatest enemy, as local heart chapters united to educate and advocate.^{2,3} The success of this public health campaign, which brought the incidence of RF cases in the United States to nearly zero, is among the AHA's greatest achievements. However, our work is not done.

Globally, RF and RHD continue unabated. RHD affects ≈40 million people and claims nearly 300 000 lives each year.⁴ The majority of those affected are socioeconomically disadvantaged, living in low- and middle-income countries (LMICs) or in marginalized populations within higher-income countries (RHD Patient Perspective Supplemental Material). For the past 50 years, advocacy, research, and program implementation to combat RHD have been largely neglected. However, we have the tools we need to achieve global control of RHD; no child born today should die of RHD. The historic passing of a World Health Assembly resolution on RF/RHD in 2018⁵ now mandates a coordinated global response. The AHA is enthusiastic about partnering in this response, working to complete one of the founding goals: to create a world free from the devastating effects of RHD.

RHD: A SIGNIFICANT AND PERSISTENT GLOBAL HEALTH PROBLEM

In the 65 years since the World Health Organization (WHO) published its first expert report detailing RHD prevention and treatment guidelines, global RHD death

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Key Words: AHA Scientific Statements
■ health resources ■ rheumatic fever
■ rheumatic heart disease

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rates have declined substantially. This decline has been the result almost entirely of large reductions in high- and upper-middle-income countries, with little or no improvement in the world's poorest countries.⁶ Indeed, the burden of RHD in LMICs and in select marginalized populations within higher-income countries (such as Indigenous communities in Australia and New Zealand) is staggering. In 2015, 82% of RHD-related deaths occurred in LMICs, with the highest number of deaths in India, China, and Pakistan.² A recent meta-analysis estimated that in endemic settings 2.7 individuals per 1000 population had clinical RHD and 21 individuals per 1000 population (2.1%) had clinically silent, echo-detected RHD.⁷

It is unlikely that RHD can be eradicated (the complete and permanent worldwide reduction to zero); RHD persists in low numbers even in high-income settings and populations. Thus, global control should be defined as bringing the rates of new cases of RHD, and eventually deaths resulting from RHD, in endemic settings equal to those in nonendemic settings. Currently, nearly 40 million people are living with RHD, many with advanced disease. Therefore, RHD-related deaths will continue for many years even if we successfully reduce the incidence of new cases. Thus, the goal should be to ramp up efforts to prevent RHD while also building global capacity to treat its consequences.

EFFORTS TO INCREASE GLOBAL ADVOCACY

In 2018, the World Health Assembly (the decision-making body of the WHO, representing all member states) passed a resolution recognizing that RHD remains a significant public health concern in many countries.⁵ The resolution was the culmination of concerted efforts to reposition RF/RHD on the global agenda to accelerate control and elimination.^{8–10} There have been 2 previous surges of RHD research and control: the first in the United States and Europe from the 1950 to 1960s and the second in the 1980s led by the WHO and the International Society and Federation of Cardiology, the predecessor to today's World Heart Federation. In comparison, the current groundswell of activity has been led by clinicians, researchers, and people affected by RHD who live and work in LMICs where the greatest disease burden exists.¹¹

Although the global resolution is a call to action for member states, stakeholders, and the director-general of the WHO, a number of nongovernmental organizations are now playing a central role in corralling international players, establishing institutional linkages, and providing technical support to assist countries in reaching their RHD targets. The World Heart Federation¹² took the initial lead in prioritizing RHD as a critical

cardiovascular disease in LMICs. The subsequent establishment of resource hubs such as RHD Action¹³ and the founding of the RHD-specific technical support organization Reach¹⁴ are improving access to best practices and up-to-date information for all stakeholders and providing technical support to ministries of health.

HOW AHA GOALS AND RECOMMENDATIONS HARMONIZE WITH THE RHD GLOBAL RESOLUTION

For nearly 100 years, the AHA, true to its original mission statement “to reduce premature death and disability from cardiovascular disease,” has been fighting heart disease and stroke, striving to save and improve lives. Although many assume that the AHA works only within the borders of the United States, the association currently has a presence in >100 countries. AHA's International Committee helps define priorities for the AHA's global agenda. In 2012, that committee adopted the WHO's “25 by 25” goal for a 25% global reduction in premature mortality from noncommunicable diseases by the year 2025, with a focus on cardiovascular diseases rather than the broader WHO focus on noncommunicable diseases.¹⁵

Adoption of this global goal, combined with recognition that cardiovascular disease was the number one killer of people around the world, spurred increased advocacy within AHA for expanding international efforts. In 2018, the AHA announced a new mission “to be a relentless force for a world of longer, healthier lives,” embracing the challenge of promoting and improving cardiovascular health on the global stage. In the association's global work, RF and RHD are priority targets.

SUPPORTING AND ENHANCING THE GLOBAL RHD AGENDA

Despite an increasing interest in achieving RHD control, it would be a mistake to infer that there is currently a coordinated global RHD agenda. A number of important issues related to RHD have yet to be resolved among the technical community, and concrete, measurable, time-bound targets to track progress on implementing the World Health Assembly resolution are lacking.

An urgent first step is the development and adoption of national action plans in countries with endemic RHD populations. This will require securing political commitment and accountability from national and regional governments. These action plans should therefore originate from within ministries of health and place RHD efforts in the context of other relevant national strategies for child and adolescent health and noncommunicable disease. Countries should develop a small set of process targets (eg, increase in coverage

of prevention interventions, establishment of a registry, reductions in time on surgical wait lists). These process targets can help measure and guide progress of RHD control strategies.

Governments can consider a wide range of interventions when developing an approach to prevent and tackle RF and RHD (Tools for Implementing Rheumatic Heart Disease Control Programmes toolkit¹⁷). A comprehensive RHD program must address (1) Streptococcal A (Strep A) infections, RF, and RHD; (2) child health, maternal/fetal health, and adult health; and (3) preprimary (village level) care, primary care, and referral care. This means that any package of interventions must be delivered through a multisectoral program that is integrated across other areas of health and government policy. For example, interventions may include maternal/child health programs and be in collaboration with ministries responsible for education.

The prevention of RHD should be a priority for countries seeking to develop or expand universal health coverage to include interventions beyond communicable, maternal, and perinatal conditions. RHD prevention is very attractive across both cost-effectiveness and health equity dimensions¹⁸ and therefore can serve as an initial step to bolstering cardiovascular care. As an infection-related disease that can be driven down to very low absolute levels, it has much in common with current global priorities, and whenever possible, it should be framed as a vital extension of that agenda rather than as just another noncommunicable disease.^{19,20}

Health systems that address access to care, health-care quality, and healthcare efficiency are desirable for the successful organization of an RHD control program. Comprehensive RHD programs also can be used as demonstration projects to strengthen health systems because these programs deploy a broad range of interventions across all levels of the health system, from school-based sore throat care to open heart surgery. Treatment of acute pharyngitis in children to prevent RF (primary prevention) and secondary prophylaxis with penicillin for RF or RHD (secondary prevention) should be included in national essential health benefits packages.¹⁹ This will, in principle, guarantee access and low cost of care to patients and provide the backbone to a strategy that prioritizes the following 4 interventions: (1) development and maintenance of an RF/RHD registry, (2) health worker training, (3) access to benzathine penicillin G (BPG), and (4) access to cardiac ultrasound. These interventions have benefits that stretch well beyond RHD. An RHD program can bolster the public health infrastructure required to combat other chronic cardiovascular conditions²¹ (ischemic heart disease, hypertensive heart disease, congenital heart disease, dilated cardiomyopathy, pulmonary hypertension, and pericardial disease) and (interventions 3 and 4) provide leverage to improve maternal health issues (BPG for

maternal syphilis and shared ultrasound for obstetric imaging).

Although the recommended priority interventions are weighted toward primary and secondary prevention, it is essential that surgery, the last opportunity to save a life, is also emphasized. Many people living with RHD lack access to safe, high-quality surgery. Therefore, when considering RHD interventions, governments should work to improve access to lifesaving affordable surgical interventions for those with advanced valvular disease caused by RHD. This will require cooperation between endemic countries and international actors to achieve.

We recognize that funding is scarce in many RHD-endemic settings with competition from other important health agendas. Thus, we also urgently need a clear value proposition tailored to a range of LMICs across a range of economic development and disease burden to demonstrate that the long-term benefit of investing in RHD prevention and treatment far exceeds the upfront cost. An ongoing project, part of the AHA Strategically Focused Research Network, is collecting data in Uganda that can inform the development of a customizable national costing model. In an era of widespread political, economic, and social uncertainty, countries (and donors) may be reluctant to take on a new ambitious agenda for a new health problem. It is critical to emphasize that efforts to address RHD will also strengthen the health system, leading to improved primary care, health security, antimicrobial resistance, and care for noncommunicable diseases. However, even cost-effective programs may be unaffordable in the short term if constrained health budgets preclude additional investments. Therefore, additional efforts will be required to mobilize domestic resources. The RHD community needs to develop collaborations with health-financing experts and health ministries to develop best practices for raising funds to pay for RHD programs, particularly for cardiac surgery.

PRIORITY AREAS FOR AHA AND ITS MEMBERS

There is much to be done on the global stage to prevent new cases of RHD for the next generation and to strengthen disease management to improve the quality and longevity of life for those affected. Here, we have highlighted 5 priority areas where immediate action is possible and likely to have a major impact and where AHA involvement and leadership are essential. This does not represent a comprehensive program for RHD control, as has been outlined in the Tools for Implementing Rheumatic Heart Disease Control Programmes toolkit.¹⁷

Table 1. What Can the AHA and Its Members Do to Increase the Availability and Uptake of BPG

What should and can be done now
Support the development of an international BPG task force
Develop and disseminate the best science on real and perceived risks of BPG administration and support research to better quantify adverse reactions
Update scientific statements to include BPG best practices, including minimization of pain with administration, considerations in advanced RHD, and improved management of adverse drug reactions
Future priorities
Support research to reformulate BPG
Work with partners to strengthen global and national supply chains to improve access to avoid BPG stockouts

AHA indicates American Heart Association; BPG, benzathine penicillin G; and RHD, rheumatic heart disease.

Benzathine Penicillin G

BPG has been the mainstay of secondary prophylaxis (Table 1) to prevent RF since the product was developed in the 1950s.²² Administered every 3 or 4 weeks, BPG reduces Strep A infections, RF recurrences, and RHD-related mortality.^{23–25} It was initially hailed as a breakthrough disease-modifying drug, but 3 key limitations of BPG have become clear with widespread use. First, BPG in its current form is often problematic for both providers and patients for clinical and economic reasons. The poorly soluble powdered formulations are difficult to inject because they clump and block even large-gauge needles, and the injections themselves can be painful.^{26,27} With regard to cost, although the drug itself is inexpensive, it must be administered by trained providers. As a result, the cost of BPG for secondary prophylaxis is determined not by drug costs but by the cost of staffing and clinic infrastructure (and transportation costs when patients have to travel long distances to a clinic where it is administered). Second, there are widespread reports of adverse drug reactions in people with severe RHD receiving BPG for secondary prophylaxis.²⁸ Many of these events have ended in sudden death, and fearful providers and patients sometimes substitute less effective oral alternatives for BPG, leading to suppressed market demand in some settings. Ironically, emerging evidence suggests that some of these deaths may have been caused by cardiac decompensation from RHD rather than anaphylaxis to BPG.²⁹ Finally, BPG is often unavailable in countries with a high burden of RHD where need is greatest.³⁰ Inefficient or inadequate manufacturing capacity, poor procurement processes within countries, and supply chain disruptions lead to frequent stockouts in LMICs. These issues are exacerbated by small market size (given a declining number of clinical indications and frequent substitutions by providers) and the absence of a consolidated

global purchaser, further discouraging pharmaceutical investment in this area.³⁰

All of these issues have emerged because BPG is an old, inexpensive drug that no longer has patent protection and therefore is of minimal commercial interest to industry. The international community has not had a coordinated, public health–driven approach to monitor the availability of BPG or to advocate for reliable supplies. Both supply-side and demand-side initiatives are needed to improve access to and acceptability of BPG. In addressing demand, providers and patients require information about indications for BPG and the safety profile of the product. This will require new data on adverse events to provide contemporary evidence of risk, as the Rheumatic Fever Study Group did in the late 1980s.³¹ Best practices in administering BPG in a way that minimizes pain and risk of severe allergic reactions need to be developed and disseminated. Training on emergency management of anaphylaxis and other adverse reactions is required at all levels of the health system. On the supply side, BPG manufacturers should be engaged in global efforts to end RHD. Supply may be supported with predictable product procurement patterns, pooled procurement by group purchaser demand estimates, and potentially, advance market commitments to incentivize reliable, high-quality supply. In parallel, research is needed to better define the pharmacokinetics of existing products and to potentiate the development of new formulations.^{29,32} For example, work is underway in Australia to determine whether subcutaneous administration of BPG is pharmacokinetically equivalent to intramuscular administration and whether this formulation is more acceptable to patients. Studies are also ongoing to develop longer-acting formulations such as implants, which would avoid the need for monthly injections.

Strep A Vaccine

RF and RHD are potentially vaccine-preventable diseases. Indeed, an effective and safe vaccine against Strep A (Table 2) is an exciting opportunity to permanently eliminate RF within the next few decades. A Strep A vaccine could be effective against not only RF/RHD but also superficial infections (eg, pharyngitis, impetigo), poststreptococcal glomerulonephritis, and invasive disease (eg, bacteremia, cellulitis, necrotizing fasciitis, and strep toxic shock syndrome). Together, these diseases cause >500 000 deaths per year, making Strep A the fifth most lethal pathogen on the planet (Figure 1).³³ Despite this, between 2007 and 2017, all-source funding for Strep A vaccine research and development was equivalent to US \$35 per annual death, compared with US \$5411 per annual death spent on research and development for an HIV vaccine (Figure 1).³⁴ Strep A

Table 2. What Can the AHA and Its Members Do to Move Strep A Vaccine Development Forward?

What should and can be done now
Support the development of the WHO Public Health Value Proposition for Strep A vaccines as proposed by the global SAVAC
Contribute expertise and research support to collaborative international groups working to close knowledge gaps related to global epidemiology, vaccine safety, vaccine design and development, vaccine efficacy, and laboratory assays to establish immune correlates
Future priorities
Support efforts for WHO prequalification of a Strep A vaccine (assurance of safe/effective vaccine with efficacy data relevant for the target populations that meet the practical needs of the vaccine program [ie, potency, thermostability, presentation, labelling])

AHA indicates American Heart Association; SAVAC, Strep A Vaccine Consortium; Strep A, Streptococcal A; and WHO, World Health Organization.

vaccine research and development expenditures were only 0.17% of the combined total spent for vaccine development for HIV, malaria, and tuberculosis, and no major vaccine manufacturer has an active Strep A vaccine program.

The development of a Strep A vaccine faces numerous challenges. Strep A has a complex global epidemiology, including geographic diversity in burden, types of presentation (skin, throat, invasive infections, immune sequelae), and *emm* type (the most studied vaccine candidate is *emm*-type specific).³⁶ More than 95% of serious Strep A diseases occur in LMICs,³⁵ where return on investment for industry is perceived to be low. Advocacy for a Strep A vaccine in high-income countries has been low, despite the fact that Strep A accounts for a high burden of devastating illness and death (much greater than pathogens such as meningococcus³⁷ that are widely recognized as such). Strep A pharyngitis causes enormous morbidity in high-income countries, costing \$224 to \$539 million in the United States alone.³⁸ Concerns about Strep A pharyngitis led to a large number of antibiotic prescriptions, thus contributing to emerging antimicrobial resistance.³⁸ There are also perceived technical concerns. In 1969, there was a single report of 3 cases of RF in the 2 years after administration of an experimental streptococcal vaccine.³⁹ Despite multiple flaws in this study, weak evidence of causality, and the use of massive doses of a very crude vaccine, this report led to a US Food and Drug Administration ban on Strep A vaccine development until 2006.⁴⁰

However, recent years have seen some progress. In addition to the 2018 WHO Global Resolution on RF/RHD, the WHO sponsored the publication of 2 consensus documents: a Group A Streptococcal Vaccine Research and Development Roadmap and a Preferred Product Characteristics document.⁴¹ In 2019, with Wellcome Trust support, SAVAC (Strep A Vaccine Consortium) was formed, and in that same year, the government of Australia committed AU \$35 million to support the progress of a Strep A vaccine into a phase

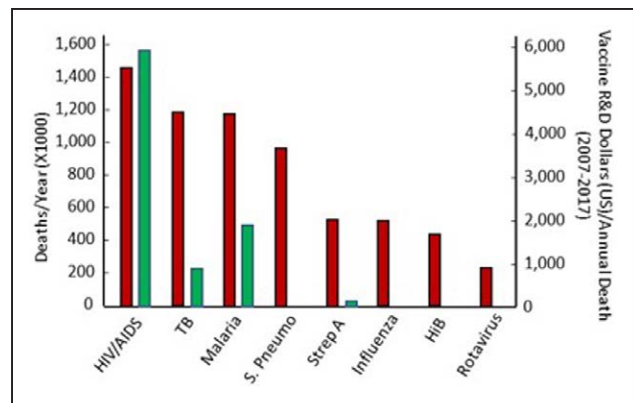


Figure 1. Annual mortality* (2010 GBD [Global Burden of Disease]³³) attributed to the 8 leading infectious agents (red) with all-source research and development (R&D) funding for vaccine development (green) for pathogens without a vaccine (G-FINDER, 2007–2017).³⁴

*Streptococcal A (Strep A) annual mortality combined from 2010 GBD³³ annual rheumatic heart disease–related deaths (345 000 per year) added to previous estimates of death resulting from invasive Strep A diseases (163 000).³⁵ Hib indicates *Haemophilus influenzae*; S. Pneumo, *Streptococcus pneumoniae*; and TB, tuberculosis.

2b efficacy trial against pharyngitis within 5 years (through ASAVI [Australian Strep A Vaccine Initiative]). The global consortium is working with the WHO to develop a Public Health Value Proposition that outlines the global health investment benefits and the industry business case for the Strep A vaccine.

Primary and Secondary Prevention of RHD

Primary prevention involves the diagnosis of Strep A sore throat and the treatment with an appropriate course of antibiotics (Table 3). There is strong evidence that primary prevention can reduce the incidence of RF by more than two-thirds.^{42,43} Primary prevention was the cornerstone of successful national RHD control programs in Cuba⁴⁴ and Costa Rica.⁴⁵ However, Strep A diagnosis is not simple, particularly in low-resource settings, and not all immunologically important Strep A infections are symptomatic. The clinical history and presentation of Strep A overlap those of viral and environmental sore throats.^{46,47} Clinical predication scores have shown only moderate discrimination between those with and those without Strep A pharyngitis.⁴⁸ Rapid antigen tests, molecular assays, and microbiological cultures (gold standard) are used in higher-income settings, but they present cost and storage challenges for low-resource settings. Strep A skin infection may contribute to RF/RHD in some areas, in particular the Pacific, but causality has not been definitely determined.⁴⁹ Despite these challenges, there is an urgent need to ramp up primary prevention efforts in RHD-endemic settings. Primary healthcare strengthening should be prioritized, including public and healthcare worker education and

Table 3. What Can the AHA and Its Members Do to Support and Enhance Primary and Secondary Prevention

What should and can be done now
Support the development of approaches to strengthen and decentralize register-based RHD care
Develop and disseminate healthcare worker training for diagnosis and treatment of Strep A sore throat, RF, and RHD
Future priorities
Support research to develop more accurate, more portable, and more affordable diagnostics for Strep A pharyngitis, RF, and RHD
Support policy and implementation research that can inform the development of integrated national RF/RHD control programs and document and disseminate best practices

AHA indicates American Heart Association; RF, rheumatic fever; RHD, rheumatic heart disease; and Strep A, Streptococcal A.

assurance of essential medications in the community, including BPG and oral penicillins.

Secondary prevention of RF/RHD (Table 3) comprises regular administration of BPG to individuals with RF or RHD to prevent recurrent Strep A sore throat.²³ Strong evidence supports that BPG can prevent RF recurrence, although data are lacking that BPG is protective against the development of chronic RHD or mortality from RHD.²³ Delivery of secondary prophylaxis is best done through registries, but further research and development efforts are needed to decentralize registry-based care in RHD-endemic settings. This includes exploring mobile health solutions to enable data entry and access in the community and to embed interactive features to strengthen clinical care. Future research advances to improve the sensitivity and specificity of RF diagnosis, to trial existing and novel therapeutics to reduce the progression from RF to RHD,⁵⁰ and to improve early diagnosis of RHD may also contribute substantially to reducing the number of people who develop advanced RHD.

Tertiary Care for RHD

Most RHD morbidity and mortality occur among people with moderate to severe valve disease and are caused by progressive heart failure (the largest contributor),⁵¹ cardiac arrhythmia, stroke, and infective endocarditis.^{6,52,53} To date, there has been very little research investment in the medical management of RHD (Table 4). There are no contemporary data on the effectiveness and safety of commonly used medications for RHD-related heart failure, anticoagulation, or arrhythmia and little ongoing research on new drugs.^{34,54} Clinical research should be complemented with (1) evaluating the implementation of strategies to manage patients with RHD; (2) collecting patient-important outcomes such as quality-adjusted survival, progression of heart failure, and incident of stroke; and (3) tracking economic outcomes such as incremental cost-effectiveness compared with usual care.

Table 4. What Can the AHA and Its Members Do to Strengthen Tertiary Care for Patients Living With RHD

What should and can be done now
Develop and disseminate the best science on delivering high-quality tertiary care for RHD in low-resource settings
Future priorities
Foster the creation of multinational RHD research consortia to identify treatments and strategies to improve patient-important clinical outcomes in established RHD
Lend support and expertise to initiatives that use telemedicine/telecardiology to improve capacity at the point of care in RHD-endemic regions, including mobile health interventions to support patient care and medical adherence

AHA indicates American Heart Association; and RHD, rheumatic heart disease.

Both clinical and economic data will be critical to convincing health systems to make additional investments in RHD prevention and treatment. The digoxin subanalysis of the REMEDY study (Global Rheumatic Heart Disease Registry)⁵⁴ and the INVICTUS trial (Investigation of Rheumatic Atrial Fibrillation Treatment Using Vitamin K Antagonists, Rivaroxaban or Aspirin Studies; URL: ClinicalTrials.gov. Unique identifier: NCT02832544) serve as models.

There is also inequity in access to tertiary services for RHD. When available, services are concentrated in urban areas and serve mainly those with higher incomes, whereas RHD tends to be concentrated in the poorest populations and in rural areas. Shortages of trained personnel and well-equipped tertiary care cardiac centers, weak referral systems, and high fixed costs⁵⁶ lead to inefficient delivery systems that have high per-patient costs. Hence, in many countries, tertiary RHD services, even when available, can be prohibitively expensive. This poses a substantial barrier to uptake among low-socioeconomic sections of the population who are disproportionately affected by RHD. One potential solution to improve access is for countries to pool resources from governmental and nongovernmental donors to develop regional centers of excellence for cardiac care, which can then serve as referral centers for advanced care and training across national borders.⁵⁷ Establishing telemedicine links with international medical centers can also help providers in poor countries seek advice on diagnosis and treatment. Several such centers already exist in parts of Africa⁵⁷ and in Brazil.⁵⁸

Investment in improved medical management and access to interventional procedures and surgery are potentially the most immediate ways to achieve the short-term mortality reductions in RHD envisaged in the Sustainable Development Goals.⁵⁹ Further research, as outlined, is needed to guide evidence-based strategies and investment. Tertiary care for RHD is a critical part of a national care program. However, it carries high capital costs that must be balanced against national strategies for primary and secondary prophylaxis, which may be

Table 5. What Can the AHA and Its Members Do to Strengthen Primordial Prevention

What should and can be done now
Develop and disseminate health promotion and education around Strep A transmission
Bring together and partner with experts in public health and government sectors to develop effective strategies
Future priorities
Support high-quality research to better quantify the association between primordial risk factors and RF/RHD development
Develop a road map for the primordial prevention of CVD (including RF/RHD)

AHA indicates American Heart Association; CVD, cardiovascular disease; RF, rheumatic fever; RHD, rheumatic heart disease; and Strep A, Streptococcal A.

more cost-effective in the long term and result in fewer patients requiring cardiac intervention.

Social Determinants of Health

Environmental exposures related to conditions of poverty contribute to the development of RF/RHD among children and explain its persistence in certain communities (Table 5).^{7,60–63} Primordial prevention, or the reduction in exposure to and transmission of Strep A, is an essential component of a comprehensive strategy to reduce the burden of RHD. However, primordial prevention is rarely discussed as a practical strategy for RHD control because (1) it is an enormous and complex undertaking, (2) there is a strong yet unsubstantiated belief that social determinants are not amenable to specific interventions, and (3) there is a challenge in identifying targets for intervention because many overlap within or vary between at-risk populations. Evaluating the impact of interventions also poses a challenge; RF is relatively rare and challenging to diagnose, so accurate surveillance systems are hard to establish in resource-limited settings. RHD, which can be diagnosed through echocardiographic screening, typically occurs after a significant time lag and therefore may not be a timely marker of success for an intervention targeting social determinants of health. Despite these hurdles, social determinants of health should remain a target of RHD prevention efforts given the critical role they play in the development of RF and many other diseases.

To effectively bring about improvements in primordial prevention, the RHD community must engage more deeply with the public health sector, local and national governments, international health and aid organizations (WHO, United Nations, United Nations Children's Fund), and people living with RHD or in high-RHD-risk communities. Identification of a set of practical environmental strategies to reduce Strep A transmission, in particular packaged to prevent a range of pediatric infectious diseases such as New Zealand's Healthy

Homes initiative,⁶⁴ is one potential strategy. Modifiable risks with the strongest evidence such as overcrowding should be prioritized. Leveraging RHD as an advocacy tool for environmental health and social equity may be another effective angle. Use of demonstration communities to systematically roll out interventions and to intensively track impact may provide needed evidence to catalyze large-scale investment.

A CALL TO ACTION TO THE AHA COMMUNITY IN THE UNITED STATES

Reducing death and disability from RHD globally will require a concerted multinational, interorganizational effort. However, specific contributions of individual AHA members and the AHA community should not be underestimated. We propose the following specific actions.

At the local level, members and local chapters across the United States should connect with local immigrant health groups to raise awareness about RHD, particularly those who work with immigrants from RHD-endemic countries.⁶ Resources for organizing such events are available online.¹³ This will benefit local immigrant populations who may experience higher rates of RHD and may forge new relationships with RHD-focused organizations in their countries of origin.

At the national level, RHD remains a condition of health disparities in the United States.⁶⁵ RHD mortality parallels other cardiovascular disease disparity, with hot spots along the Mississippi River Valley, southern states, and western states.⁶⁶ Available data suggest an urgent need to improve epidemiological surveillance in these areas and among other high-risk groups such as Native Americans,⁶⁷ Alaskan Natives, Hawaiian Natives, and those living in Puerto Rico or one of the US Pacific territories. Recent echocardiographic surveillance in American Samoan youth detected RHD at endemic rates.⁶⁸ AHA community members living in high-risk areas or working with high-risk populations should ensure proficiency with these conditions and work to educate other healthcare providers about local RHD efforts. The continued presence of RHD among the nation's most underserved communities highlights the continued role that the AHA must play in advocating for improved RHD detection and prevention efforts.

Within the AHA, the Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee is charged with developing RF guidelines, scientific statements, and conference programming related to RHD; however, each AHA council should consider how RHD can be incorporated into the activities and vision of that council. As an example, the Epidemiology Council has long maintained a section of the Heart Disease and Stroke

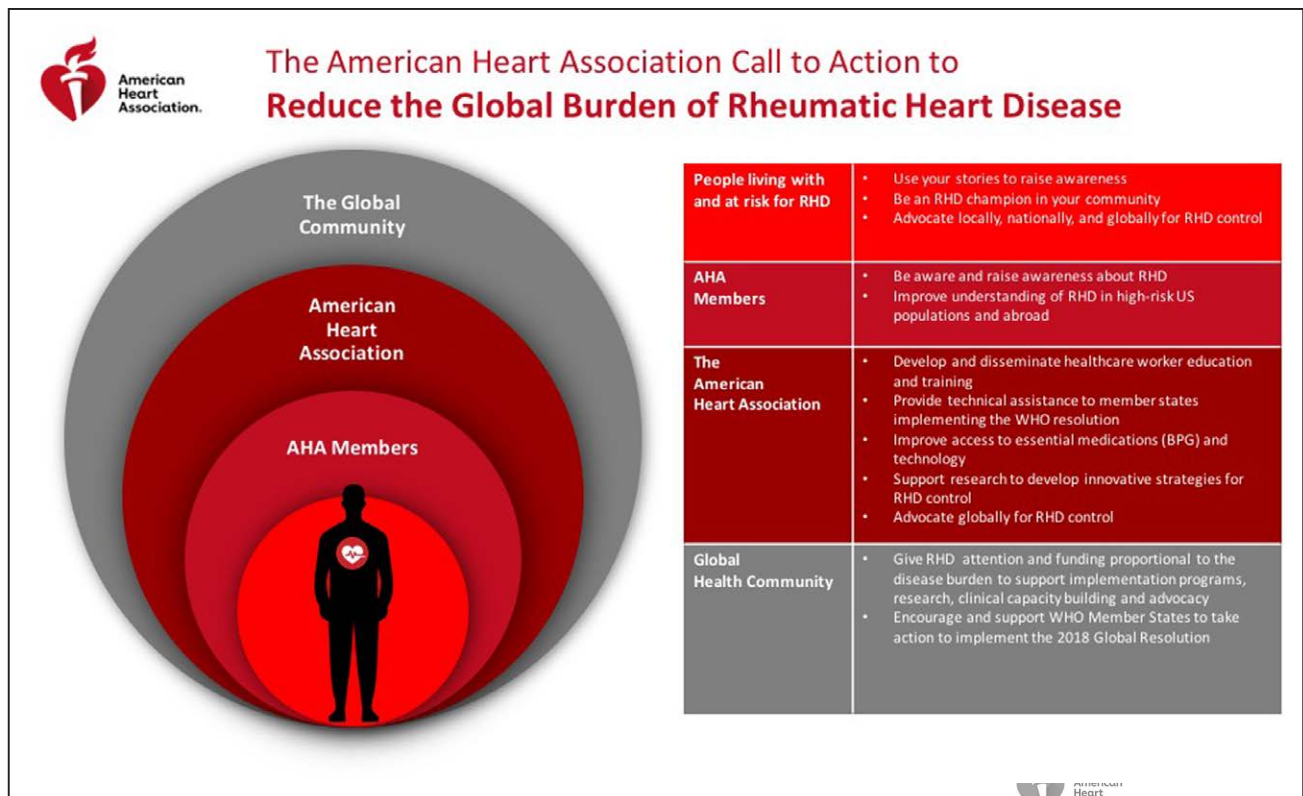


Figure 2. The American Heart Association’s (AHA) call to action to reduce the global burden of rheumatic heart disease (RHD). BPG indicates benzathine penicillin G; and WHO, World Health Organization.

Statistics⁶⁹ document devoted to RF and RHD. Furthermore, we call on AHA members to develop innovative basic, clinical, and population health research that will overcome existing barriers to RHD control.

4. We will support research to advance innovative solutions for the prevention, diagnosis, and treatment of RF/RHD.
5. We will advocate for increased global awareness, resources, and capacity for RHD control.

In bolstering the efforts of the AHA to combat RHD, we hope to inspire others to collaborate, communicate, and contribute (Figure 2).

THE AHA COMMITMENT

Ninety-five years after its foundation, the AHA renews its commitment to serve as a global champion and leader in RHD care and prevention. We believe that, through partnership with other nongovernmental organizations, sister societies, and ministries of health in affected countries, disparities in RHD disease burden can be greatly reduced. We commit to keeping people living with RHD and at risk for RHD at the center of our strategy and pledge support in 5 key areas over the next 5 years:

1. We will develop and disseminate professional healthcare worker education and training on evidence-based strategies for RF/RHD prevention and management.
2. We will provide technical support for the implementation of evidence-based strategies for RF/RHD prevention and control by governments.
3. We will facilitate the access of at-risk populations to essential medications (including BPG) and technologies.

ARTICLE INFORMATION

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This policy statement was approved by the American Heart Association Advocacy Coordinating Committee on July 15, 2020, and the American Heart Association Executive Committee on August 10, 2020. A copy of the document is available at <https://professional.heart.org/statements> by using either “Search for Guidelines & Statements” or the “Browse by Topic” area. To purchase additional reprints, call 215-356-2721 or email Meredith.Edelman@wolterskluwer.com.

Supplemental materials are available with this article at <https://www.ahajournals.org/doi/suppl/10.1161/CIR.0000000000000922>.

The American Heart Association requests that this document be cited as follows: Beaton A, Kamalembo FB, Dale J, Kado JH, Karthikeyan G, Kazi DS, Longenecker CT, Mwangi J, Okello E, Ribeiro ALP, Taubert KA, Watkins DA, Wyber R, Zimmerman M, Carapetis J; on behalf of the American Heart Association Young Hearts Rheumatic Fever, Endocarditis and Kawasaki Disease Committee of the Council on Lifelong Congenital Heart Disease and Heart Health in the Young; Advocacy Coordinating Committee; Council on Cardiovascular and Stroke Nursing; and Council on Clinical Cardiology. The American Heart Association’s call to action for reducing the global burden of rheumatic heart

disease: a policy statement from the American Heart Association. *Circulation*. 2020;142:e000–000. doi: 10.1161/CIR.0000000000000922

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Disclosures

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*Modest.
†Significant.

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REFERENCES

- Shulman ST. Rheumatic fever. In: Kleigman RM, Stamdpm BF, St. Geme J, Shor NF eds. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia, PA: Elsevier; 2016: 1332–1337.
- Chapelle C. *The New York Heart Association: Origins and Development 1915–1965*. New York; New York Heart Association; 1966.
- Churchill JF. American Heart Association: its plan and work. *Cal West Med*. 1928;28:776–779.
- GBD Disease Injury Incidence Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392:1789–1858. doi: 10.1016/S0140-6736(18)32279-7
- World Health Organization. Rheumatic fever and rheumatic heart disease, 2018: Executive Board, 141st Session: resolutions and decisions, annexes, summary records. Geneva, Switzerland. https://www.who.int/cardiovascular_diseases/publications/trs923/en. Accessed July 25, 2020.
- Watkins DA, Johnson CO, Colquhoun SM, Karthikeyan G, Beaton A, Bukhman G, Forouzanfar MH, Longenecker CT, Mayosi BM, Mensah GA, et al. Global, regional, and national burden of rheumatic heart disease, 1990–2015. *N Engl J Med*. 2017;377:713–722.
- Rothenbühler M, O'Sullivan CJ, Stortecy S, Stefanini GG, Spitzer E, Estill J, Shrestha NR, Keiser O, Jüni P, Pilgrim T. Active surveillance for rheumatic heart disease in endemic regions: a systematic review and meta-analysis of prevalence among children and adolescents. *Lancet Glob Health*. 2014;2:e717–e726. doi: 10.1016/S2214-109X(14)70310-9
- Watkins D, Zuhlke L, Engel M, Daniels R, Francis V, Shaboodien G, Kango M, Abul-Fadl A, Adeoye A, Ali S, et al. Seven key actions to eradicate rheumatic heart disease in Africa: the Addis Ababa communiqué. *Cardiovasc J Afr*. 2016;27:184–187. doi: 10.5830/CVJA-2015-090
- AMA report card on indigenous health 2016: a call to action to prevent new cases of rheumatic heart disease in Indigenous Australia by 2031. 2016. <https://ama.com.au/article/2016-ama-report-card-indigenous-health-call-action-prevent-new-cases-rheumatic-heart-disease>. Accessed July 25, 2020.
- Colquhoun SM, Carapetis JR, Kado JH, Steer AC. Rheumatic heart disease and its control in the Pacific. *Expert Rev Cardiovasc Ther*. 2009;7:1517–1524. doi: 10.1586/erc.09.145
- Carapetis JR, Zühlke LJ. Global research priorities in rheumatic fever and rheumatic heart disease. *Ann Pediatr Cardiol*. 2011;4:4–12. doi: 10.4103/0974-2069.79616
- World Heart Federation. <https://www.world-heart-federation.org/>. Accessed July 28, 2020.
- RHD Action. <http://rhdaction.org/>. Accessed July 28, 2020.
- Reach. <https://stoprhd.org/>. Accessed July 28, 2020.
- Sacco RL, Roth GA, Reddy KS, Arnett DK, Bonita R, Gaziano TA, Heidenreich PA, Huffman MD, Mayosi BM, Mendis S, et al. The Heart of 25 by 25: achieving the goal of reducing global and regional premature deaths from cardiovascular diseases and stroke: a modeling study from the American Heart Association and World Heart Federation. *Circulation*. 2016;133:e674–e690. doi: 10.1161/CIR.0000000000000395
- Deleted in proof.
- Wyber R, Grainger Gasser A, Thompson D, Kennedy D, Johnson T, Taubert K, Carapetis J. *Tools for Implementing RHD Control Programmes (TIPS) Handbook*. Perth, Australia; World Heart Federation and RhEACH; 2014.
- Watkins DA, Jamison DT, Mills T, Atun T, Danforth K, Glassman A, Horton S, Jha P, Kruk ME, Norheim OF, et al. Universal health coverage and essential packages of care. In: Jamison DT, Gelband H, Horton S, Jha P, Laxminarayan R, Mock CN, Nugent R, eds. *Disease Control Priorities: Improving Health and Reducing Poverty*. Washington, DC; International Bank for Reconstruction and Development/The World Bank; 2017.
- Watkins DA, Yamey G, Schäferhoff M, Adeyi O, Alleyne G, Alwan A, Berkley S, Feachem R, Frenk J, Ghosh G, et al. Alma-Ata at 40 years: reflections from *The Lancet* Commission on Investing in Health. *Lancet*. 2018;392:1434–1460. doi: 10.1016/S0140-6736(18)32389-4
- Katzenellenbogen JM, Ralph AP, Wyber R, Carapetis JR. Rheumatic heart disease: infectious disease origin, chronic care approach. *BMC Health Serv Res*. 2017;17:793. doi: 10.1186/s12913-017-2747-5
- Longenecker CT, Kalra A, Okello E, Lwabi P, Omagino JO, Kityo C, Kanya MR, Weibel AR, Simon DI, Salata RA, et al. A human-centered approach to CV care: infrastructure development in Uganda. *Glob Heart*. 2018;13:347–354. doi: 10.1016/j.gheart.2018.02.002
- Wyber R, Carapetis J. Evolution, evidence and effect of secondary prophylaxis against rheumatic fever. *J Pract Cardiovasc Sci*. 2015;1:9–14.
- Manyemba J, Mayosi BM. Penicillin for secondary prevention of rheumatic fever. *Cochrane Database Syst Rev*. 2002;CD002227. doi: 10.1002/14651858.CD002227
- de Dassel JL, de Klerk N, Carapetis JR, Ralph AP. How many doses make a difference? An analysis of secondary prevention of rheumatic fever and rheumatic heart disease. *J Am Heart Assoc*. 2018;7:e010223. doi: 10.1161/JAHA.118.010223
- Okello E, Longenecker CT, Beaton A, Kanya MR, Lwabi P. Rheumatic heart disease in Uganda: predictors of morbidity and mortality one year after presentation. *BMC Cardiovasc Disord*. 2017;17:20. doi: 10.1186/s12872-016-0451-8
- Wyber R, Taubert K, Marko S, Kaplan EL. Benzathine penicillin G for the management of RHD: concerns about quality and access, and opportunities for intervention and improvement. *Glob Heart*. 2013;8:227–234. doi: 10.1016/j.gheart.2013.08.011
- Wyber R, Boyd JB, Colquhoun S, Currie JB, Engel M, Kado J, Karthikeyan G, Sullivan M, Saxena A, Sheel M, et al. Preliminary consultation on preferred product characteristics of benzathine penicillin G for secondary prophylaxis of rheumatic fever. *Drug Deliv Transl Res*. 2016;6:572–578. doi: 10.1007/s13346-016-0313-z
- Marantelli S, Hand R, Carapetis J, Beaton A, Wyber R. Severe adverse events following benzathine penicillin G injection for rheumatic heart disease prophylaxis: cardiac compromise more likely than anaphylaxis. *Heart Asia*. 2019;11:e011191. doi: 10.1136/heartasia-2019-011191
- Montagnat OD, Webster GR, Bullita J, Landersdorfer C, Wyber R, Sheel M, Carapetis JR, Boyd BJ. Lessons learned in the development of sustained release penicillin drug delivery systems for the prophylactic treatment of rheumatic heart disease (RHD). *Drug Deliv Transl Res*. 2018;8:729–739. doi: 10.1007/s13346-018-0482-z
- Nurse-Findlay S, Taylor MM, Savage M, Mello MB, Saliyou S, Lavayen M, Seghers F, Campbell ML, Birgirirmana F, Ouedraogo L, et al. Shortages of benzathine penicillin for prevention of mother-to-child transmission of syphilis: an evaluation from multi-country surveys and stakeholder interviews. *PLoS Med*. 2017;14:e1002473. doi: 10.1371/journal.pmed.1002473

31. Markowitz M, Kaplan E, Cuttica R, Berrios X, Huang Z, Rao X, Wahi P, Bali H, Millard D, Choi J, et al. Allergic reactions to long-term benzathine penicillin prophylaxis for rheumatic fever: International Rheumatic Fever Study Group. *Lancet*. 1991;337:1308–1310.
32. Hand RM, Salman S, Newall N, Vine J, Page-Sharp M, Bowen AC, Gray K, Baker A, Kado J, Joseph J, et al. A population pharmacokinetic study of benzathine benzylpenicillin G administration in children and adolescents with rheumatic heart disease: new insights for improved secondary prophylaxis strategies. *J Antimicrob Chemother*. 2019;74:1984–1991. doi: 10.1093/jac/dkz076
33. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn SY, 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;380:2095–2128. doi: 10.1016/S0140-6736(12)61728-0
34. Policy Cures Research. G-FINDER data portal. <https://gfinderdata.policycuresresearch.org/>. Accessed July 25, 2020.
35. Carapetis JR, Steer AC, Mulholland EK, Weber M. The global burden of group A streptococcal diseases. *Lancet Infect Dis*. 2005;5:685–694. doi: 10.1016/S1473-3099(05)70267-X
36. Steer AC, Law I, Matatolu L, Beall BW, Carapetis JR. Global emm type distribution of group A streptococci: systematic review and implications for vaccine development. *Lancet Infect Dis*. 2009;9:611–616. doi: 10.1016/S1473-3099(09)70178-1
37. Bisno AL, Rubin FA, Cleary PP, Dale JB; National Institute of Allergy and Infectious Diseases. Prospects for a group A streptococcal vaccine: rationale, feasibility, and obstacles: report of a National Institute of Allergy and Infectious Diseases workshop. *Clin Infect Dis*. 2005;41:1150–1156. doi: 10.1086/444505
38. Pfoh E, Wessels MR, Goldmann D, Lee GM. Burden and economic cost of group A streptococcal pharyngitis. *Pediatrics*. 2008;121:229–234. doi: 10.1542/peds.2007-0484
39. Massell BF, Honikman LH, Amezcua J. Rheumatic fever following streptococcal vaccination: report of three cases. *JAMA*. 1969;207:1115–1119.
40. Dale JB, Batzloff MR, Cleary PP, Courtney HS, Good MF, Grandi G, Halperin S, Margarit IY, McNeil S, Pandey M, et al. Current approaches to group A streptococcal vaccine development. In: Ferretti JJ, Stevens DL, Fischetti VA, eds. *Streptococcus pyogenes: Basic Biology to Clinical Manifestations*. Oklahoma City, OK: University of Oklahoma Health Sciences Center; 2016.
41. Vekemans J, Gouvea-Reis F, Kim JH, Excler JL, Smeesters PR, O'Brien KL, Van Beneden CA, Steer AC, Carapetis JR, Kaslow DC. The path to group A streptococcus vaccines: WHO research and development technology roadmap and preferred product characteristics. *Clin Infect Dis*. 2019;69:877–883. doi: 10.1093/cid/ciy1143
42. Spinks A, Glasziou PP, DelMar CB. Antibiotics for sore throat. *Cochrane Database Syst Rev*. 2013;CD000023. doi: 10.1002/14651858.CD000023.pub4
43. Robertson KA, Volmink JA, Mayosi BM. Antibiotics for the primary prevention of acute rheumatic fever: a meta-analysis. *BMC Cardiovasc Disord*. 2005;5:11. doi: 10.1186/1471-2261-5-11
44. Nordet P, Lopez R, Dueñas A, Sarmiento L. Prevention and control of rheumatic fever and rheumatic heart disease: the Cuban experience (1986–1996–2002). *Cardiovasc J Afr*. 2008;19:135–140.
45. Arguedas A, Mohs E. Prevention of rheumatic fever in Costa Rica. *J Pediatr*. 1992;121:569–572. doi: 10.1016/S0022-3476(05)81146-1
46. Cornfeld D, Hubbard JP, Harris TN, Weaver R. Epidemiologic studies of streptococcal infection in school children. *Am J Public Health Nations Health*. 1961;51:242–249. doi: 10.2105/ajph.51.2.242
47. Danchin MH, Rogers S, Kelpie L, Selvaraj G, Curtis N, Carlin JB, Nolan TM, Carapetis JR. Burden of acute sore throat and group A streptococcal pharyngitis in school-aged children and their families in Australia. *Pediatrics*. 2007;120:950–957. doi: 10.1542/peds.2006-3368
48. Fischer Walker CL, Rimoin AW, Hamza HS, Steinhoff MC. Comparison of clinical prediction rules for management of pharyngitis in settings with limited resources. *J Pediatr*. 2006;149:64–71. doi: 10.1016/j.jpeds.2006.03.005
49. Parks T, Smeesters PR, Steer AC. Streptococcal skin infection and rheumatic heart disease. *Curr Opin Infect Dis*. 2012;25:145–153. doi: 10.1097/QCO.0b013e3283511d27
50. Cilliers A, Adler AJ, Saloojee H. Anti-inflammatory treatment for carditis in acute rheumatic fever. *Cochrane Database Syst Rev*. 2015;CD003176. doi: 10.1002/14651858.CD003176.pub3
51. Zühlke L, Karthikeyan G, Engel ME, Rangarajan S, Mackie P, Cupido-Katya Mauff B, Islam S, Daniels R, Francis V, Ogendo S, et al. Clinical outcomes in 3343 children and adults with rheumatic heart disease from 14 low- and middle-income countries: two-year follow-up of the Global Rheumatic Heart Disease Registry (the REMEDY Study). *Circulation*. 2016;134:1456–1466. doi: 10.1161/CIRCULATIONAHA.116.024769
52. Wang D, Liu M, Lin S, Hao Z, Tao W, Chen X, Luan R, Dong W. Stroke and rheumatic heart disease: a systematic review of observational studies. *Clin Neurol Neurosurg*. 2013;115:1575–1582. doi: 10.1016/j.clineuro.2013.06.017
53. Karthikeyan G, Ananthkrishnan R, Devasenapathy N, Narang R, Yadav R, Seth S, Singh S, Goswami KC, Bahl VK. Transient, subclinical atrial fibrillation and risk of systemic embolism in patients with rheumatic mitral stenosis in sinus rhythm. *Am J Cardiol*. 2014;114:869–874. doi: 10.1016/j.amjcard.2014.06.016
54. Karthikeyan G, Devasenapathy N, Zühlke L, Engel ME, Rangarajan S, Teo KK, Mayosi BM, Yusuf S; Global Rheumatic Heart Disease Registry (REMEDY) Investigators. Digoxin and clinical outcomes in the Global Rheumatic Heart Disease Registry. *Heart*. 2019;105:363–369. doi: 10.1136/heartjnl-2018-313614
55. Deleted in proof.
56. Zilla P, Yacoub M, Zühlke L, Beyersdorf F, Sliwa K, Khubulava G, Bouzid A, Mocumbi AO, Velayoudam D, Shetty D, et al. Global unmet needs in cardiac surgery. *Glob Heart*. 2018;13:293–303. doi: 10.1016/j.ghheart.2018.08.002
57. Yacoub M, ElGuindy A, Afifi A, Yacoub L, Wright G. Taking cardiac surgery to the people. *J Cardiovasc Transl Res*. 2014;7:797–802. doi: 10.1007/s12265-014-9598-9
58. Lopes EL, Beaton AZ, Nascimento BR, Tompsett A, Dos Santos JP, Perlman L, Diamantino AC, Oliveira KK, Oliveira CM, Nunes MDCP, et al; Programa de Rastreamento da Valvopatia Reumática (PROVAR) Investigators. Telehealth solutions to enable global collaboration in rheumatic heart disease screening. *J Telemed Telecare*. 2018;24:101–109. doi: 10.1177/1357633X16677902
59. United Nations Department of Social and Economic Affairs. *The Sustainable Development Goals Report 2018*. New York, NY: United Nations; 2018.
60. Brown A, McDonald MI, Calma T. Rheumatic fever and social justice. *Med J Aust*. 2007;186:557–558.
61. Riaz BK, Selim S, Karim MN, Chowdhury KN, Chowdhury SH, Rahman MR. Risk factors of rheumatic heart disease in Bangladesh: a case-control study. *J Health Popul Nutr*. 2013;31:70–77. doi: 10.3329/jhpn.v31i1.14751
62. Steer AC, Carapetis JR, Nolan TM, Shann F. Systematic review of rheumatic heart disease prevalence in children in developing countries: the role of environmental factors. *J Paediatr Child Health*. 2002;38:229–234. doi: 10.1046/j.1440-1754.2002.00772.x
63. Coffey PM, Ralph AP, Krause VL. The role of social determinants of health in the risk and prevention of group A streptococcal infection, acute rheumatic fever and rheumatic heart disease: a systematic review. *PLoS Negl Trop Dis*. 2018;12:e0006577. doi: 10.1371/journal.pntd.0006577
64. Ministry of Health, New Zealand. <https://www.health.govt.nz>. Accessed July 25, 2020.
65. Doukky R, Abusin SA, Bayissa YA, Kelly RF, Ansari AH. Rheumatic heart disease in modern urban America: a cohort study of immigrant and indigenous patients in Chicago. *Int J Cardiol*. 2014;175:178–180. doi: 10.1016/j.ijcard.2014.04.207
66. Global Burden of Cardiovascular Diseases Collaboration, Roth GA, Johnson CO, Abate KH, Abd-Allah F, Ahmed M, Alam K, Alam T, Alvis-Guzman N, Ansari H, Arnlov J, et al. The burden of cardiovascular diseases among US states, 1990–2016. *JAMA Cardiol*. 2018;3:375–389. doi: 10.1001/jamacardio.2018.0385
67. Gordon J, Kirlew M, Schreiber Y, Saginur R, Bocking N, Blakelock B, Haavaldsrud M, Kennedy C, Farrell T, Douglas L, et al. Acute rheumatic fever in First Nations communities in northwestern Ontario: social determinants of health “bite the heart.” *Can Fam Physician*. 2015;61:881–886.
68. Huang JH, Favazza M, Legg A, Holmes KW, Armsby L, Eliapo-Unutoa I, Pilgrim T, Madriago EJ. Echocardiographic screening of rheumatic heart disease in American Samoa. *Pediatr Cardiol*. 2018;39:38–44. doi: 10.1007/s00246-017-1724-4
69. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Delling FN, et al; on behalf of the American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2020 update: a report from the American Heart Association. *Circulation*. 2020;141:e139–e596. doi: 10.1161/CIR.0000000000000757