

The WHF Roadmap for Reducing CV Morbidity and Mortality Through Prevention and Control of RHD



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ABSTRACT

Rheumatic heart disease (RHD) is a preventable non-communicable condition that disproportionately affects the world's poorest and most vulnerable. The World Heart Federation Roadmap for improved RHD control is a resource designed to help a variety of stakeholders raise the profile of RHD nationally and globally, and provide a framework to guide and support the strengthening of national, regional and global RHD control efforts. The Roadmap identifies the barriers that limit access to and uptake of proven interventions for the prevention and control of RHD. It also highlights a variety of established and promising solutions that may be used to overcome these barriers. As a general guide, the Roadmap is meant to serve as the foundation for the development of tailored plans of action to improve RHD control in specific contexts.

1. INTRODUCTION

Rheumatic heart disease (RHD) is a preventable non-communicable condition that disproportionately affects the world's poorest and most vulnerable. Globally, 32 million people suffer from the condition, which kills 275,000 people annually [1]. Driven by poverty, poor access to health services and other health system weaknesses, the majority of people with RHD live in low- and middle-income countries, with the remainder in vulnerable communities of wealthy countries [2].

In recent years, the need for concerted global action to control non-communicable diseases, including RHD and other cardiovascular diseases (CVD), has become a high priority on the global health agenda. This prioritisation is evident in the UN political declarations on the Prevention and Control of Non-Communicable Diseases ('25 by 25' target), the WHO Global NCD Action Plan, and the UN Sustainable Development Goals [3,4].

With CVD as the leading cause of premature mortality worldwide, and more than 80% of deaths occurring in low- and middle-income countries, the World Heart Federation (WHF), as the world's leading global CVD organization, launched its Roadmap Initiative in 2014 to guide and support those seeking to improve CVD control.

The WHF Roadmaps are global implementation strategies designed to help governments, employers, non-governmental organizations (NGOs), health activists, academic and research institutions, health care providers and people who have been affected by CVD, take action to better prevent and control CVD [5,6]. The Roadmaps

synthesise existing evidence on the efficacy, feasibility and cost-effectiveness of various strategies. They also identify potential barriers (roadblocks) to their implementation, and propose potential solutions to bypass them.

The WHF Roadmap for reducing morbidity and mortality through improved prevention and control of RHD complements existing roadmaps on tobacco control [7], raised blood pressure [8], and the use of secondary prevention for CVD [9], and follows the 2013 WHF position statement on the prevention and control of RHD [10].

As part of its 2013 statement on RHD, the WHF endorsed the ambitious goal of achieving a 25% reduction in premature deaths from rheumatic fever (RF) and RHD among individuals aged <25 years by 2025 [10]. To achieve this, the WHF also defined five targets:

- Foster at least one prominent public figure as an 'RHD champion' in every country where RHD is endemic,
- Ensure that 90% of countries with endemic RHD have integrated and comprehensive control programmes by 2025,
- Ensure the availability of high-quality benzathine penicillin G for 90% of patients with RHD in 90% of countries with a high burden of this disease,
- Establish at least one hub of training, research, and advocacy for RF and RHD in each WHO-defined geographic region by 2025,
- Test a group A β -haemolytic streptococcal vaccine in phase III clinical trials in RHD-endemic countries within 10 years [10].

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The WHF RHD Roadmap will contribute to reaching these targets by acting as a resource to raise the profile of RHD nationally and globally, and by providing a framework to guide and support the strengthening of national, regional and global RHD control efforts.

The Roadmap's content is derived from searches for relevant systematic and narrative reviews of existing evidence found in Medline and the Cochrane Library; a synthesis of relevant peer-reviewed and grey literature published since 2012; and an iterative process of expert consultation involving 11 Writing Committee and 12 Reviewing Committee members drawn from the global WHF membership network and key stakeholders in RHD control.

Given the diverse settings in which RHD is endemic and the array of opportunities for intervention (even within individual countries), this Roadmap is best considered a generic framework for local adaptation and is intended to serve as a basis for developing region- or country-specific roadmaps.

Developing and effectively implementing country-specific roadmaps will require a coalition of the following stakeholders: health professionals; government departments and agencies; in-country and regional health organizations; NGOs; and industry, patient and community groups to advocate for the inclusion of RHD in national NCD action plans and various other national planning instruments.

The process also requires a range of local expertise that includes knowledge of medicine, cardiology, cultural and social contexts, prevention, health promotion, health systems, economics, and government priorities. Section 10 discusses this process further.

2. WHAT ARE RF AND RHD?

Rheumatic fever is an inflammatory disease involving the joints, skin, heart and brain, which develops following an untreated or partially treated group A β -haemolytic streptococcal (GAS) infection of the throat (streptococcal pharyngitis). Up to 30% of sore throats in children and young people are caused by GAS, and 0.3% to 3% of young people with an untreated GAS sore throat will develop RF [11,12].

Personal susceptibility, the type of GAS strain and poor socio-economic conditions that facilitate bacterial transmission and exposure, particularly overcrowded housing, are key risk factors for RF (see Fig. 1). In some regions, streptococcal skin infection has also been implicated in the disease process [13].

After recovery from the initial episode of RF, up to 60% to 65% of patients develop valvular heart disease [11,14] and the risk of RF recurrence following GAS infection rises to 50% [15,16]. Repeated GAS infections without appropriate treatment with benzathine penicillin G lead to RF recurrences and progressive valve damage—the defining characteristic of RHD—which can, in turn, cause atrial fibrillation, heart failure, stroke and endocarditis.

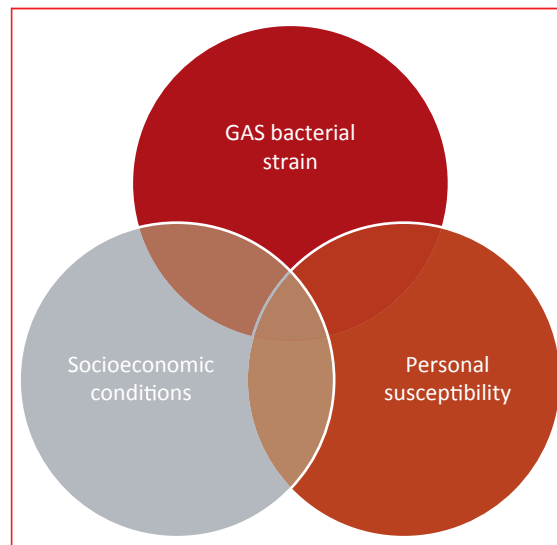


FIGURE 1. The interplay of risk factors for rheumatic fever.

A key determinant of disease progression is the number of times RF recurs in an individual [17]. As cardiac impairment worsens, disability increases and quality of life decreases. Surgery or cardiac catheterisation often become necessary, and patients who do not have access to such treatment ultimately die prematurely from RHD and its complications. In a large study conducted in 14 low- and middle-income countries, the median age of death was 28.7 years [18].

3. CHANGING BURDEN OF A PREVENTABLE DISEASE

By the 1980s, RF and RHD had virtually disappeared from high-income regions of North America and Europe [19,20]. However, the disease burden persists in low- and middle-income countries, home to 79% of people living with RHD [2], and in some indigenous populations of higher-income countries [21,22].

According to the WHO Global Health Estimates, the overall burden of RHD has declined over the past decade, though progress has been uneven [23]. Figures 2 and 3 illustrate the total deaths and disability-adjusted life-years (DALYs) estimated for each WHO region during 2000 and 2012. DALYs are a summary measure of health that capture both premature mortality and morbidity among prevalent cases in a single statistic. Reflecting morbidity in measures of burden is important as many people living with RHD are disabled by its long-term complications, which include heart failure, atrial fibrillation, stroke, infective endocarditis, and pregnancy-related complications.

At the global level, the number of deaths and DALYs attributed to RHD have decreased by 0.75% and 1.33%, respectively, since 2000. Progress was most notable in high-income countries and in middle-income countries in Europe and Southeast Asia. However, the total number of

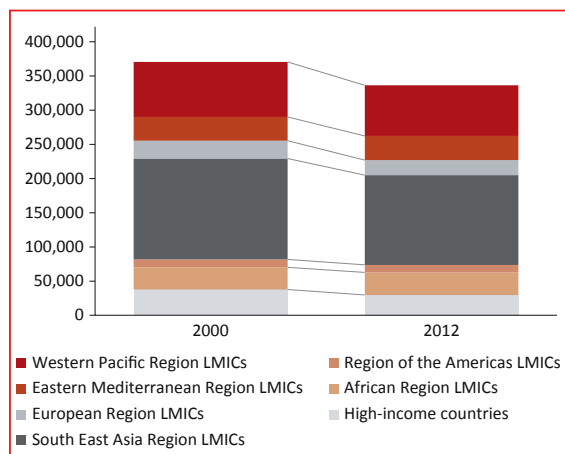


FIGURE 2. Global deaths from RHD by WHO region, 2000-2012. Adapted from WHO Global Health Estimates (GHE) database. LMIC, low- and middle-income country.

deaths in Africa and the Eastern Mediterranean increased over this period.

Burden of disease estimates have also been produced by the Global Burden of Disease (GBD) studies from the Institute for Health Metrics and Evaluation. The GBD 2013 study estimated 275,000 deaths globally (95% uncertainty interval [UI]: 222,600-353,900) for 2013 in comparison to the WHO estimate of 337,335 deaths [24]. The GBD 2013 study also estimated 32.9 million (31.6 to 34.0 million) prevalent cases and 9.5 million (7.9 million to 12.0 million) DALYs from RHD in 2013 [1,24]. Together, these findings suggest that the reductions in mortality may be resulting in an increased prevalence.

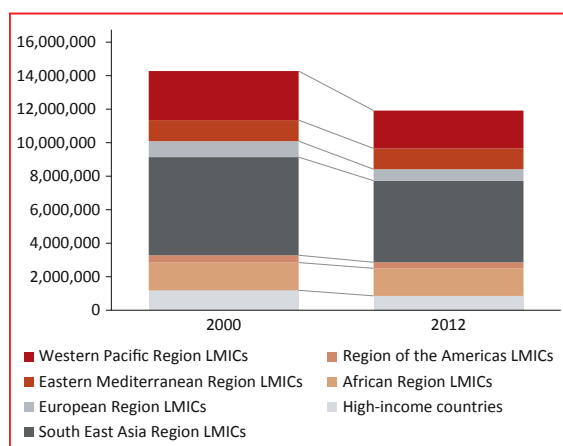


FIGURE 3. Disability-adjusted life years due to RHD by WHO region, 2000-2012. Adapted from WHO Global Health Estimates (GHE) database. LMIC, low- and middle-income country.

4. WHY CONTROL RF AND RHD?

There are a number of compelling reasons to act on RHD, in addition to the total global burden of disease [25]. As noted above, progress on RHD has been uneven, with some low-income areas experiencing increases in mortality as compared to high-income areas where mortality has decreased. Therefore, RHD contributes to rising health inequality at the global level.

Unlike many other CVDs, RHD is a preventable condition acquired in childhood that is amenable to early and effective intervention. This presents a rare opportunity to avert the immense personal burden and social costs associated with premature cardiovascular morbidity and mortality [26]. The potential economic gains from a societal perspective are even greater, as the burden of RHD is disproportionately borne by young, economically active people in low-income countries [26,27]. Therefore, controlling RHD supports overall economic and social development, both directly and indirectly.

RHD acts as a tracer condition that reveals issues in the performance of health systems. Comprehensive RHD control spans the whole health system, requiring robust primary care systems all the way up to specialised tertiary and quaternary care. RHD control programmes also present an opportunity to model good practice in the delivery of services to those with chronic conditions that require ongoing management. If done well, the learning and experience can be transferred to benefit other public health programmes.

Given the elevated risk associated with poverty and the impoverishing effects of the disease, addressing RHD is also an issue of equity in all affected countries, regardless of income level. It is also a matter of equity for women's health, as pregnancy and labour are particularly dangerous for women with RHD [28].

5. THE HEALTH CARE JOURNEY IN RHD

Although local differences in health services can be profound, people with streptococcal pharyngitis ('strep throat'), RF and RHD share a number of common health care needs. These common pathways are illustrated in Figure 4, which draws on the Continuum of Care (CoC) Framework for Health Systems developed by Medtronic Foundation. The framework acknowledges the interrelated nature of strep throat, acute RF and RHD, and traces a stylised version of the patient journey through the types (and level) of intervention required at each stage. These are numbered CoC1 to CoC10 in the Figure.

For instance, an unwell individual or their caregiver must initially decide to seek care for the illness (CoC2), and then engage with the health system (CoC3) where they should be appropriately diagnosed (CoC4) either with strep throat (path 1), rheumatic fever (path 2) or rheumatic heart disease (path 3). Those with strep throat should receive appropriate treatment with intramuscular benzathine penicillin G (BPG), ideally at the primary care level (CoC6). Those diagnosed with rheumatic fever should begin secondary prophylaxis

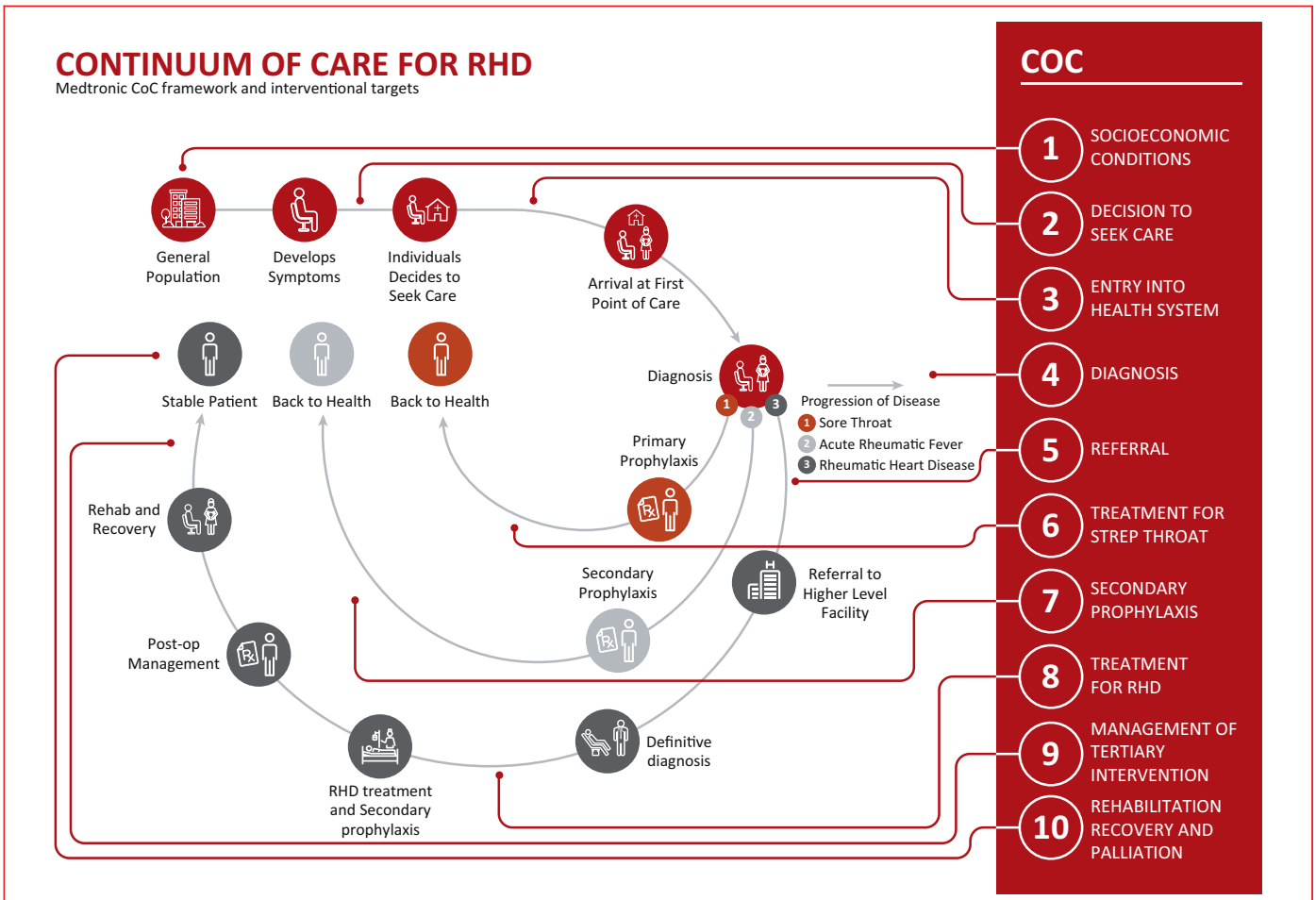


FIGURE 4. RF and RHD Continuum of Care. RF, rheumatic fever; RHD, rheumatic heart disease.

using BPG (CoC7) also at the primary care level, and be referred for appropriate investigation at higher levels. And those with RHD should be referred (CoC5) for appropriate treatment at higher levels of care (CoC8), after which they should receive the appropriate follow-up care (CoC9 and CoC10). The framework also underscores the roles that poverty and the social determinants of health play as crucial risk factors for RHD (CoC1).

As a patient-centred framework, the CoC facilitates an understanding of the care seeking process from the individual's—or their caregiver's—perspective, while permitting the systematic identification and categorisation of the various needs and opportunities of patients, providers, communities and the wider health system to manage cases of GAS sore throat, RF and RHD appropriately, and prevent the progression of disease.

6. KEY INTERVENTIONS FOR TREATMENT AND PREVENTION

Underpinning the CoC are a number of evidence-based interventions to alter the outcome of disease. The WHF and

RhEACH have developed a matrix (Figure 5) to summarise these treatments and a wide range of supporting interventions into a resource called the TIPS (Tools for Implementing RHD Control Programmes) Handbook [29]. These are typically considered in four domains:

- Primordial (address the underlying social determinants of health that exacerbate GAS exposure and RHD risk)
- Primary (treatment of strep throat to prevent the development of RF following GAS infection)
- Secondary (prevent development of new GAS infections following the first episode of acute RF to prevent subsequent RF recurrences and delay or prevent development of severe RHD)
- Tertiary (control RHD symptoms and extend the life of those living with RHD)

6.1. Primordial prevention

As a disease with aetiology and risk factors strongly associated with poverty, structural interventions designed to address the social determinants of health are believed to be

		Research				
Tertiary prevention		Medical management of RF and RHD	Anticoagulation	Triage and preoperative planning	Postoperative planning	Provision of interventional services
Secondary prevention		RF/RHD Register	BPG and other antibiotic supply	Provision of secondary prophylaxis	Priority based follow up (clinical review)	Active case finding (echocardiography screening)
Primary prevention		Community education	Sore throat diagnosis and treatment guidelines	Provision of primary prophylaxis	Active case finding (sore throat clinics)	Vaccine development
Baseline health systems		Government engagement	Disease notification	Human resources	Health worker training	Programme evaluation
		Burden of disease data	Governance and the RF/RHD Advisory Committee	Funding	Laboratory services	Integration with primary care and health systems
		Poverty	Overcrowding	Malnutrition	Access to healthcare	

FIGURE 5. TIPS matrix of RHD control supporting interventions. RHD, rheumatic heart disease; TIPS, Tools for Implementing RHD Control Programmes.

critical for RF and RHD control [30,31]. These interventions aim to reduce exposure to GAS infection by addressing household overcrowding and other social determinants of health.

While such interventions traditionally lie beyond the scope of health system strengthening, there may be scope for primordial activity, such as education on overcrowding, to be combined with other RHD control efforts [29]. In addition, a wide range of government policies outside the health sector may also influence the primordial determinants of RHD. Therefore, advocacy on the association between RHD and poverty will help to ensure that governments, development partners, non-governmental organizations and other important actors view RHD control as a priority.

6.2. Primary prevention

Primary prevention involves prompt diagnosis and treatment of GAS throat infections in young people, with effective use of antibiotics to prevent the development of RF. This requires patients or their caregivers to seek care, receive appropriate diagnosis and adhere to prescribed treatment. A systematic review evaluating the effectiveness of antibiotics in preventing RF found a substantial protective effect: in patients with a sore throat and symptoms suggestive of a GAS infection, antibiotic treatment using intramuscular BPG could reduce the risk of RF by up to

80% [32]. A more recent review has endorsed penicillin as the antibiotic of choice for GAS pharyngitis [33].

However, many roadblocks exist to the provision of effective primary prevention. From the patient's perspective:

- Since most sore throats are viral in nature and tend to be self-limiting, sore throat may not be considered an illness that warrants medical care, or its link with RF/RHD may be poorly understood, consequently affecting the uptake of effective care,
- Access to preventive services and medication may be hindered by distance or costs, particularly if paid for out-of-pocket (e.g. transport, fees for diagnosis and medications) [30],
- Poor adherence to antibiotic treatments may result from a lack of understanding of the purpose of treatment, and fear of injections, among other things.

From the health systems perspective, the delivery of effective primary prevention may be hindered by:

- Shortages and stock outs of essential antibiotics, including quality BPG, which may result from inefficient procurement and supply chain management practices, or supply issues at the production/manufacture level [34],
- Poor understanding among health professionals about the purpose of treating sore throat and the link with RHD,

- Insufficient knowledge or systems at primary care level for the effective management of sore throat,
- Absence of standardised clinical guidelines,
- Inadequate training, resources or capacity to act on clinical guidelines which may be due to a lack of practical local clinical guidelines or, where they do exist, ineffective dissemination and uptake of guidelines among health professionals,
- Limited geographic coverage of existing primary healthcare services,
- Reluctance to administer penicillin out of concern for anaphylaxis [35], resulting in onerous skin testing before administration in some settings and, in others, blanket bans on penicillin administration.

While primary prevention is ideally delivered through the existing primary care system, alternative approaches, such as school-based sore throat clinics, have been suggested as a means of identifying GAS infections within the community and overcoming some of the aforementioned barriers to seeking care. While available evidence on the effectiveness of such programmes in preventing RF is limited [36], the recent experience of the sore throat management component of New Zealand's RF primary prevention programme suggests that school-based approaches may be beneficial when focused on areas of high RF incidence [37]. However, the high costs, workloads and logistical challenges associated with its delivery will likely limit its application in resource-constrained settings.

Currently there is no effective vaccine for GAS (discussed further in Section 8).

6.3. Secondary prevention

The mainstay of secondary prevention involves the use of antibiotic prophylaxis in those with a history of RF to prevent subsequent recurrences, with the aim of limiting progression to severe RHD.

The preferred antibiotic is intramuscular BPG, which must be administered every 28 days (shorter dose intervals may be used in some settings based on evidence about the duration of the protective effect of BPG, logistics of delivery and acceptability to patients), consistently for a minimum of 10 years after the first acute RF episode. Oral regimens provide inferior protection from RF recurrence, but may be required for people with a penicillin allergy [38-40].

Effective delivery of secondary prevention requires identification of all individuals at risk of RF recurrence, prompt initiation of antibiotic prophylaxis using BPG and on-going antibiotic delivery until the period of risk has passed. Consequently, adherence to secondary prophylaxis may be low. One study in Uganda noted that 46% of patients received less than 80% of the required injections over a 6-month period [41].

Because secondary prophylaxis is similar to primary prevention in that it is ideally delivered through the primary care system and relies on BPG as the antibiotic of

choice, many of the potential roadblocks are also similar. From the patient perspective:

- RF may go undiagnosed because symptoms are mild or absent, or because families cannot afford to seek care,
- The costs associated with the long duration of prophylaxis may be prohibitive, particularly if families must pay for BPG out-of-pocket [42]. The indirect costs of travel for injections may also be high, further increasing the risk for non-adherence, especially among patients or caregivers who do not value or understand the purpose of on-going follow up and treatment, or the benefits of monitoring one's disease status,
- Poor adherence may also arise due to pain from regular injections,
- Poor acceptability due to lack of trust or confidence in the care provided or a perceived lack of patient/carer support may also affect adherence [42].

From the health systems perspective:

- Clinicians may not have the training or resources to diagnose RF accurately [43],
- Lack of local guidelines, or their ineffective implementation can lead to inconsistent diagnosis, treatment and management of patients,
- Unreliable supply of quality antibiotics, especially BPG, and injection equipment is an important determinant of non-adherence [34,44],
- Concerns about anaphylaxis, particularly among asymptomatic children, may make some health professionals reluctant to administer BPG [35], and in some settings this has led to bans on penicillin administration,
- Lack of primary care infrastructure to support delivery of secondary prevention.

The core supporting intervention for the delivery of secondary prophylaxis is the national RF and RHD register, which has remained a critical part of RHD control since the 1970s. Registers benefit those living with RF/RHD in various ways. They improve the delivery of consistent and standardised secondary prophylaxis, help to ensure that care is prioritised by need, and help to identify and support people with poor adherence. As a national information system, registers also contain important information about mortality, surgeries received and medical histories of individual patients, in addition to incidence and prevalence data and other important indicators over time [29,45].

RHD may be asymptomatic for years or decades, particularly if the first episode of RF was mild or undiagnosed. Identifying subclinical RHD cases through echocardiography screening has been advocated as a tool to support secondary prevention. In order to standardise the criteria used to diagnose subclinical RHD using echocardiography, a group of international experts under the auspices of the WHF has published evidence-based criteria for echocardiographic diagnosis of subclinical RHD in screening programmes [46].

However, the priority of RHD control programmes should be to deliver effective secondary prophylaxis services before implementing echocardiographic screening programmes. The utility and cost-effectiveness of screening and treating subclinical cases should also be further investigated in more diverse settings [47].

6.4. Tertiary intervention

Tertiary RHD interventions aim to treat symptoms, reduce disability and ultimately delay death from RHD. Depending on the type and severity of a patient's condition, tertiary interventions may include surgical valve repair, valve replacement, balloon mitral valvuloplasty or medical management of the complications of RHD.

In the context of a developing country, it may be reasonable to include tertiary medical and surgical services within the remit of RHD control programmes where capacity and resources permit [45]. Valve repair has been shown to be preferable to replacement as patient survival is better and anticoagulation is not needed; however, repeat operations are often required [48,49].

Patients with valve replacements require lifelong anticoagulation using warfarin. This gives rise to a number of additional roadblocks in resource-limited settings as effective anticoagulation involves regular monitoring, regular dose adjustments and requires a reliable medicine supply.

Making anticoagulation management available at primary care level has been suggested to improve access for these postoperative patients and for others requiring anticoagulation for arrhythmias and heart failure. Providing surgeries in these contexts may be prohibitively expensive for governments and patients alike [50].

In many developing countries, cardiac surgery facilities do not exist; the small minority of patients who do receive tertiary care either travel overseas, or benefit from international teams who visit on short-term bases [51]. Several countries such as South Africa, India, and Brazil have increased capacity to deliver tertiary interventions [52]. Others in Africa have initiated surgical training programmes to address this gap, but this has not yet started to address the scale of the problem given that the vast majority of RHD cases in the region present with established disease and severe complications [53].

While the ability to deliver tertiary interventions is important, where such capacity does not already exist, efforts should be made to invest in improving primary and secondary prevention, which are much more affordable and likely to reduce the future burden of disease, even if they cannot address the need for treatment [54].

7. KEY HEALTH SYSTEM REQUIREMENTS FOR RHD CONTROL

Examining the roadblocks at each level of intervention reveals several core health system features that are required

for the effective implementation of RHD control programmes.

7.1. Human resources

A complementary range of clinical, allied health, public health and administrative skills that reflects the local burden of disease is required to implement RHD control programmes. However, experience from successfully implemented programmes has revealed the importance of a single key contact dedicated to developing and delivering the programme [29].

Engaging existing networks of community health workers and nurses, who operate in rural and remote areas, presents an opportunity to greatly expand programme coverage and explore new delivery models for RHD control. In low- and middle-income countries, community health workers have been shown to be effective at delivering a variety of primary care interventions, including malaria case management [55], family planning services, and antenatal counselling and referral [56]. Their skill set and position within communities make them an ideal channel to administer RHD awareness campaigns and provide support to patients and carers.

7.2. Healthcare delivery

Many core components of RHD control programmes are well suited for a primary care approach, including delivery of primary and secondary prophylaxis, diagnosis of suspected RF and patient/community education. The renewed drive toward universal access to primary care provided by the Sustainable Development Goals presents a unique window of opportunity to achieve this integration [57].

In addition to increasing service access for patients, the efficiencies gained from the sharing of infrastructure and resources also contributes to the sustainability of RHD control programmes. In Nepal, a national programme focused on promoting community awareness, the delivery of secondary prophylaxis, RHD register development, health worker training, and guideline development has been integrated into primary care since 2007; and in 2013 a pilot primary prevention project was initiated at 42 primary health centres [35].

The devastating consequences of RHD during pregnancy and labour also require RHD control to be integrated with maternal care. Ensuring adequate counselling for women of childbearing age living with RHD, adequate antenatal case detection services and appropriate care during the perinatal period are essential components of a comprehensive RHD program. There are also recent initiatives that seek to integrate RHD care into other existing chronic disease management programmes. One innovative approach being trialled in Uganda aims to integrate RHD surveillance and treatment within the existing HIV/AIDS infrastructure that has been successfully scaled-up after many years of domestic and foreign investment [58].

7.3. Physical resources

A continuous supply of affordable, quality intramuscular BPG for use as primary and secondary prophylaxis is a critical input for successful RHD control programmes. Invented in 1928, this antibiotic has been included on the WHO Essential Medicines List since the first edition was published in 1977. However, several important concerns remain about BPG shortages at production level, efficacy and quality, and persistent stock outs which continue to limit access [34].

To improve availability of BPG and other essential medicines required for control programmes, they must be registered with the national pharmaceutical regulator and included on national formularies/essential medicines lists. RHD control programmes must also have sufficient capacity to forecast, quantify, procure and distribute medicine supplies.

Because BPG is also used to prevent transmission of syphilis in pregnant women to the foetus, and as prophylaxis in children with sickle cell disease, information flow is critical to inform each of these processes and to minimise the risk of stock outs.

For example, in Fiji, BPG usage data collected through the Rheumatic Fever Information System are used by the Fiji Pharmaceutical Biomedical Services to help ensure a more consistent supply of BPG to health facilities across the country. Where there is insufficient capacity in procurement and supply chain management, support is available from alternative procurement agents including UN agencies, and a range of international and non-governmental organizations [59].

7.4. Clinical resources

Clear, practical, evidence-based clinical guidelines must be developed for each intervention provided and adapted to the particular context. To ensure they are used to inform the care provided, guidelines must be widely available at primary care level, translated into local languages as needed, and health care providers must be aware and trained on how to use them.

To embed them further into clinical practice, guidelines may be integrated into medical education and the process of professional audit. Guidelines for RHD control should also include advice on how to educate patients about the risks of sore throat, RF and RHD; how to support patient adherence to secondary prophylaxis; and how to administer BPG injections safely, comfortably and confidently.

7.5. Governance and advocacy

Embedding RHD control programmes within the Ministry of Health and other public health infrastructure is crucial for ensuring continued leadership, finance and, consequently, a sustainable and coordinated national response. However, successful experiences from Nepal and Sudan have shown that collaborations between government and

NGOs, such as national heart foundations and professional societies, also provide effective models for programme governance [35,60].

Where government support and recognition of the need for RF/RHD control is lacking, advocacy must be used to mobilise political will and raise RHD control as a priority. A key advocacy figure at country level is the national or even regional 'RHD Champion' to whom the WHF targets refer in Section 1. RHD Advisory Committees, comprised of a broad and inclusive range of stakeholders, are another important channel for conducting such advocacy, and can also play a role in the design, implementation and oversight of control programmes.

7.6. Financing

Programmes require sustained long-term funding to realise population-level impact, and therefore rely on strong advocacy and a good understanding of programme costs. In resource-constrained settings, public sources should finance primary and secondary prevention, as they are cost-effective and represent good value for money [12,61-64]. Public financing for prevention should aim to deliver care that is free at the point of service or that poses minimal cost to patients.

Financing tertiary care and making it affordable to patients in these settings, if included, presents a great challenge given the socio-economic position of those most affected and the high costs of building and maintaining the required capacity and infrastructure. Where these resources do not exist, tertiary care could initially be financed and delivered through alternative models [51]; and where there are shortfalls in public financing, additional funds may be available from various external sources such as international donor agencies, professional organizations and charities [29]. However, ensuring equitable and affordable access to tertiary care requires effective financial protection, such as that provided by comprehensive insurance and universal health coverage.

Ultimately, the goal of RHD control is to reduce the incidence of acute RF and the prevalence of RHD, which, over time, will decrease the need for costly tertiary interventions.

7.7. Information systems

As discussed in Section 6, national RF and RHD registers are essential to support the delivery of secondary prophylaxis, and are important information systems that provide data to assess disease burden, target interventions according to need, and evaluate programme impact over time. Recently, an open-source, low-cost software application, called eRegister, has been developed by the Pan-African Society of Cardiology for RHD treatment and prevention programmes [65]. Based on the WHF framework for RHD patient registers, the software ensures the capture of standardised data, facilitating the production of indicators for programme monitoring and evaluation. It is

also designed as a readily adaptable, cloud-based, mobile platform that allows for simultaneous data collection by field workers using mobile devices, and by providers using computer terminals in clinics and hospitals.

7.8. Patients and caregivers

Ensuring patients, parents, schoolteachers, carers and communities are aware of the risks posed by untreated sore throat, RF and RHD through campaigns has been a core element of many successful RHD control programmes [35,66,67]. Raising awareness aims to increase the likelihood of seeking prompt care for sore throat, or when one shows signs and symptoms consistent with acute RF.

Successful community-level campaigns have taken a multichannel approach, targeting several areas, as well as mass media, to reach as many people as possible. School and educational institutions should also be targeted, as the most vulnerable population for GAS infections are school-aged children [68]. In Kenya, the use of an interactive digital module to train school-going children on RHD was shown to increase knowledge and awareness [69].

8. OPPORTUNITIES TO BRIDGE THE KNOWLEDGE-PRACTICE GAP

While the efficacy of the clinical interventions and elements required for successful implementation of RHD control programmes are relatively well understood, the continuing global burden of this preventable disease highlights the ongoing knowledge-practice gap in RHD control. There are a number of important unanswered questions (Table 1), which will require robust research in order to produce the high-quality evidence needed to influence public health policy and programmes.

Innovative approaches that address roadblocks to effective care will also be required to close the knowledge-practice gap in RHD control. The remainder of this section explores a selection of these potential solutions, some of

which address RHD and others which draw inspiration from innovative solutions used to address other conditions. Note that many of the innovative approaches described below require further research, development and evidence from trials before they can be adopted and scaled-up for RHD control. Such points could inform the long-term RHD research agenda. Other ideas, however, could be pursued immediately.

8.1. Diagnosis of sore throat

Although throat cultures remain the gold standard for the diagnosis of GAS pharyngitis, the availability of rapid point-of-care antigen detection tests and clinical decision rules have created opportunities for new diagnostic approaches [70]. However, evaluations of available rapid tests have found considerable variation in their specificity and sensitivity [70-73], and the tests have not been validated in all endemic regions, so product selection must be carefully considered. The current cost of rapid tests is also likely to limit their use in resource-constrained settings [70]. Alternatively, a meta-analysis evaluating seven clinical decision rules suggested that the Joachim protocol could potentially be used either alone or in combination with a rapid test to guide treatment decisions in some settings [74].

8.2. RHD diagnosis and screening

As described in Section 6, the application of echocardiography for identifying subclinical RHD cases is currently under investigation. However, the introduction of new devices and the decreasing cost of equipment have increased the potential to apply this approach more widely in developing countries for RHD diagnosis and screening. For example, one recent study in Uganda, which evaluated the use of a relatively affordable handheld ultrasound device against standard portable echocardiography for diagnosis, found it to be highly sensitive (90.2%) and specific

TABLE 1. Unanswered questions related to the knowledge practice gap in RHD control

- What factors determine effective integration of RHD control activities into primary care or other existing programmes (e.g. chronic disease, perinatal or sexual health services)?
- What programme characteristics contribute to improved delivery, uptake and adherence to secondary prophylaxis?
- How can the supply and demand for BPG be better linked, or a more acceptable product be developed to control RHD?
- How can successful experiences of implementing and scaling up comprehensive RHD control programmes be replicated? And what are the key factors that contributed to their success?
- What is the relative cost-effectiveness of different approaches to RHD control, including different models for delivering primary prophylaxis and comprehensive RHD control programmes?
- What is the clinical impact and cost-effectiveness of echocardiographic screening and other early case detection strategies, and how can it be made more practical and affordable?
- What are the best approaches for increasing the availability and quality of epidemiological data on RHD disease burden, particularly in low- and middle-income countries?
- How can people living with RHD be best empowered to improve self-management and outcomes?

Adapted from Carapetis and Zühlke [52].

(92.9%) in distinguishing between normal patients and those with RHD, when images were blindly reviewed according to the 2012 WHF guidelines [75].

The use of portable echocardiograms by trained nurses for screening has also recently been studied in Fiji [76,77]. Following brief focused training, participating nurses in one study were able to obtain adequate-quality images and make reliable assessments on the presence and extent of valvular regurgitation in more than 2000 children [77]. While further research is required, these early studies do show some promise for models that include task shifting as a means of introducing population-level screening in high-prevalence, resource-poor settings.

8.3. Acceptability of BPG

The success of primary and secondary prophylaxis would benefit from improved acceptability of BPG. In practice, this requires a regular supply of a high-quality product that can be readily administered with minimal pain. The development of longer-acting BPG formulations would support adherence by reducing the frequency of injections and the financial burden of administering prophylaxis for both patients and programmes [52]. In the interim, an innovative low-cost device that uses vibration to reduce discomfort from BPG injections has been trialled in New Zealand. When used with a local anaesthetic, the device reduced the pain and fear reported by children [78].

Incentive-based interventions have been used to improve medication adherence for conditions such as drug or alcohol dependence, HIV and tuberculosis. A review found that such incentives increased adherence by a mean of 20 percentage points, but that effects varied widely [79]. Incentive-based interventions have been frequently used to influence health-seeking behaviour in low- and middle-income countries (e.g., to encourage antenatal care and immunisations), and there is potential for secondary prophylaxis to benefit from such schemes.

8.4. mHealth solutions

The use of mobile devices to support the delivery of medical care or public health services is collectively termed mHealth. Despite being a relatively new area of intervention, there have been many pilot studies of a wide range of applications. While there continues to be some debate about the evidence base supporting the scale-up of mHealth [80], there are a few applications that have the potential to benefit RHD control. Applications have been developed to support adherence to antiretroviral and tuberculosis treatment, many of which have been designed for use and trialled in developing country settings [81,82].

The SMS for Life application is a text message-based platform for reporting stock levels of artemether-lumefantrine (AL), the first line treatment for uncomplicated malaria, and also of rapid diagnostic tests (RDTs) for malaria at peripheral facilities. In one pilot study conducted among selected public facilities in Kenya, weekly

stock counts of AL packs and RDTs were sent via a structured incentivised SMS communication process from health workers' personal mobile phones to a web-based system accessed by district managers. At the end of the pilot period, stock-outs of AL were eliminated and RDT stock-outs declined by 24 percentage-points. The platform has since been scaled up in Tanzania to include over 5,000 public health facilities across the country [83,84].

8.5. Patient and community empowerment

Strategies that seek to engage and empower people living with RHD and their carers have the potential to greatly enhance the RHD response. A diverse array of approaches has been developed, largely as part of the response to HIV/AIDS [85] and increasingly for non-communicable diseases, which target different levels of individual involvement. At one end of the spectrum, interventions such as healthy living training for patients, one-to-one counselling and patient support groups aim to increase knowledge about the disease, influence treatment-seeking behaviour and improve overall quality of life. For example, some programmes have adopted the use of patient-held records and RHD calendars that act as treatment reminders, while providing health information messages [52].

Approaches at the other end of the spectrum aim to empower affected individuals to be more active advocates and champions of a wider response. In Kenya, patients are being enabled to provide each other with health education and peer support [86]. In Fiji, a young RHD patient-advocate currently sits as a permanent member on the national RHD technical advisory committee, which provides high-level technical advice to the Ministry of Health. RHD patients and their carers in Fiji are also represented on a national working group formed specifically to better understand and address poor patient adherence rates [87].

8.6. Access to tertiary interventions

With growing capacity for cardiac surgery in a number of low- and middle-income countries, there is scope to implement bilateral or regional programmes that allow RHD patients living in countries with insufficient capacity to access tertiary interventions abroad [52]. Such a reciprocal agreement has existed between Malta and the United Kingdom since 1975 [88]. Under the agreement, nearly 300 Maltese nationals are referred annually for specialist care in ophthalmology, cardiac surgery, oncology and neurology, with one third of these patients being children.

8.7. GAS vaccine

The search for a GAS vaccine began in the 1950s yet, despite early human trials, no effective product for clinical use is available. Vaccine development faces several challenges, including limited commercial viability, the regional

TABLE 2. Potential solutions to address barriers to improved RHD control

Level of intervention	Roadblock	Potential solutions
Primary	Prompt medical care is not sought for sore throat in children and young people Poor adherence to antibiotics	<ul style="list-style-type: none"> • Targeted school- and community-level education and awareness campaigns • Targeted school- and community-level education and awareness campaigns • Ensure affordable and easy access to effective treatment • Provide single dose of injectable BPG rather than longer course of oral antibiotics • Support and enable health care professionals to deliver BPG injections confidently and safely • Reformulate BPG to make injections more acceptable to patients and providers
	Inappropriate management of sore throat in primary or community care services	<ul style="list-style-type: none"> • Ensure practical, evidence-based local guidelines are available and accessible • Provide professional training on use of guidelines • Integrate guidelines into clinical education and professional audit • Consider use of point-of-care diagnostics and clinical decision rules to improve diagnosis
	Reluctance to administer BPG due to concerns for anaphylaxis	<ul style="list-style-type: none"> • Ensure guidelines include safe administration techniques • Deliver training to providers on the risk of anaphylaxis and safe administration techniques • Ensure emergency kits and epinephrine (adrenaline) syringes are available
Secondary	RF cases are not identified	<ul style="list-style-type: none"> • Ensure primary care staff are sufficiently trained to identify suspected RF cases • Ensure robust protocols exist for referring suspected cases for definitive diagnosis • Support access to essential technologies including simple blood tests and echocardiography
	No register-based programme	<ul style="list-style-type: none"> • Advocate for public investment in register infrastructure, including the implementation of electronic register platforms (eRegister) • Seek external sources of funding and technical support
	Cases do not enrol or are not promptly enrolled into a register-based programme	<ul style="list-style-type: none"> • Targeted school- and community-level education and awareness campaigns about the value of secondary prevention • Increase health workers' awareness and appreciation of register-based system
	Enrolled cases are poorly managed	<ul style="list-style-type: none"> • Ensure practical, evidence-based, local treatment guidelines are available to support delivery of standardised care

(continued)

TABLE 2—continued. Potential solutions to address barriers to improved RHD control

Level of intervention	Roadblock	Potential solutions
	<p>Reluctance to administer BPG due to concerns for anaphylaxis</p> <p>Poor adherence to long term prophylaxis</p>	<ul style="list-style-type: none"> • Provide professional training on use of guidelines • Integrate guidelines into clinical education and professional audit • Implement electronic register platform (eRegister) to support follow-up and patient review • Ensure guidelines include safe administration techniques • Provide training for providers on safe administration techniques • Ensure emergency kits and epinephrine (adrenaline) syringes are available • Train staff to administer secondary prophylaxis confidently and safely with minimal pain • Ensure guidelines include advice on how to support patient adherence • Include reminder and recall systems in register-based programmes • Introduce outreach services to follow up non-adherent patients • Consider decentralised dispensing and mobile injection delivery where feasible • Consider mHealth reminder and incentive-based solutions • Implement empowerment strategies, including patient/carer support groups and awareness sessions • Reformulate BPG to make injections more acceptable to patients and providers
Tertiary	Poor access to surgical interventions	<ul style="list-style-type: none"> • Develop bilateral or regional programmes to provide cross-border care • Develop regional centres of excellence for cardiac surgery in appropriate countries
Health systems	<p>RHD control is not prioritised</p> <p>Insufficient funds</p>	<ul style="list-style-type: none"> • Conduct advocacy for RHD control • Gather data on local burden of disease, its economic impact and the benefits of investing in RHD control • Identify national RHD champions • Mobilise RHD Advisory Committee • Ensure RHD control is embedded within government ministry/department of health • Conduct RHD control advocacy to mobilise funding from government and other sources • Generate cost savings by integrating RHD control into existing primary care and other programmes • Generate cost savings by employing efficient medicines procurement strategies

(continued)

TABLE 2—continued. Potential solutions to address barriers to improved RHD control

Level of intervention	Roadblock	Potential solutions
	Poor availability of BPG and other essential medicines for RHD control	<ul style="list-style-type: none"> • Ensure all required medications are registered with national regulator and included on national formulary/essential medicines list • Train programme staff on effective forecasting, quantification, procurement and distribution • Strengthen information systems used to manage procurement and distribution of medicines • Consider mHealth solutions to reduce risk of stock outs • Advocate for BPG production solutions at a global level
	Limited coverage of current RHD control programmes	<ul style="list-style-type: none"> • Integrate RHD control into existing primary care and other programmes • Provide training on RHD prevention and control to primary health care workers
	Preventive services are unaffordable	<ul style="list-style-type: none"> • Targeted campaigns to increase awareness of where to obtain affordable/public preventive care
	Poor access to diagnostics in peripheral settings	<ul style="list-style-type: none"> • Ensure availability of essential laboratory services and echocardiography in selected sites • Consider implementing anticoagulation management in primary care, where feasible • Document the utility of rapid point-of-care diagnostics for GAS infection to help build the market case for these devices

variability of GAS strains and a theoretical risk of stimulating an autoimmune response [70,89].

However, research has progressed and several vaccine candidates against GAS infection are currently in various stages of pre-clinical and clinical development. These include M protein-based vaccines (N-terminal vaccine candidates and M protein conserved region vaccines), and non-M protein vaccine candidates representing conserved GAS antigens [90,91].

In addition to preventing sore throat and RF, a GAS vaccine could potentially provide protection against skin infection/impetigo and severe invasive GAS disease including pneumonia, bacteraemia, necrotising fasciitis and streptococcal toxic shock syndrome. Unlike RF/RHD, these invasive diseases cause significant morbidity and mortality in high-income settings; a GAS vaccine relevant to both high- and low-resource settings may provide a compelling economic opportunity [89].

This market segmentation approach and the feasibility of developing a viable product has recently garnered the attention of the WHO Product Development for Vaccines Advisory Committee [92]. Once available, a product

development partnership model may help to accelerate progress towards the registration of an effective GAS vaccine. Since the 1990s, a number of these international public-private collaborations have introduced a plethora of new medications, vaccines and diagnostics to benefit populations in low- and middle-income settings [93-95].

9. ROADMAP TO ADDRESS EXISTING ROADBLOCKS

Overcoming the barriers—whether individual, community or system-related—that prevent individuals from receiving care for sore throat, RF and RHD are crucial to achieving optimal population-level RHD control. While the roadblocks obstructing this journey will vary by setting, Table 2 charts a map of potential solutions that may be used to overcome them.

10. ADAPTING TO DEVELOP REGIONAL AND NATIONAL RHD ROADMAPS

The examples of successful, cost-effective and comprehensive RF/RHD control programmes implemented in resource-constrained settings demonstrate the great

potential for impact in other settings with high RHD burdens [35,63,66,67].

As discussed above, the RHD and other WHF Roadmaps describe only general principles that must be adapted to produce region- or country-specific roadmaps. The WHF has described this process in a companion article [96], but it generally involves:

- Developing and convening a multi-sectoral coalition to undertake the adaptation,
- Conducting a situation analysis to characterise the epidemiologic profile, the healthcare system and policy environment,
- Conducting policy dialogues to identify and discuss specific barriers and potential strategies that are appropriate to the given context,
- Developing a plan of action and a process to evaluate the implementation of the selected strategies.

The process requires a broad range of stakeholders (e.g., public health specialists, health care professionals, government organizations, regional health organizations, industry, advocacy and patient groups) and a broad range of expertise (e.g., knowledge of medicine, cardiology, prevention, health promotion, health systems, economics, governmental priorities, and cultural and social contexts).

To support this general process, a set of tools has been developed to adapt the WHF RHD Roadmap to specific national contexts. RhEACH has prepared a detailed Needs Assessment Tool to conduct the situation analysis and to develop, implement, monitor and evaluate adapted roadmaps.

In parallel, the WHF is developing additional guidance for convening multi-sectoral coalitions and conducting policy dialogues at national level. RHD country and global scorecards will also be developed to facilitate progress monitoring, international comparisons and evaluation of attaining targets.

Over time, country and regional experiences will be reported back and integrated with other emerging evidence to inform the updating and revision of the WHF Roadmaps.

11. CONCLUSION

Effective interventions to prevent the devastating consequences of RHD have existed for many decades. Yet, many people die prematurely each year due to RHD related complications, most of whom are from low- and middle-income countries or from poor and vulnerable groups in countries where the disease has, otherwise, disappeared.

The WHF Roadmap for improved RHD control identifies the various barriers that limit access to and uptake of these proven interventions. It also highlights a variety of proven and promising solutions that could be used to overcome these 'roadblocks'. As a general guide, this Roadmap is meant to serve as the foundation for the development of tailored plans of action to improve RHD control in specific contexts.

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REFERENCES

1. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015;386:743-800.
2. Carapetis JR, Steer AC, Mulholland EK, Weber M. The global burden of group A streptococcal diseases. *Lancet Infect Dis* 2005;5:685-94.
3. United Nations. Transforming our world: the 2030 agenda for sustainable development. New York, NY: United Nations; 2015.
4. World Health Organization. Global action plan for the prevention and control of noncommunicable diseases. Geneva, Switzerland: WHO; 2013.
5. Perel P, Bianco E, Poulter N, et al. Reducing Premature Cardiovascular Mortality By 2025: The World Heart Federation Roadmap. *Glob Heart* 2015;10:97-8.
6. Yusuf S, Perel P, Wood D, Narula J. Reducing Cardiovascular Disease Globally: The World Heart Federation's Roadmaps. *Glob Heart* 2015; 10:93-5.
7. Grainger Gasser A, Welch C, Arora M, et al. Reducing Cardiovascular Mortality Through Tobacco Control: A World Heart Federation Roadmap. *Glob Heart* 2015;10:123-33.
8. Adler AJ, Prabhakaran D, Bovet P, et al. Reducing Cardiovascular Mortality Through Prevention and Management of Raised Blood Pressure: A World Heart Federation Roadmap. *Glob Heart* 2015;10: 111-22.
9. Perel P, Avezum A, Huffman M, et al. Reducing Premature Cardiovascular Morbidity and Mortality in People With Atherosclerotic Vascular Disease: The World Heart Federation Roadmap for Secondary Prevention of Cardiovascular Disease. *Glob Heart* 2015;10: 99-110.
10. Remenyi B, Carapetis J, Wyber R, Taubert K, Mayosi BM, World Heart Federation. Position statement of the World Heart Federation on the prevention and control of rheumatic heart disease. *Nat Rev Cardiol* 2013;10:284-92.
11. Denny FW. T. Duckett Jones and rheumatic fever in 1986. T. Duckett Jones Memorial Lecture. *Circulation* 1987;76:963-70.
12. Irlam J, Mayosi BM, Engel M, Gaziano TA. Primary prevention of acute rheumatic fever and rheumatic heart disease with penicillin in South African children with pharyngitis: a cost-effectiveness analysis. *Circ Cardiovasc Qual Outcomes* 2013;6:343-51.

13. Parks T, Smeesters PR, Steer AC. Streptococcal skin infection and rheumatic heart disease. *Curr Opin Infect Dis* 2012;25:145–53.
14. Marijon E, Mirabel M, Celermajer DS, Jouven X. Rheumatic heart disease. *Lancet* 2012;379:953–64.
15. Couzos S, Murray R, editors. Aboriginal primary health care: an evidence-based approach. 2nd ed. South Melbourne, Australia: Oxford University Press; 2003.
16. Rose G, editor. Cardiovascular Diseases, in Oxford Textbook of Public Health: Applications in Public Health, Vol. 3. Oxford: United Kingdom; 1991.
17. Meira ZM, Goulart EM, Colosimo EA, Mota CC. Long term follow up of rheumatic fever and predictors of severe rheumatic valvar disease in Brazilian children and adolescents. *Heart* 2005;91:1019–22.
18. Zühlke L, Karthikeyan G, Engel ME, 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; 134:1456–66.
19. Gordis L. The virtual disappearance of rheumatic fever in the United States: lessons in the rise and fall of disease. T. Duckett Jones memorial lecture. *Circulation* 1985;72:1155–62.
20. Kaplan EL. T. Duckett Jones Memorial Lecture. Global assessment of rheumatic fever and rheumatic heart disease at the close of the century. Influences and dynamics of populations and pathogens: a failure to realize prevention? *Circulation* 1993;88:1964–72.
21. Gordon J, Kirlew M, Schreiber Y, et al. Acute rheumatic fever in First Nations communities in northwestern Ontario: Social determinants of health “bite the heart”. *Can Fam Phys* 2015;61:881–6.
22. Parnaby MG, Carapetis JR. Rheumatic fever in indigenous Australian children. *J Paediatr Child Health* 2010;46:527–33.
23. WHO. Global Health Estimates 2014. Available at: http://www.who.int/healthinfo/global_burden_disease/en/. Accessed May 8, 2016.
24. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015;385: 117–71.
25. Wyber R, Zühlke L, Carapetis J. The case for global investment in rheumatic heart-disease control. *Bull World Health Organ* 2014;92: 768–70.
26. Robertson KA, Mayosi BM. Rheumatic heart disease: social and economic dimensions. *S Afr Med J* 2008;98:780–1.
27. 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.
28. 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.
29. Wyber R, Grainger-Gasser A, Thompson D, et al. Tools for Implementing RHD Control Programmes (TIPS) Handbook. Perth, Australia: World Heart Federation and RhEACH; 2014.
30. Okello E, Kakande B, Sebatta E, et al. Socioeconomic and environmental risk factors among rheumatic heart disease patients in Uganda. *PLoS One* 2012;7:e43917.
31. 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; 38:229–34.
32. Robertson KA, Volmink JA, Mayosi BM. Antibiotics for the primary prevention of acute rheumatic fever: a meta-analysis. *BMC Cardiovasc Disord* 2005;5:11.
33. Spinks A, Glasziou PP, Del Mar CB. Antibiotics for sore throat. *Cochrane Database Syst Rev* 2013;11:CD000023.
34. 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;8:227–34.
35. Regmi PR, Wyber R. Prevention of rheumatic Fever and heart disease: nepalese experience. *Glob Heart* 2013;8:247–52.
36. Lennon D, Kerdelmelidis M, Arroll B. Meta-analysis of trials of streptococcal throat treatment programs to prevent rheumatic fever. *Pediatr Infect Dis J* 2009;28:e259–64.
37. Jack S, Williamson D, Galloway Y, et al. Interim Evaluation of the Sore Throat Component of the Rheumatic Fever Prevention Programme — Quantitative Findings. Porirua, New Zealand: The Institute of Environmental Science and Research Ltd.; 2015.
38. Manyemba J, Mayosi BM. Penicillin for secondary prevention of rheumatic fever. *Cochrane Database Syst Rev* 2002;3:CD002227.
39. Manyemba J, Mayosi BM. Intramuscular penicillin is more effective than oral penicillin in secondary prevention of rheumatic fever—a systematic review. *S Afr Med J* 2003;93:212–8.
40. van Driel ML, De Sutter AJ, Keber N, Habraken H, Christiaens T. Different antibiotic treatments for group A streptococcal pharyngitis. *Cochrane Database Syst Rev* 2010;10:CD004406.
41. Musoke C, Mondo CK, Okello E, et al. Benzathine penicillin adherence for secondary prophylaxis among patients affected with rheumatic heart disease attending Mulago Hospital. *Cardiovasc J Afr* 2013;24:124–9.
42. Bassili A, Zaher SR, Zaki A, Abdel-Fattah M, Tognoni G. Profile of secondary prophylaxis among children with rheumatic heart disease in Alexandria, Egypt. *East Mediterr Health J* 2000;6:437–46.
43. Gewitz MH, Baltimore RS, Tani LY, et al. Revision of the Jones Criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: a scientific statement from the American Heart Association. *Circulation* 2015;131:1806–18.
44. Taubert K, Marko S. Access to essential medicines: illuminating disparities in the global supply of benzathine penicillin G in the context of rheumatic fever/rheumatic heart disease. *J Am Coll Cardiol* 2013; 61(Suppl 10):e-2004.
45. McDonald M, Brown A, Noonan S, Carapetis JR. Preventing recurrent rheumatic fever: the role of register based programmes. *Heart* 2005; 91:1131–3.
46. Reményi 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.
47. 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.
48. Michota F. Transitions of care in anticoagulated patients. *J Multidiscip Healthc* 2013;6:215–28.
49. Wang Z, Zhou C, Gu H, Zheng Z, Hu S. Mitral valve repair versus replacement in patients with rheumatic heart disease. *J Heart Valve Dis* 2013;22:333–9.
50. Colquhoun SM, Carapetis JR, Kado JH, Steer AC. Rheumatic heart disease and its control in the Pacific. *Expert Rev Cardiovasc Ther* 2009;7:1517–24.
51. Ferratini M, Marianeschi S, Santoro F. Valvulopathies in sub-Saharan African children: patterns, humanitarian interventions and cardiac surgical problems. *Int J Cardiol* 2013;165:237–41.
52. Carapetis JR, Zühlke LJ. Global research priorities in rheumatic fever and rheumatic heart disease. *Ann Pediatr Cardiol* 2011;4:4–12.
53. Zühlke L, Engel ME, Karthikeyan G, et al. Characteristics, complications, and gaps in evidence-based interventions in rheumatic heart disease: the Global Rheumatic Heart Disease Registry (the REMEDY study). *Eur Heart J* 2015;36:1115a–22a.
54. Finucane K, Wilson N. Priorities in cardiac surgery for rheumatic heart disease. *Glob Heart* 2013;8:213–20.
55. Smith Paintain L, Willey B, Kedenge S, et al. Community health workers and stand-alone or integrated case management of malaria: a systematic literature review. *Am J Trop Med Hyg* 2014;91:461–70.
56. Scott VK, Gottschalk LB, Wright KQ, et al. Community Health Workers’ Provision of Family Planning Services in Low- and Middle-Income Countries: A Systematic Review of Effectiveness. *Stud Fam Plann* 2015;46:241–61.
57. Markbreiter J. Integration, integration, integration: Why Rheumatic Heart Disease Must be Incorporated into Universal Health Coverage. Geneva, Switzerland: RHD Action Alliance and World Heart Federation; 2015.

58. Longenecker CT, Lwabi P, Kityo C, et al. O087 Leveraging existing HIV/AIDS infrastructure for rheumatic heart disease care in Uganda: a collaborative disease surveillance and management program. *Glob Heart* 2014;9:e55.
59. Rao R, Mellon P, Sarley D. Procurement Strategies for Health Commodities: An Examination of Options and Mechanisms within the Commodity Security Context. Arlington, VA: DELIVER, for the U.S. Agency for International Development; 2006.
60. Shetty P, Sulafa Ali: a pioneer of paediatric cardiology in Sudan. *Lancet* 2014;383:687.
61. Irlam JH, Mayosi BM, Engel ME, Gaziano TA. A cost-effective strategy for primary prevention of acute rheumatic fever and rheumatic heart disease in children with pharyngitis. *S Afr Med J* 2013;103:894–5.
62. Manji RA, Witt J, Tappia PS, Jung Y, Menkis AH, Ramjiawan B. Cost-effectiveness analysis of rheumatic heart disease prevention strategies. *Expert Rev Pharmacoecon Outcomes Res* 2013;13:715–24.
63. Watkins DA, Mvundura M, Nordet P, Mayosi BM. A cost-effectiveness analysis of a program to control rheumatic fever and rheumatic heart disease in Pinar del Rio, Cuba. *PLoS One* 2015;10:e0121363.
64. Zühlke LJ, Karthikeyan G. Primary prevention for rheumatic fever: progress, obstacles, and opportunities. *Glob Heart* 2013;8:221–6.
65. van Dam J, Musuku J, Zühlke LJ, et al. An open-access, mobile compatible, electronic patient register for rheumatic heart disease ('eRegister') based on the World Heart Federation's framework for patient registers. *Cardiovasc J Afr* 2015;26:227–33.
66. Bach JF1, Chalons S, Forier E, et al. 10-year educational programme aimed at rheumatic fever in two French Caribbean islands. *Lancet* 1996;347:644–8.
67. 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;19:135–40.
68. Zühlke LJ, Steer AC. Estimates of the global burden of rheumatic heart disease. *Glob Heart* 2013;8:189–95.
69. Matheka DM, Murgor M, Kibochi E, Nigel S, Nderitu J, Selnow G. O028 Role of Technology In Creating Rheumatic Heart Disease Awareness Among School-Going Children In Kenya. *Global Heart* 2014;9(Suppl 1):e7–8.
70. de Dassel JL, Ralph AP, Carapetis JR. Controlling acute rheumatic fever and rheumatic heart disease in developing countries: are we getting closer? *Curr Opin Pediatr* 2015;27:116–23.
71. Little P, Hobbs FD, Moore M, et al. Clinical score and rapid antigen detection test to guide antibiotic use for sore throats: randomised controlled trial of PRISM (primary care streptococcal management). *BMJ* 2013;347:f5806.
72. Toepfner N, Henneke P, Berner R, Hufnagel M. Impact of technical training on rapid antigen detection tests (RADT) in group A streptococcal tonsillopharyngitis. *Eur J Clin Microbiol Infect Dis* 2013;32:609–11.
73. Upton A, Farrell E, Stewart J, Lennon D. Disappointing performance of rapid antigen detection tests for group A streptococcus in the Auckland school-based sore throat programme. *N Z Med J* 2014;127:103–5.
74. Le Marechal F, Martinot A, Duhamel A, Pruvost I, Dubos F. Streptococcal pharyngitis in children: a meta-analysis of clinical decision rules and their clinical variables. *BMJ Open* 2013;3:e001482.
75. Beaton A, Lu JC, Aliku T, et al. The utility of handheld echocardiography for early rheumatic heart disease diagnosis: a field study. *Eur Heart J Cardiovasc Imaging* 2015;16:475–82.
76. Colquhoun SM, Carapetis JR, Kado JH, et al. Pilot study of nurse-led rheumatic heart disease echocardiography screening in Fiji—a novel approach in a resource-poor setting. *Cardiol Young* 2013;23:546–52.
77. Engelman D, Kado JH, Reményi B, et al. Screening for rheumatic heart disease: quality and agreement of focused cardiac ultrasound by briefly trained health workers. *BMC Cardiovasc Disord* 2016;16:30.
78. Russell K, Nicholson R, Naidu R. Reducing the pain of intramuscular benzathine penicillin injections in the rheumatic fever population of Counties Manukau District Health Board. *J Paediatr Child Health* 2014;50:112–7.
79. DeFulio A, Silverman K. The use of incentives to reinforce medication adherence. *Prev Med* 2012;55(Suppl):S86–94.
80. Tomlinson M, Rotheram-Borus MJ, Swartz L, Tsai AC. Scaling up mHealth: where is the evidence? *PLoS Med* 2013;10:e1001382.
81. Catalani C, Philbrick W, Fraser H, Michael P, Israelski DM. mHealth for HIV Treatment & Prevention: A Systematic Review of the Literature. *Open AIDS J* 2013;7:17–41.
82. Devi BR, Syed-Abdul S, Kumar A, et al. mHealth: An updated systematic review with a focus on HIV/AIDS and tuberculosis long term management using mobile phones. *Comput Methods Programs Biomed* 2015;122:257–65.
83. Githinji S, Kigen S, Memusi D, et al. Reducing stock-outs of life saving malaria commodities using mobile phone text-messaging: SMS for life study in Kenya. *PLoS One* 2013;8:e54066.
84. Mikkelsen-Lopez I, Shango W, Barrington J, Ziegler R, Smith T, deSavigny D. The challenge to avoid anti-malarial medicine stock-outs in an era of funding partners: the case of Tanzania. *MALAR J* 2014;13:181.
85. Medley A, Kennedy C, O'Reilly K, Sweat M. Effectiveness of peer education interventions for HIV prevention in developing countries: a systematic review and meta-analysis. *AIDS Educ Prev* 2009;21:181–206.
86. Matheka D, Musambayi L. Launch of Nairobi RHD Patient Support Club on 8th March 2014 at the School Of Medicine, University of Nairobi, Kenya 2014. Available at: <http://www.clanchildhealth.org/content/download/1580/8711/file/Kenya%20RHD%20Support%20Club%20Report%20-%20140914.pdf>. Accessed April 25, 2016.
87. Ministry of Health and Medical Services. National acute rheumatic fever and rheumatic heart disease policy. Fiji Islands: Fiji Rheumatic Heart Disease Control Program and Ministry of Health and Medical Services. 2015.
88. Saliba V, Muscat NA, Vella M, et al. Clinicians', policy makers' and patients' views of pediatric cross-border care between Malta and the U.K. *J Health Serv Res Policy* 2014;19:153–60.
89. Maurice J. Rheumatic heart disease back in the limelight. *Lancet* 2013;382:1085–6.
90. Dale JB, Fischetti VA, Carapetis JR, et al. Group A streptococcal vaccines: paving a path for accelerated development. *Vaccine* 2013;31(Suppl 2):B216–22.
91. Sheel M, Moreland NJ, Fraser JD, Carapetis J. Development of Group A streptococcal vaccines: an unmet global health need. *Expert Rev Vaccines* 2016;15:227–38.
92. Giersing BK, Modjarrad K, Kaslow DC, et al. Report from the World Health Organization's Product Development for Vaccines Advisory Committee (PDVAC) meeting, Geneva, 7-9th Sep 2015. *Vaccine* 2016;34:2865–9.
93. Bethony JM, Cole RN, Guo X, et al. Vaccines to combat the neglected tropical diseases. *Immunol Rev* 2011;239:237–70.
94. Mahoney RT. Product Development Partnerships: Case studies of a new mechanism for health technology innovation. *Health Res Policy Syst* 2011;9:33.
95. Pratt B, Loff B. Linking research to global health equity: the contribution of product development partnerships to access to medicines and research capacity building. *Am J Public Health* 2013;103:1968–78.
96. Perel P, Bianco E, Poulter N. Adapting the World Heart Federation Roadmaps at the National Level: Next Steps and Conclusions. *Glob Heart* 2015;10:135–6.