Scientific Advances in Rheumatic Fever/Rheumatic Heart Disease Control

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Contributor: Andrew Chang, JOSELYN RWEBEMBERA, Bruno Galdino

Despite the fact that rheumatic fever (RF) and rheumatic heart disease (RHD) have largely been eradicated from high-income countries, the disease spectrum remains endemic in many low- and middle-income countries (LMICs), extacting a grim health and socioeconomic impact. Over 33 million people are believed to be living with RHD worldwide, claiming nearly a third of a million lives annually. Regrettably, the neglect of RHD as a global health priority was further exacerbated by competing infectious disease outbreaks, chief among them the human immunodeficiency virus (HIV) epidemic. Nevertheless, the prior two decades have seen a slowly resurgence of interest in RF/RHD control. Substantial recent advances in the field of RF/RHD continuum control, however, have been realized over this time period. Such primary advances include a better understanding the genetic predisposition to RHD, progress in Group A Streptococcus (GAS) vaccine development, and improved diagnostic strategies for GAS pharyngitis. Echocardiographic screening for RHD, in particular, has represented a major advance which has unearthed the prevailing high burden of RHD. Lastly, the recent demonstration of benefit of secondary antibiotic prophylaxis on halting progression of latent RHD has marked a major step forward in averting progression of end-stage valvular disease in LMIC settings.

Keywords: rheumatic fever ; rheumatic heart disease ; RHD ; RF ; global health ; public health ; neglected tropical disease

1. Advances in Characterizing the Global Burden of Rheumatic Heart Disease

A number of factors over the past decade have dramatically improved our ability to estimate the prevailing burden of Rheumatic heart Disease (RHD), with estimates ranging from 15 million cases in 2005 [1] increasing to 40.5 million estimated cases in 2019 with refinement in epidemiologic methodology [2]. More granularly, however, individual nation-level studies have shown shifting prevalences even within LMICs. Echocardiographic surveys in some settings such as in India have revealed consistent decline in the burden of RHD before and after 2000, using similar screening methods among school children. This particular decline was associated with improvement in the indicators of socioeconomic state and health-care services. Three main advances have led to the knowledge gain of the global burden of RHD, including (a) screening echocardiography; (b) RHD registries and country-wide administrative health data; and (c) big data sources, namely the Global Burden of Disease repository.

1.1. Advances in Screening Echocardiography

RHD remains largely clinically silent until patients become symptomatic with the advanced form of disease. Echocardiographic (echo) screening [3], which has been one of the chief advancements in our understanding of the global burden of RHD, has resulted from school, community, and clinical echo screening to define the epidemiological burden of the disease. In particular, echo screening is responsible for the birth of the ‘latent RHD’ paradigm (namely the identification of subclinical echo-detected disease)—rallied as an opportunity for early intervention to prevent disease progression. Active case finding through echo screening has gained further traction in the past decade particularly following the publication of standardized diagnostic criteria by the World Heart Federation (WHF) in 2012 [4]. The value of echo screening in the control of RHD has been a subject of debate [5] in recent years [6]. Nevertheless, robust data from a landmark randomized-controlled trial strongly suggest that secondary antibiotic prophylaxis prevents the progression of latent RHD to moderate or severe stages of disease, thus supporting the clinical need for screening, even among asymptomatic individuals [7].

Key developments toward pragmatic echocardiographic screening capacity in LMICs have included: (a) development of handheld echo devices which are less expensive, generate smaller and shareable file sizes, and have a smaller profile without reliance on wired electricity [5]; (b) task-shifting of echo image acquisition from highly trained cardiologists and licensed sonographers to other healthcare workers such as nurses, allowing for expansion of screening capabilities; (c)

supportive cloud-based telemedicine programs for remote echo image interpretation; and finally, (d) expanding technological advances [8][9], with several companies now offering artificial intelligence guidance technology built into hand-held devices, thus empowering novice operators to perform screening echoes even after only minimal training, and promising deep learning approaches for automated flagging of abnormalities in the near future [10]. There is also an ongoing effort to improve and simplify the WHF criteria for the diagnosis of latent RHD [11], with additional development of risk scores to predict outcomes in both borderline and definite latent RHD [11].

1.2. Establishment of RHD Registries and Big Data Resources

With the increasing interest in meeting the RHD challenge in endemic countries, a number of large disease-specific registries have been established in LMICs. These have illuminated the dire epidemiologic situation of clinical RHD in these settings [2][12][13]. The hospital-based sub-Saharan Africa Survey of Heart Failure (THESUS-HF) registry study showed that RHD was the second major cause of acute heart failure hospitalizations, with an inpatient mortality rate of 4.2% and a 180-day mortality rate of 17.8% [14]. The VALVAFRIC [15], REMEDY [16], and certain national [17][18] registry studies provide the most recent descriptions of chronic RHD complications in patients residing in low- and middle-income countries. In general, they have established that clinical RHD in LMICs is characterized by late presentation with substantial established complications [17][18]. The clinical course is thus punctuated by recurrent hospitalizations and unacceptably early mortality (mean age at death of 29.4 years), with most of these deaths occurring within the first three months following diagnosis.

On the global scale, contemporary surveys continue to reveal worldwide RHD disparities, with low-income countries bearing a disproportionate burden of the disease. RHD currently affects 40.5 million people across the globe and accounts for 306,000 deaths annually—representing 1.6% of all mortality from cardiovascular disease, the leading cause of death worldwide [2]. The increased prevalence of RHD detected in recent studies, when compared to historical surveys, is most likely related to improved case detection attributable to the increased availability of echocardiography, better survival of affected individuals, and the chronic nature of the disease [2]. Sub-Saharan Africa retains the highest prevalence of clinically-apparent RHD [19], and there is some evidence that the true burden of RHD in some African countries may be much higher than previous estimates [20]. Today, the highest age-standardized disability-adjusted life year (DALY) rates attributable to RHD are in the regions of Oceania (627.4 per 100,000) and South Asia (348.5 per 100,000). In Australia and New Zealand, the highest rates of RF and RHD are found among indigenous populations [21][22]. Unfortunately, epidemiological data on RHD prevalence is least robust from the most affected regions [23]. National, regional and global RHD registries continue to report female predominance, however no gender-based differences in complications such as heart failure, atrial fibrillation, stroke and pulmonary hypertension have been noted.

2. Advances in Elucidating the Pathogenesis of RF/RHD

The general academic consensus remains that an immune-mediated pathologic process is the hallmark of RHD. Nevertheless, the exact mechanisms underlying this complex process have yet to be completely unveiled. Traditional dogma has held that GAS pharyngitis is responsible for triggering the immune reaction that leads to RHD pathology [24]. However, more recently, other superficial streptococcal infections, such as impetigo and pyoderma, have been found to be associated with RHD [25][26]. There is also emerging evidence potentially implicating group C and group G streptococcus in contributing to the pathogenesis of RHD [27][28][29][30][31].

The most widely accepted hypothesis in the pathogenesis of RF/RHD [32][33] is that molecular mimicry is responsible for the autoimmune phenomena of the disease, but more recent data suggests a more complex cascade of events, such as collagen-associated neo-antigens [34][35] epitope spreading [36], and T-cell receptor (TCR) degeneracy [37][38][39] may participate in the resultant pathology. Additionally, specific CD4+ T cells, as well as NK cells and CD4-CD8- T cells, might be important players in cardiac tissue destruction seen in RHD [40]. Recent efforts have been developed to take advantage of the intense GAS antigen-associated immune response for the creation of RF/RHD vaccines, but these have remained elusive largely due to lack of academic and financial investment [41]. Dissecting the immunopathogenic responses using state-of-the-art methods such as single cell RNA sequencing combined with TCR CDR3 region usage may open new insights to advance this field.

Furthermore, despite the widespread socioeconomic risk factors for RHD development present in LMICs, only a minority (roughly 3–6%) of GAS-endemic populations develop RF [24]. Furthermore, RHD is largely believed to have a complex genetic risk profile [42]. Historical RHD studies in twins have supported this postulation [43][44], and more recent modern genetic interrogation studies have she new light on RHD pathogenesis and predisposition.

Genetic associations in RHD have been explored through numerous candidate gene studies—for example, those reviewed by Martin et al. [45] and Muhamed et al. [46] elicited genetic associations in RHD through candidate gene studies. These have yielded conflicting and heterogeneous results, implicating a variety of genes with several listed study limitations [43][45][46] including those that have reported the association of human leukocyte antigen (HLA) molecules, encoded by genes on chromosome 6, and susceptibility to developing RF/RHD [43][47][48][49][50][51]. Within HLA genes, class II genes have been widely reported, with the majority linking HLA-DR7 [43][50] and HLA-DR4 [45][49][52] to the development of RHD.

There has also been interest in evaluating genetic polymorphisms coding for inflammatory mediators in RHD and their phenotypic expression. Polymorphisms in IL-2, IL-4, IL-6 and IL-10 genes have been associated with clinical disease, and the discriminative value of IL-4 to differentiate latent versus clinical RHD has been demonstrated [53]. Additionally, interleukins IL-4, IL-8 and IL-1RA seem to predict progression from latent to clinical RHD, while in individuals with advanced RHD, co-regulated expression of IL-6 and TNF-α are associated with severe valvular dysfunction, with higher IL-10 and IL-4 levels predicting adverse clinical outcomes [54].

The biggest advance in the field of RHD genetics has been genome-wide association studies (GWAS), of which four major studies have been published to date (**Table 1**) [47][55][56][57]. GWAS are considered more suitable studies for complex diseases in which large numbers of variants can be tested by comparing single-nucleotide polymorphism (SNP) distributions in patients with the disease against selected controls [58]. These GWAS studies have generated support for the presence of significant heritability in RHD, which is likely to be polygenic. The RhEumatiC Heart diseAse Genetics (RECHARGE) study is ongoing in Rwanda, using next-generation genetic sequencing on a sample of approximately 1000 participants (ClinicalTrials.gov Identifier: NCT02118818). It is expected to be completed in 2024. The importance of investing resources in the genetic association of RHD lies not just in the potential to substantially contribute towards understanding disease pathogenesis and etiology, but also the prospect of identifying novel or repurposed therapeutics and vaccine development [46].

3. Advances in Management of the RF/RHD Continuum

3.1. Progress Towards a Group A Streptococcus Vaccine

Efforts to create a vaccine to prevent GAS infections have been ongoing since 1923. However, the first vaccines were ineffective and highly reactogenic, raising concerns, though likely unfounded or overblown, about the potential for vaccines to increase ARF predisposition; this resulted in the US Food and Drug Administration (FDA) stopping GAS vaccine trials in the 1970s for over 30 years [59][60]. In the past two decades, studies on vaccine development have improved with advances in genomics, proteomics, and immunomics; still, most vaccines are in pre-clinical testing, and few have reached Phase I and II trials. Currently, there are no licensed vaccines of GAS available in any settings [60].

Vaccine candidates, however, include multivalent M protein-based vaccines, M protein vaccines containing conserved C-repeat epitopes, cell wall carbohydrate vaccines, and non-M protein multi-component vaccines. **Table 1** provides a summary of vaccines that are in the development pipeline. Vaccines based on group A carbohydrate (GAC), a polysaccharide present in *Streptococcus pyogenes* cell wall, have not shown expressive results yet [60].

Table 1. Group A *Streptococcus* vaccines that are in the development pipeline. * Pioneered by University of Tennessee and Dalhousie, Canada; ** Pioneered by Queensland Institute of Medical Research, Australia; Pioneered by University of São Paulo, Brazil.

Type of Vaccine	Stage of Development
StreptAvax: 26-valent vaccine	**Phase I and II trials demonstrated good safety, tolerance and immunogenicity [61][62]; however further studies stopped for commercial reasons**
StreptAnova *: 4 recombinant proteins	**The 4 recombinant proteins represent 30 different M-types prevalent in North America and Europe Phase I trial: demonstrated good tolerance and immunogenicity in adults [63].**
MJ8VAX **: based on C-terminus of the M protein	**Phase I trial: demonstrated that a single intramuscular dose of the vaccine was safe, well tolerated and immunogenic, but anti-J8 IgG concentration decreased after 180 days post immunization [64].**
StreptInCor: peptide vaccine containing T and B cell epitopes of the M protein CRR	**Good results in models [65].**

Type of Vaccine	Stage of Development
Multi-component vaccines [60]	3-Combo: SpyCEP, SpyAD, SLO; provides protection in models 5-Combo: ADI, TF, C5a peptidase, SpyCEP and SLO 5-CP: demonstrated protection against intranasal, skin and systemic challenges of GAS Spy-7: showed significant reduction in the dissemination of types M1 and M3 GAS

Prevailing challenges in vaccine development are multifactorial, ranging from incomplete understanding of the basic science of GAS/RF/RHD to lack of commercial stakeholder interest. Specific challenges for GAS vaccine development include: (a) extensive genomic heterogenicity of Strep A and subsequent protein sequence variations, limiting the effectiveness of the vaccine over different populations [60]; (b) complexity of global GAS epidemiology; (c) incomplete understanding of ARF pathogenesis; (d) risk of serious autoimmune reactions to vaccines [59]; (e) dependence on controlled human infection models for vaccine development as GAS is strictly a human pathogen, thus precluding the use of animal models [66]; (f) lack of consensus on clinical endpoints for establishment of proof of concept, (g) limited market in high-income countries; and h) lack of commercial interest [60].

In order to overcome the myriad challenges in GAS vaccine development, in 2018 the World Health Assembly (WHA) launched a Global Resolution calling for improved control and prevention of GAS infections and RHD [67]. In 2019, the Strep A Vaccine Consortium (SAVAC) was formed to work along the World Health Organization (WHO) [60]. Furthermore, through the Coalition to Advance Vaccines Against Group A Streptococcus (CANVAS), the Australian and New Zealand governments have designated significant funding to support the development of a vaccine against GAS pharyngitis [68].

3.2. Advances in Primary Prevention

Diagnosis of Group A Strep Pharyngitis

Microbiological culture of a throat swab remains the gold standard for diagnosing GAS pharyngitis, despite the prohibitive cost of this modality at a population level, the long turn-around time precluding confirmed diagnosis in a single clinic visit, and lack of readily available culture-able laboratories in LMICs. Recognizing these limitations, alternative diagnostic tests which are less resource-intensive have been developed and continue to evolve.

Clinical decision rules can obviate the need for expensive bacteriological diagnostic tools since they do not require specialized equipment and are easy for providers to implement [69][70][71]. There has been a proliferation of Clinical Decision Rules (CDRs) for diagnosis of GAS pharyngitis in recent years [69][70][72][73][74][75][76][77]. Recent developments relevant to RHD endemic regions include: (a) validation studies of existing CDRs in RHD endemic regions [78] that have concluded that diagnostic performance varies considerably in different regions of the world, thus highlighting the importance of evaluating and validating CDRs in local settings before they are rolled out as the standard of care; and, (b) development of CDRs in RHD endemic regions such as the Cape Town Clinical Decision Rule [69] in South Africa. The Cape Town Clinical Decision Rule is likely a more relevant application to similar settings in sub-Saharan Africa. Tailoring decision rules to a specific population is a critical research area for population specific investment in LMICs.

Rapid Antigen Detection Tests (RADTs) have been in clinical use for four decades, with attractive features such as a quick turn-around time (<10 min), low cost, and ease of use. Recently, some external performance factors were learned, such as inadequate staff training, substantially reduce the accuracy of these tests [79]. There is also greater understanding of factors that potentially increase heterogeneity of testing results that have similar sensitivity and specificity [80] such as differences in throat culture sample collection [80][81], experience of the person performing the RADT, absence of a universally accepted blood agar plate culture method to serve as a reference standard [82], patient-level characteristics such as clinical presentation and inoculum size [83], and spectrum bias [84]. However, despite multiple advantages, RADTs remain vastly unavailable and are considered expensive for many low-resource settings. There is an overarching need to make existing RADTs available and affordable for use in such settings.

More recent progress in point-of-care tests for GAS pharyngitis include Nucleic Acid Amplification Tests (NAATs), which have much better sensitivity and specificity than RADTs [85]. For example, the sensitivity and specificity of the Illumigene assay are estimated to be in excess of 99% [85][86][87]. This high performance, coupled with speed of results, makes NAATs ideal candidates for point-of-care use in the clinical environment. Several NAATs have received approval over the past six years [88], but their high cost has precluded widespread use. Despite the prevailing cost, NAATs are being increasingly investigated as low-cost, integrated tools for use in low resource settings [89][90]. Research should strive towards the development of molecular diagnostic tests using a “pharyngitis panel” of targets.

Electrochemical detection methods, which use DNA, have been proposed as an affordable, effective method for diagnosing GAS; results are available in 30 minutes with 100% specificity, have been reported [91][92].

Machine learning and artificial intelligence techniques are also in development to aid in the diagnosis of strep throat through throat image processing [93] and automated examination of throat cultures to identify GAS [94]. Neural networks have also been suggested to assist in diagnosis, with reported correct diagnosis of pharyngitis in 95.4% of test cases in one study [95]. The Strepic® device, a qualitative point-of-care clinical prototype, has been designed specifically as a viable, low-cost, commercially realizable autofluorescence-based diagnostic test (ClinicalTrials.gov Identifier: NCT03777098).

Treatment of Group A Strep Pharyngitis

Penicillin remains the first line recommendation for the treatment of GAS pharyngitis, with two Cochrane reviews supporting this recommendation [96][97]. Monthly intramuscular injections of benzathine benzyl penicillin (BPG) remain the gold standard for secondary antibiotic prophylaxis for the prevention of RHD [98][99]. Recent strategies to diminish pain [100] associated with BPG administration include the addition of lidocaine to BPG solution [101][102] and the use of pain distraction methods (buzzy R) [102][103][104][105]. There is also work underway in developing implantable and longer acting BPG delivery devices [106][107][108]. The WHO added BPG to the essential medicines list for member states as a way to increase access, however, disruptions in global and local BPG supply chains are not uncommon [109][110]. Regrettably, a recent report described geographically widespread reduced in-vitro susceptibility of *Streptococcus pyogenes* to beta-lactam antibiotics associated with mutations in the pbp2× gene [111], warranting enhanced surveillance and further epidemiological and molecular genetic study of this potential emergent antimicrobial threat.

Community and provider knowledge and awareness of the RHD-GAS relationship remain a pillar of primary prevention strategies. While previous awareness campaigns heavily utilized print and mass media [112][113][114], increasing availability of sophisticated personal technologies such as mobile devices and internet access (particularly in low-resource settings), have resulted in the employment of new electronic avenues of patient, public, and stakeholder education about RHD [115].

Additionally, it has been noted that streptococcal carriage rates often vary between communities and by season, especially in endemic countries [116][117]. It has thus been postulated that the GAS carrier state is not implicated in the pathogenesis of RF/RHD, and that transmission of GAS is almost limited exclusively to individuals with acute GAS infection [118][119]. Therefore, antibiotic treatment for eradication of GAS has been recommended only for individuals with acute GAS infection. However, this traditional benign dogma of the carrier state is being challenged and revisited, with additional investigation necessary to determine if this paradigm holds true in endemic regions of the globe.

3.3. Advances in Secondary Prevention

The Jones criteria for the diagnosis for ARF were first established in 1944 [120]. Since their inception, the criteria have undergone multiple revisions and updates, most recently in 2015 [121]. This most recent revision addressed two significant features: it (a) distinguished criteria between low-risk and moderate-to-high risk populations based on ARF incidence or RHD prevalence; and (b) recommended echocardiography of all suspected cases of ARF and incorporated subclinical carditis as evidenced by echocardiography as a major criteria. Differentiating criteria for low-risk and moderate-to-high risk populations aimed to increase sensitivity in endemic regions while retaining specificity in low-risk areas, thus making the criteria more globally relevant. However, ARF still remains a clinical diagnosis with no single confirmatory test, and there is ongoing work attempting to identify a unique immune signature that could be used to reliably diagnose ARF [122]. For example, in routine clinical practice it is often not feasible to obtain both acute and convalescent sera and therefore, the absolute quantitative measure of anti-streptolysin (ASO) titers is used more for diagnostic value [123]. However, there is wide geographic variability of the 80th percentile upper limit of normal (ULN) cutoffs for ASO titers [124][125]. It is therefore important to establish ULN ranges of ASO titers for various age groups in different geographic locations. Accordingly, there have been recent studies in some RHD endemic regions describing their population-specific streptococcal antibody titers [126].

This is particularly relevant, because, as previously mentioned, there is recent evidence for the benefit of secondary penicillin prophylaxis for prevention of progressive cardiac disease in latent RHD [7]. The recent GOAL trial demonstrated that among children and adolescents 5 to 17 years of age with latent RHD, secondary antibiotic prophylaxis reduced the risk of RHD progression at two years followup time [7]. This new evidence provides added justification for echocardiographic screening and active case detection of RHD as a key step in the control of RHD sequelae in susceptible populations.

3.4. Procedural and Medical Advances in Tertiary Care

Procedural Advances in RHD-Associated Valvular Disease

There is a growing body of evidence to support the use of PBMV for RHD-associated mitral stenosis, and the indications have considerably expanded in the past decade to include challenging and unfavorable MV involvement. Furthermore, additional prognostic parameters have been investigated—such as asymmetrical commissural fusion and atrioventricular compliance—and the Wilkins score has been updated with parameters derived from international RHD cohorts [127]. Meanwhile, percutaneous valve interventions continue to evolve worldwide, with transcatheter aortic valve implantation for the treatment of aortic stenosis (more below) being a prime example of such advances [128]. With its successful implementation, percutaneous valve intervention is gaining attention as a feasible treatment for both mitral and aortic valve disease, as well as an option for second valvular interventions after the failure of the primary valve surgery—common in RHD—with additional outcome information to be established in the upcoming decades [129][130].

TAVR is an established minimally invasive alternative to surgical aortic valve replacement (SAVR) in patients with severe aortic stenosis (AS) and calcific aortic valve disease [131][132]. In RHD with aortic involvement, SAVR is still the first choice of intervention due to the lower degree of valve calcification seen in rheumatic valves in most cases [132][133], younger age of patients, and limited scientific evidence of TAVR for RHD-associated AS [133]. Until recently, knowledge surrounding the application of TAVR for RHD patients was limited to case series and reports [132][134][135][136]. However, there is contemporary evidence for non-inferiority of TAVR to SAVR in rheumatic AS, safety of TAVR, and short and intermediate term outcomes of TAVR [132][135]. These novel data have changed the perspective of TAVR for RHD, suggesting it as a feasible approach for RHD patients with predominant aortic valve involvement. However, wider spectrum studies with larger subject numbers and long-term outcomes reports in RHD-specific patient populations are warranted in order to achieve generalization of such findings.

Advances in Medical Management of Clinical RHD

Given the limitation of surgical treatment options for many patients with symptomatic RHD in low-income regions, medical management remains a critical cornerstone of therapy for those awaiting or unable to obtain operative management of advanced valvular RHD. Unfortunately, medical therapy to date has yet to demonstrate slowed progression of the disease. As such, pharmacologic treatment has targeted symptom relief by addressing underlying left ventricular dysfunction and heart failure or by addressing the end-stage complications of RHD [137].

Atrial fibrillation (AF) is a major cause of morbidity and mortality in patients with RHD [16][137][138]. Anticoagulation is recommended to reduce the risk of cardioembolic events in patients with AF, often associated with advancing valvular pathologies [16][138][139]. Oral Vitamin K antagonists are the recommended drugs of choice for this purpose [137], but they are associated with challenges both for health care providers and patients in monitoring and maintaining their effectiveness [138][139]. New evidence may revolutionize anticoagulation in rheumatic atrial fibrillation, as novel oral anticoagulants (NOACs)—not yet formally recommended for AF in the presence of RHD—have proven to be non-inferior to warfarin in a Brazilian trial which allowed the inclusion of RHD patients with atrial fibrillation and bioprosthetic mitral valves [140]. The multicenter INVICTUS trial [141] examining warfarin versus rivaroxaban in rheumatic AF is nearing completion and may bring more definite conclusions in the near future. However, even if NOACs become a standard for anticoagulation in RHD, access and cost-effectiveness will require careful discussion for their use in LMICs, given the higher present market price of these drugs [142].

Another chief clinical concern among advanced RHD patients remains that of infective endocarditis in both prosthetic valves and diseased native heart valves. Given the lack of scientific evidence in reducing infective endocarditis (IE) burden in the absence of prosthetic valves or previous history of IE, antibiotic prophylaxis for dental procedures has been relegated to a limited role in recent professional society guidelines [143]. Currently, recommendations for such chemical prophylaxis is limited to high-risk patients—noticeably those following valve replacement or those with a previous IE episode—undergoing high-risk procedures with potential bacterial translocation [144]. Good dental hygiene and regular dental cleanings, however, still play an important role in IE prevention and should be emphasized [143].

4. RHD Policy Advances

4.1. Understanding of RHD-Associated Costs in Endemic Regions

RHD costing data from endemic countries and regions has historically been quite sparse. However, cost-effectiveness analyses comparing primary, secondary, and tertiary prevention of RHD in the African setting have recently been

conducted [145]. Such findings have revealed that scaling up primary prevention would be a cost-saving approach, with a negative incremental cost-effectiveness ratio (ICER) of -$2539 USD per DALY averted, whilst putting efforts into secondary prevention programs would be cost-effective (USD $752 per DALY averted) [145]. The investments required for local surgical capacity development were high with limited impact (ICER of USD $23,827 per DALY averted for constructing a local surgical center) [145]. Several other analyses have separately explored optimal cost-effective strategies for primary prevention [146], secondary prevention [147][148][149][150], and a combination of both [150][151][152]. A recent modeling study for the prevention and management of RHD in the African Union concluded that, “In the short term, costs of secondary prevention and secondary and tertiary care for RHD are lower than for primary prevention, and benefits accrue earlier [153]”. Most analyses make use of Markov models, and similar challenges relating to lack of precise transition probabilities on which to base the calculations have been reported [145][148][151].

Additionally, recent studies regarding the cost of illness have described the substantial economic impact of RHD at the household, health system, and national level in endemic countries such as Uganda [154], South Africa [155][156], India [157][158], and others [159].

4.2. Global Efforts, Advocacy, and Stakeholder Engagement in the Fight against RHD

The growing research and healthcare/awareness projects in RHD worldwide, combined with a considerable increase in research interest over the past two decades, has raised multisectoral attention regarding this neglected disease. This has resulted in international coordination of efforts which have been multifaceted, with ambitious aims (**Table 2**).

Table 2. Summarized aims of global efforts in the fight against RHD, and key charges from the 2018 WHA resolution to member states. Abbreviations: RHD, rheumatic heart disease; WHO, World Health Organization; WHF, World Heart Federation; WHA, World Health Assembly.

Summarized Aims of Global Efforts in the Fight against RHD
• **Developing a collaborative agenda to address the key health impacts of RHD worldwide (premature morbidity and mortality, maternal deaths)** • **Improving access to basic healthcare, from prophylaxis to more advanced therapies** • **Sensitizing stakeholders and the political sector on the importance of RHD and the need for reducing its burden, especially in the hardest hit regions** • **Developing position statements, guidelines, and calls-to-action focused on RHD** • **Including RHD as a priority in the world agenda, establishing action plans and goals led by international organizations such as the WHO, WHF, and key cardiovascular societies**
Key Charges from the 2018 WHA Resolution to Member States [160][161][162]
• **Accelerate multisectoral efforts to improve socioeconomic determinants of RHD** • **Estimate the burden of disease and implement multisectoral RHD programs** • **Improve access to primary health care, including RHD prevention and control** • **Ensure access to cost-effective essential laboratory technologies and medicines for RHD** • **Strengthen national and international cooperation to address RHD.**

As an example of practical outcomes of this international coordination, in 2011 the United Nations set key targets to reach by 2025, including a reduction in the risk of premature noncommunicable disease death–markedly cardiovascular disease–by 25% by 2025; with RHD notably included in this agenda [163]. Consequently, multiple authoritative individuals [164][165], societies, task forces, unions and federations, at regional, continental and international levels have published position statements [163][166][167][168][169], serving as a basis for guiding research and healthcare initiatives, helping define “next steps” and priorities for the global scientific agenda. The WHF has played a particularly pivotal role in such initiatives, with its first broad position statement on RHD released in 2013 reinforcing key aims and actions in a similar direction of preceding African statements [169]. More recently, there was a re-dedication of the American Heart Association (AHA) on the RHD agenda [170] with resumption of its intensive work on the development of guidelines and statements [121][137], research funding through its councils, and a working group dedicated to RF and RHD control.

These aforementioned position publications and statements from different organizations and regions, combined with the intensive collaborative multisectoral efforts worldwide, were recognized by the 2018 World Health Assembly Global Resolution to end RHD [160][161][162]. The key charges that this resolution brought to member states are listed in **Table 2**. In light of this unprecedented collaborative resolution, health systems should move towards enacting its actionable recommendations, increasing investment in primary care and general health infrastructure, sanitation and housing, medical supply and building capacity for RHD prevention and management.

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