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Research priorities for the secondary prevention and management of acute rheumatic fever and rheumatic heart disease: a National Heart, Lung, and Blood Institute workshop report

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ABSTRACT

Secondary prevention of acute rheumatic fever (ARF) and rheumatic heart disease (RHD) involves continuous antimicrobial prophylaxis among affected individuals and is recognised as a cornerstone of public health programmes that address these conditions. However, several important scientific issues around the secondary prevention paradigm remain unresolved. This report details research priorities for secondary prevention that were developed as part of a workshop convened by the US National Heart, Lung, and Blood Institute in November 2021. These span basic, translational, clinical and population science research disciplines and are built on four pillars. First, we need a better understanding of RHD epidemiology to guide programmes, policies, and clinical and public health practice. Second, we need better strategies to find and diagnose people affected by ARF and RHD. Third, we urgently need better tools to manage acute RF and slow the progression of RHD. Fourth, new and existing technologies for these conditions need to be better integrated into healthcare systems. We intend for this document to be a reference point for research organisations and research sponsors interested in contributing to the growing scientific community focused on RHD prevention and control.

SUMMARY BOX

- ⇒ Important scientific issues around the rheumatic heart disease (RHD) secondary prevention paradigm remain unresolved.
- ⇒ We need a better understanding of RHD epidemiology to guide programmes, policies, and clinical and public health practice.
- ⇒ We need better strategies to find and diagnose people affected by acute rheumatic fever (ARF) and RHD.
- ⇒ We urgently need better tools to manage acute RF and slow the progression of RHD.
- ⇒ New and existing technologies for ARF and RHD need to be better integrated into healthcare systems.

INTRODUCTION

For over 70 years, we have known that individuals affected by acute rheumatic fever (ARF) and rheumatic heart disease (RHD) experience poor outcomes when they are repeatedly exposed to group A Streptococcus (GAS) infection or recurrent episodes of ARF.[1] Evidence and international consensus since that time have supported the use of continuous antimicrobial prophylaxis ('secondary prevention') to prevent such recurrences. Secondary prevention is the cornerstone of WHO-endorsed ARF and RHD control programmes[2] and has been argued to be the most cost-effective strategy for reducing RHD mortality.[3]

Despite the widespread acceptance of secondary prevention, several critical scientific and practical questions remain unresolved. For example, formulations of penicillin, the antimicrobial of choice, have not been modernised, and guidelines for its duration and dose are based on historical practices.[4] In addition, susceptibility to and patterns of presentation of ARF and RHD are probably driven by genetic factors and systemic autoimmunity, but the mechanisms of pathogenesis, markers for diagnosis and therapeutics remain incompletely understood and largely unexplored.[5] Finally, when large-scale secondary prevention programmes have been deployed—largely in better resourced

countries, such as Australia—they have not achieved the expected level of success,[6] suggesting that we need to reconsider long-standing assumptions and truisms about treatment approaches and programme implementation.

In November 2021, the US National Heart, Lung, and Blood Institute held a workshop on research for RHD prevention and control. This paper is a report from the Secondary Prevention Working Group that was tasked with identifying critical gaps in scientific knowledge regarding RHD secondary prevention and management. These topics presented in this paper were identified through literature review and deliberation among the Working Group members. We view them as the most urgent and highest-priority research topics in RHD secondary prevention and management. The research priorities centre around four pillars, further elaborated in this report:

1. We need a better understanding of RHD epidemiology to guide programmes, policies and practice.
2. We need better strategies to find and diagnose people affected by ARF and RHD.
3. We urgently need better tools to manage ARF and slow the progression of RHD.
4. New and existing technologies need to be better integrated into healthcare systems.

KEY RESEARCH TOPIC 1: IMPROVE RHD DESCRIPTIVE EPIDEMIOLOGY AND OUTCOMES MEASUREMENT

Gap analysis

Disease surveillance is a critical health system function, and the ability to track fatal and nonfatal outcomes from RHD over time is essential to determine the effectiveness of secondary prevention programmes. Such data inform policy development and programme design, and monitoring and evaluation. Through numerous systematic reviews[7] and modelling studies (eg, the Global Burden of Disease Study[8]), we now have a good understanding of the prevalence of RHD in low-income and middle-income countries, especially among schoolchildren. RHD appears to affect 1%–3% of these populations, with subclinical and 'borderline' cases comprising the vast majority. Fewer studies have looked at RHD in community settings and among adults, but these have generally found a higher prevalence than in schools.[9] From longitudinal and data linkage studies, we have a reasonable understanding of complication rates and adverse events among the minority of individuals with symptomatic RHD.[10 11]

By contrast, we know very little about long-term outcomes among individuals with asymptomatic RHD through echocardiography studies. It is possible that many of these individuals will have a less aggressive form of RHD, with little to gain from long-term antibiotic prophylaxis. These heterogeneous types of RHD with potentially different trajectories means that estimates of complication and case-fatality rates in studies of symptomatic RHD could potentially overestimate the burden of RHD at the population level by sampling only from the sickest individuals. There are also data gaps regarding preceding GAS infections and ARF attacks among individuals with severe RHD, obscuring our ability to quantify the health benefits of primary prevention interventions.

Another critical missing link in disease measurement is mortality risk. The challenge is that most countries where RHD is endemic have no vital registration or sample registration systems, so mortality estimates for these countries, produced by the WHO and by the Global Burden of Disease Study, come from statistical models that use cause-of-death data from other countries with lower RHD rates.[8] As a result, existing mortality estimates for RHD are probably too low, with deaths in younger adults being misclassified by these models as deaths from ischaemic heart disease or stroke rather than RHD. A recent modelling study explored the potential risks of undercounting RHD deaths in this region.[3]

Suggested approaches

To improve global estimates of RHD burden, we need two critical types of data that do not currently exist. First, we need longitudinal studies of disease progression, complication rates and excess mortality risk among representative samples of persons with RHD in the general population, not highly biased samples from tertiary hospitals. Second, we need detailed, nationally representative cause-of-death data for RHD—perhaps in tandem with measurements of other cardiovascular diseases—in countries that do not currently have good vital registration systems.

These two types of data could be obtained by establishing surveillance sites with sufficient resources to do frequent screening for RHD among the public and follow individuals for many years, with linkages to healthcare utilisation datasets and death certification. In principle, these sites could have substantial benefits beyond RHD, for example, by screening for other structural heart diseases and doing assessments related to ischaemic heart disease and stroke and their major risk factors. The Health and Demographic Surveillance Sites model could be adapted to gain insights into long-term trends in cardiovascular-specific outcomes in the general population.[12] Such research efforts should be done in partnership with local governments to strengthen health information systems and vital registration systems rather than compete with or inadvertently undermine them.

KEY RESEARCH TOPIC 2: IMPROVE DIAGNOSIS OF ARF

Gap analysis

There is no diagnostic test for ARF; diagnosis relies on recognition of clinical features, imaging tests and non-specific laboratory tests that are generally unavailable in low-resource settings,[13] home to over 80% of people living with RHD. Yet early ARF diagnosis is critical: without it, children and young adults cannot benefit from secondary prevention. When the first iteration of the Jones Criteria

was published in 1944, the set of clinical and laboratory criteria that were proposed were intended to be a placeholder until an ARF diagnostic test was developed. Yet in the 80 years since, there has been relatively little investment in ARF diagnostics and major gaps exist in our understanding of ARF pathogenesis, in improving case presentation, recognition and diagnosis using existing knowledge and tools in low-resource communities, and in applying modern scientific methodology to identification of biomarkers that could inform diagnosis.

Suggested approaches

Approach 1: improve our understanding of ARF pathogenesis

An improved understanding of ARF pathogenesis is critical to improving ARF diagnosis and developing ARF therapeutic approaches to prevent progression to chronic RHD. While a dominant paradigm of ARF pathogenesis, which centres around the concepts of autoimmunity and 'molecular mimicry',[14] has long been supported, our understanding of these mechanisms is incomplete. In this traditional model, repeated GAS infections can, in susceptible individuals, lead to a cytokine and T-cell driven response that also stimulates autoantibody production by B cells, promoting inflammation and fibrosis.[15] The term 'mimicry' reflects similarities in the group A carbohydrate and streptococcal M protein and intracellular proteins or glycosylated expressed in various human tissues that are affected by autoantibodies and T cells that cross-react with heart valve tissues and others. Development of RHD is characterised by fibrosis of the heart valves, especially the mitral valve, which is driven by anticardiac myosin and potentially anticollagen autoantibodies and T cells.

More recently, other mechanisms affecting disease initiation and progression have been proposed.[16] The preferential and near-universal involvement of the mitral valve in ARF and RHD, and the development of RHD in previously unaffected pulmonary valves following the Ross procedure, suggest an interaction between haemodynamic stress and epigenetic priming during ARF, potentially influencing progression of valvular disease. Experimental studies suggest that activation of the TGF-β pathway could underlie this interaction. Further, histopathological studies have demonstrated increased TGF-β expression in heart valve tissue, and patients with RHD appear to have a higher prevalence of genetic polymorphisms that facilitate TGF-β signalling. Identifying alternative mechanisms of disease progression can help identify new drugs with therapeutic potential. Losartan, for example, modulates TGF-β signalling and could thus slow disease progression,[16] though its effect still needs to be demonstrated in clinical trials.

To improve our understanding of ARF pathogenesis, we need studies that can better understand early-stage versus late-stage disease. Such a distinction would help confirm the role of ongoing autoimmunity in progression to RHD and could help identify both biomarkers (for developing gold-standard diagnostic tests, see below) and potential mechanisms that could be targeted by novel or repurposed disease-modifying agents (see below). In addition, the role of genetic risks in ARF is largely unexplored. Twin and family studies support the notion of genetic susceptibility to ARF (heritability=0.60).[17] One recent candidate gene study found an association of the mannose-binding lectin 2 gene with risk of ARF, including among individuals with ARF who never developed RHD.[18] This discovery raised the question of the role of complement activation in ARF and RHD, suggesting yet another pathogenic pathway. We need large-scale genome-wide association studies (GWASs) of ARF like we have for RHD (see below) to further explore these promising findings.

Approach 2: make better use of existing tools and strategies to improve ARF case detection

Worldwide, most patients who are diagnosed with RHD receive their diagnosis when the disease is advanced. Very few can recall a history consistent with ARF and even fewer were ever diagnosed with this preceding condition. Lack of ARF diagnosis represents an enormous opportunity loss to initiate secondary prevention, the only medical intervention known to improve outcomes. Improving diagnosis of ARF in low-resource settings is a critical priority.

Currently, diagnosing ARF in resource-limited settings is very challenging. One obstacle is lack of community awareness of ARF and RHD, for example, fewer than one in five individuals in a study from Cameroon.[19] Furthermore, a related obstacle is also the lack of awareness of ARF and RHD among healthcare workers.[20] The biggest obstacles, however, are the logistical barriers to diagnosing ARF. For example, the lack of specialised laboratory tests and cardiac ultrasound at the district level in Uganda substantially lowered the predictive value of other tests (ie, components of the Jones criteria) that were available; only at the country's tertiary cardiac centre was diagnostic capacity adequate.[21]

There is some evidence that these challenges can be overcome. Recently, an active community ARF surveillance programme in northern and western Uganda used healthcare worker education and community-based education (mass media, school-based education, village health teams, etc) to increase awareness that fever and joint pain could be ARF.[22] This approach rapidly increased the volume of ARF evaluations over the study period, with hundreds of children being confirmed to have possible or definite ARF.

Since the Jones Criteria require diagnostics that are rarely available in high-risk communities, high-value research would focus on developing simplified algorithms to enable at least provisional diagnosis until a full evaluation can be completed. The American Heart Association, Reach and the World Heart Federation recently developed such an algorithm, but its feasibility, effectiveness and cost-effectiveness are unclear. In addition, we need better strategies to improve health-seeking

behaviour in high-risk populations and raise awareness among frontline providers.

Approach 3: identify ARF biomarkers and translate these biomarkers into diagnostic tests

A diagnostic biomarker for ARF could be transformative. Recent small-scale studies have shown that identification of such a biomarker is possible, perhaps using GAS antibodies, autoantibodies, and complement and other soluble factors.[23] In addition, others are applying systems biology approaches to prospectively collected ARF cases and controls.[24] These studies may identify novel biomarkers that deepen our understanding ARF pathogenesis and potentially lead to better ARF diagnostics.

However, diagnostics research for ARF should be based in endemic countries. Biomarker discovery and validation need to use biological samples from children and adolescents living in endemic settings. Sampling approaches should have sufficient diversity and numbers to capture the heterogeneity of ARF presentations and outcomes and ensure global applicability of findings and future diagnostic tools. As no true gold standard for ARF diagnosis exists, these studies need rigorous, blinded case and control adjudication and comparison to the current standard, the 2015 Jones criteria.

When considering candidates, an ideal ARF biomarker would have high global discriminative ability (as compared with diseases with clinical overlap), feasibility in ARF-endemic settings (assay complexity/cost considered), and ideally, biological plausibility. As biomarkers are identified, it will be important to form partnerships with industry and philanthropy to ensure a final product that is available and affordable in endemic countries. In addition to its clinical uses, a low-cost ARF biomarker could be useful for conducting public health surveillance to identify outbreaks and to evaluate the impact of RHD prevention programmes.

KEY RESEARCH TOPIC 3: IMPROVE DIAGNOSIS OF RHD

Suggested approaches

Approach 1: Improve our understanding of RHD risk

While it has long been established that there are both genetic and environmental risks for developing RHD, the nuances of those risks are unclear. We have yet to fully understand the drivers of risk between GAS infection and development of ARF, the factors that influence if a person who suffers from ARF will develop chronic RHD, and how this knowledge could improve identification of high-risk individuals. Understanding why only some affected by ARF go on to develop RHD can help us tailor recommendations regarding use and duration of secondary prevention based on individual risk to reduce the burden on healthcare systems and patients and rationalise the long-term use of antibiotics.

Environmental susceptibility

Most of the differences in RHD risk across populations are probably the result of environmental factors, but the contribution of individual factors is less clear, since most are associated with conditions of socioeconomic disadvantage.[25] The best-described environmental risk is household crowding,[26] which may also be the most amenable to targeted interventions. Little has been done in research for primordial RHD prevention, but a pilot study of a community-led programme including primordial and primary prevention in Northern Australia suggests this approach could be feasible.[27] Future research on environmental susceptibility as it relates to secondary prevention should focus on improving the understanding of risk for progression, need for cardiac intervention and mortality. This work could identify important environmental modifications and have an impact of risk stratification to inform secondary prevention strategies and duration.

Genetic susceptibility

While environmental exposure to the GAS trigger is probably the most important determinant, only some exposed people develop ARF, and only a subset of these go on to develop RHD[1]; implying genetic factors are also at play. A recent RHD GWAS confirmed that RHD susceptibility was polygenic, and the narrow-sense heritability was somewhere in the middle (0.49), suggesting that its variability is due to a combination of genetic and environmental factors.[28]

Since the 1980s, candidate gene studies have identified associations of >75 different genetic factors with ARF/RHD, including *HLA* and other genes. However, only ~9% of these genetic factors have been replicated in larger studies such as GWASs, and <10% supported by a systematic review of 42 candidate genes from 66 global studies.[29] Thus, novel, more powerful, genome-wide methods were used for four recent GWASs, which identified novel genetic influences determining disease susceptibility to RHD,[28 30–33] with a higher replication rate (67%).[28] Since, the first few GWAS findings have raised more questions than answers, and the numerous older candidate gene study findings have a low replication rate, more up-to-date genetic work is required to reduce our knowledge gaps.

To improve our understanding of the genetic influences determining disease susceptibility, development and progression in RHD, we need several critical data that do not currently exist, as well as leverage the latest genetic data available from large consortia. First, we need to perform more case–control and population-based genetic studies in diverse populations, where there is an elevated burden of RHD. Preferably, the genetic material can be run through whole genome sequencing technology to run wholistic genetic analyses from GWASs (for common variants) to rare variant association studies (to better understand genetic factors for disease severity). Furthermore, integrating multiomics could help determine the role or function of candidate genetic factors in RHD development.

Second, we need to meta-analyse all available genetic data to find candidate key genetic risk factors that could be routinely used to screen for an elevated disease risk or susceptibility, across several high-risk populations, and establish candidate alternative targets for therapeutic and vaccine development purposes. We could also use these genetic data to develop and use polygenic risk scores for the early detection of high-risk individuals, that would need specialised prevention/vaccines.[34]

Third, we need to leverage the latest genetic data available (eg, from large consortia) to test causal relationships of different complex traits, biomarkers and drugs on RHD via Mendelian randomisation.[35] This may assist in the discovery of novel RHD risk factors, intermediate phenotypes or outcomes and candidate drugs.

Risk stratification

Ultimately, a more nuanced approach to antibiotic prescription and duration would ensure optimal outcomes and efficient use of limited resources. Good risk stratification would leverage a range of variables, including initial echocardiographic presentation, environmental risks and potentially genetic risks. A simplified score to predict RHD outcome at the time of presentation was recently developed and validated retrospectively in cohorts in Uganda and Brazil[36]; another study found that it had good performance in discriminating cases in other countries.[37]

Risk stratification has relevance for children found to have latent RHD. In a trial of secondary prevention among children with latent RHD, nearly half showed echocardiographic improvement, with most having normal echocardiograms after 2 years whether they received antibiotic prophylaxis or not.[38] A planned subanalysis of risk factors for progression among these children is ongoing, and a follow-up study will refine recommendations around the duration of secondary prevention in this group (ClinicalTrials.gov: NCT05211024).

Approach 2: Develop scalable, sustainable models for active case-finding

Active case-finding is a missing link to increasing uptake of secondary prevention. Over four in five persons with RHD are diagnosed late in the disease course when the opportunity to benefit from secondary prevention has largely passed. Developing effective strategies to identify more people with early RHD is crucial. Echocardiographic screening has been used for 15 years to characterise the burden of RHD in low-resource populations, mainly by screening schoolchildren. We know that it is feasible to screen in low-income settings using portable devices[39] and that such devices have good sensitivity and specificity for RHD[40] in the hands of nurses and other non-expert providers.[41] While some work has been done to develop and test standardised training curriculums,[42] these have not been tested or rolled out into general practice.

Future research on active case-finding should focus on scalable models for training and competency testing, including approaches such as train-the-trainer courses. These studies should not be confined to clinical research settings: they should be real-world studies that emphasise linkage to care and provision of secondary prevention through the general healthcare system. We also need empirical evidence that active case-finding is cost-effective and sustainable in countries whose primary healthcare systems are already overstretched. One promising approach to reducing the cost of active case-finding is the use of artificial intelligence tools, which could support image acquisition by laypersons and guide image interpretation.

Finally, we note that current and novel genetic technologies and findings, combined with other 'omics' approaches to disease screening, could be used to develop less-invasive or non-invasive ways to screen for RHD in low-resource settings, potentially reducing the need for echocardiography-based mass screening.

KEY RESEARCH TOPIC 4: IMPROVING MANAGEMENT OF ARF AND RHD

At present, ARF is managed largely by providing supportive care until symptoms resolve. The lack of effective treatment options for ARF means that, when people are diagnosed with the condition and are at a key point of contact with the health system, they can only be offered supportive care and secondary prevention.

Suggested approaches

Approach 1: Develop new technologies to improve outcomes of ARF

There are important gaps in our knowledge about disease-modifying agents to treat ARF to prevent or mitigate RHD to complement secondary prevention. Trials of corticosteroids, adrenocorticotrophic hormone, cortisone, aspirin, non-steroidal anti-inflammatory drugs and intravenous immunoglobulin in ARF have failed to show improvement in RHD outcomes.[43] Unfortunately, many of these trials were conducted more than half a century ago, used clinical instead of echocardiographic endpoints, and had unclear treatment allocation and blinding and generally low quality by modern standards. Contemporary trials of ARF therapeutics are of high priority. Initial trials could focus on existing low-cost therapeutics that can be repurposed in ARF, and future trials of therapeutics may be informed by emerging discoveries about ARF pathogenesis coming from unbiased approaches, as outlined above.

As an example, hydroxychloroquine, a widely used, safe and inexpensive immunomodulatory agent, has emerged as a potential treatment for ARF, with case reports of its safety and possible efficacy in rheumatic carditis.[44] The rationale came from in vitro studies described above in which hydroxychloroquine suppressed the overproduction of proinflammatory cytokines in children with

ARF.[45] A safety and tolerability study of hydroxychloroquine in rheumatic carditis is currently being undertaken to address this question,[46] with a randomised trial anticipated to follow. The repurposing of hydroxychloroquine suggests that other immunomodulatory therapies successful in related conditions such as rheumatoid arthritis and multiple sclerosis (eg, rituximab) could specifically target the B cell antigen-presenting or autoantibody response and slow or halt disease progression. Plasmapheresis, although unconventional, has also been proposed for use in Sydenham chorea and could alleviate symptoms within 48 hours.[47]

Approach 2: Innovate strategies to improve adherence to secondary prevention

Long courses of antibiotic prophylaxis are challenging to maintain. The minimum duration in most guidelines is 10 years; in severe cases, lifelong prophylaxis may be recommended.[4] Even modest non-adherence raises the risk for recurrent ARF, a key driver of RHD.[43] In a 2017 systematic review that included studies in 19 diverse populations, intramuscular penicillin adherence was less than 50% in eight studies, with another seven studies reporting an adherence of 50%–80% and only four studies reporting adherence of >80% (the accepted threshold of adequate adherence).[47]

Research into the drivers of intramuscular penicillin non-adherence has consistently identified both patient-level barriers (including pain of injections, missed work/school and high out-of-pocket travel costs) and health system barriers (including infrastructure, cost, staff time and healthcare worker training) as contributors to low adherence. Unfortunately, intervention studies in real-world conditions have had little success in improving adherence, even in higher-resourced settings.[6]

We do know that adherence can be optimised. The GOAL trial[38] used community engagement groups to design strategies for retention and adherence. A two-pronged system, including (1) case managers who formed bonds with families and provided personalised support and (2) every 4-week peer play and support groups, resulted in high retention (97%) and high adherence (99%) to monthly intramuscular penicillin injections. As this was in the context of a trial, these strategies had access to resources that might not be available in everyday clinical practice. A new pragmatic trial, CAMPS (ClincialTrials.gov: NCT05502042), is determining the feasibility of implementing this approach in the public healthcare system in Uganda, deploying village health team members to serve as case managers and peer group coordinators.

Interestingly, there is a lack of implementation science-oriented research on RHD secondary prevention despite its widespread use in cardiovascular research more generally. There are several promising implementation strategies that have been explored for RHD,[48] such as awareness-raising campaigns, clinical decision support tools, integrated quality improvement tools and use of electronic registries—some of which have been tested under the guise of clinical research. What is needed is to re-examine these strategies and test them rigorously using implementation science theories, models and frameworks.[49]

The ongoing Active Case Detection and Decentralized Dynamic Registry to Improve the Uptake of Rheumatic Heart Disease Secondary Prevention (ADD-RHD) study is one example of an implementation science approach to secondary prevention. Registry-based care is recommended as the most effective way to deliver secondary prevention, but registries are not being used on the front lines in most countries. Further, most individuals with RHD must travel long distances to hospitals to get routine outpatient care, posing financial and logistical barriers. ADD-RHD is developing a cloud-based registry called the Active Community Case Management Tool and teaching primary healthcare nurses in northern Uganda how to use it, along with providing general training on administration of secondary prevention. Once these workers are trained, patients with RHD, who are currently only able to get their injections at far-off regional referral hospitals, will have their care decentralised to the communities where they live. ADD-RHD uses a hybrid effectiveness-implementation design to test these implementation strategies and assess via mixed-methods approaches whether they can increase retention in care and adherence while maintaining safety and patient satisfaction.

We stress that future innovations in adherence support will need to be codesigned with communities and health systems in mind, acknowledging that there will always be major challenges posed by needing to provide long-term, monthly intramuscular injections to children and adolescents. This work could also borrow on success in other areas, such as HIV treatment adherence, where community action groups, accountability partners and community-based delivery of medications through village health teams have been effective strategies in achieve high adherence to medications in low-income and middle-income countries.[50]

Approach 3: Drug discovery and development for secondary prevention

Existing clinical guidelines give preference to 3–4 weekly intramuscular benzathine penicillin G over other drug regimens.[4] These recommendations come from decades-old studies showing that penicillin can reduce recurrences of ARF and that injectable, long-acting forms are more effective than oral forms.[51] However, there are important reasons to re-evaluate these recommendations. The data are based on four small randomised controlled trials (around 1000 patients), all from the USA, in an era that predated echocardiography. Endpoints for these studies included recurrent ARF and GAS pharyngitis; the studies did not measure clinically relevant outcomes, such as progression of heart disease, mortality and adverse events. The quality of these studies was also low, with most having unclear treatment allocation and

blinding and absence of prophylaxis adherence data, among other concerns.[9] Further, the oral penicillin given in these studies used a less bioavailable form of oral penicillin (30% compared with >60% in modern formulations).

Older studies support the notion that oral penicillin is associated with a low frequency of ARF recurrence, comparable to intramuscular penicillin. In addition, oral penicillin remains an option in most major guidelines and is already preferred by many practitioners. What is needed are new experimental research studies to definitively establish the appropriateness of oral versus intramuscular penicillin in patients representing a range of RHD severity.

Research is also needed to explore new preparations of penicillin and to explore the efficacy of alternate antibiotic regimens. Very long-acting formulations of penicillin—such as subcutaneous or implantable products—have the potential for improved pharmacokinetic properties and may allow for better adherence.[52] More importantly, antimicrobials that are equivalent or superior to benzathine penicillin—in terms of efficacy, safety and acceptability to patients—are desperately needed but do not appear near on the research horizon.

THE NEED TO ESTABLISH AN INTERNATIONAL ARF/RHD CLINICAL NETWORK

As underscored throughout this report, the volume of clinical research on ARF and RHD has steadily increased in recent years, but research efforts have often been fragmented and of variable quality, leaving many key questions unanswered. The existing landscape of relatively small-scale, localised studies is both ineffective and inefficient. Without having the momentum of practice-changing research, it can be challenging to engage researchers and clinicians. The failure to work together on clinical research leads to missed opportunities to improve the lives of people and communities affected by RHD.

Research networks allow for the study of several related questions in large numbers of patients, magnifying the impact of resources.[53 54] For example, acute coronary syndrome registries led to tools such as the Global Registry of Acute Coronary Events score, which helps optimise patient care for this condition.[55] Due to its protracted nature, RHD presents problems associated both with rare diseases, for example, the relatively small number of identified ARF cases and scarce tissue specimens for laboratory-based research, and with commonly encountered ones, for example, the large number of patients with established valve disease and their wide variation in treatment patterns and outcomes. Multinational studies can effectively address these problems. Further, demonstrating improvements in clinical outcomes relies on high-quality, adequately powered studies. These studies often require many more participants than can be recruited from single centres or even from one country.

In addition, a network centred on South-South collaborations that target marginalised, Indigenous,

Table 1 Overview of research priorities in the secondary prevention and management of ARF and RHD

Key research topics	Suggested approaches	Example outputs
Measurement of RHD burden and outcomes	Population-based cohort research	In-depth data on progression and mortality in the general population (identified via echo screening)
Diagnosis of ARF	ARF pathogenesis research	Better understanding of early versus late ARF and mechanisms for progression amenable to treatment
	Optimise existing tools for case detection	Simplified diagnostic algorithms tailored to low-resource settings and epidemiology
	Biomarker research and new diagnostics	Novel, low-cost, omics-based gold standard test for ARF to supplant the Jones criteria
Diagnosis of RHD	Understanding risk factors	GWAS-informed point-of-care test for RHD risk to tailor secondary prevention recommendations
	Scalable models for active case-finding	Novel AI-driven approaches to RHD diagnosis and to performance of echo screening by laypersons
Management of ARF and RHD	ARF therapeutics research	Repurposing of immunomodulatory drugs (eg, rituximab) for ARF to slow RHD progression
	Adherence to existing penicillin regimens	Model package of proven implementation strategies for use in RHD programmes
	Research and development for new secondary prevention drugs	Very long-acting (eg, implantable) formulations of penicillins and other drugs Genomics-driven drug discovery based on disease-susceptibility genes

ARF, acute rheumatic fever; GWAS, genome-wide association study; RHD, rheumatic heart disease.

and resource-limited populations will have the greatest potential to generate practice-changing outcomes and address stark inequities in the distribution of research initiatives. This network could build research capacity in low-income and middle-income countries that would generate benefits beyond RHD. Related efforts have already produced useful results.[56 57] What is needed is catalytic support for a research network that includes a coordinating role, for example, harmonising study protocols and overseeing the equitable distribution of resources across diverse sites. An early priority for this network would be developing a portfolio of trials that tackle many of the issues discussed previously regarding new ARF treatments and better approaches to secondary prevention.

CONCLUSIONS

RHD is a neglected disease of poverty. Despite all that is known about ARF and RHD pathogenesis, clinical management and outcomes, the condition suffers from a lack of research investment—even compared with other neglected tropical diseases.[58] On secondary prevention, clinicians and health planners largely rely on low-quality to moderate-quality evidence that is over four decades old. Table 1 summarises the recommendations of our Working Group for secondary prevention-related research.

Historical experience with ARF and RHD in selected middle-income countries[59] suggests that these conditions can be eliminated in a relatively short timeframe (on the order of ten years[60]) with concerted public health efforts. We contend that more can be done to build the toolkit for ARF elimination and accelerate this trajectory. Critical investments in new knowledge, technologies and implementation research can modernise the playbook for RHD prevention and control and lead to better, more sustainable reductions in RHD than were achieved in the past, and hopefully at lower cost. Because of their medical complexity and wide-ranging implications for health systems, ARF and RHD can serve as useful models for cardiovascular research in an international context, and secondary prevention represents an exciting opportunity to achieve important and transformative quick wins.

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