Acute rheumatic fever

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Lancet 2025; 405: 2164–78

Published Online June 5, 2025 https://doi.org/10.1016/S0140-6736(25)00185-0

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Acute rheumatic fever (ARF) is an autoimmune disorder resulting from Group A Streptococcus (GAS) pharyngitis or impetigo in children and adolescents, which may evolve to rheumatic heart disease (RHD) with persistent cardiac valve damage. RHD causes substantial mortality and morbidity globally, predominantly among socioeconomically disadvantaged populations, with an interplay of social determinants of health and genetic factors determining overall risk. ARF diagnosis is based on a constellation of clinical and laboratory features as defined by the 2015 Jones Criteria, although advances in molecular point-of-care testing and the ongoing search for ARF biomarkers offer the potential to revolutionise diagnostics. There are persistent gaps in ARF pathophysiology with little progress in therapeutics over the last several years. The greater focus towards primordial, primary, and secondary prevention such as advances in GAS vaccine development, innovations in digital health technology, improved antibiotic formulations for secondary prevention, and decentralised programmatic implementation to improve health-care delivery offer feasible solutions towards reducing future ARF burden globally.

Introduction

Acute rheumatic fever (ARF) is a systemic autoimmune syndrome involving the joints, heart, brain, skin, subcutaneous tissues, or a combination, that develops following exposure to Group A Streptococcus (*Streptococcus pyogenes*; GAS) pharyngitis or impetigo. Although most symptoms resolve within weeks to months, approximately half of those with rheumatic carditis will progress to have rheumatic heart disease (RHD) with persisting cardiac valve damage.

Despite recent advances in medical research and health-care delivery, ARF and RHD continue to result in substantial death and disability worldwide, largely affecting socioeconomically vulnerable populations. This Seminar presents key updates on ARF with advances in research and health-care delivery since the last Seminar, published in 2018,[1] highlighting ongoing gaps in knowledge and research priorities.

Search strategy and selection criteria

We searched PubMed from Jan 1, 2018, to July 31, 2024, for English-language articles using the terms "acute rheumatic fever", "rheumatic fever", and "ARF" alone and in combination with other terms including "rheumatic heart disease", "RHD", "*Streptococcus pyogenes* ", "Group A Streptococcus", "GAS", "epidemiology", "social determinants of health", "pathophysiology", "autoimmune", "molecular mimicry", "genetics", "genome-wide association studies", "biomarker", "corticosteroids", "benzylpenicillin", "echocardiogram", "primordial prevention", "primary prevention", "secondary prophylaxis", and "vaccine". Using snowballing, we selected relevant publications from the reference lists of the retrieved articles and reviews. All types of study were considered for inclusion, including randomised controlled trials (RCTs), cohort studies, case–control studies, cross-sectional studies, case reports, systematic reviews, and meta-analyses; however, priority was given to studies with high-quality evidence, particularly RCTs, systematic reviews, and large observational studies. We chose to include more recent publications (within the past 5 years) over older ones that illustrated the same point. To provide readers access to more articles, we have included citations to other comprehensive reviews on the subject.

Epidemiology

ARF is a precursor condition of RHD, which contributes to considerable mortality and morbidity among disadvantaged populations globally. The predicted global burden of ARF is likely inaccurate and underestimated.[2–5] Variability in clinical diagnostic practices, the absence of an accurate diagnostic test, constrained echocardiography resources, and the absence of national epidemiological surveillance systems affect confirmatory diagnosis and accurate data collection.

GAS is estimated to have caused 618 million new infections and half a million cases of ARF annually in 2019.[6] There has been an overall decline in the global incidence of ARF, particularly in certain middle-income and high-income countries (HICs), since the early 20th century, largely due to improved public health conditions. However, emergence of new rheumatogenic GAS strains and changes in host susceptibility have resulted in occasional ARF outbreaks in HICs.[7–9]

The annual incidence of ARF was estimated to range from 8 to 51 per 100 000 children and young people in the previous ARF Seminar in 2016, based on prospective studies conducted largely within health-care settings.[1] Although many countries have strengthened their RHD surveillance in the past decade, there are limited data relating to the incidence and prevalence of ARF in the last decade, with great variation within different regions of affected countries, and marked ethnic variability. Some countries, such as Australia, New Zealand, Uganda, and Sudan have made greater investment towards ARF, generating more comprehensive epidemiological and research data.[10–13]

There have been greater efforts to collect national and global epidemiological data for RHD, partly reflecting cases of undiagnosed ARF resulting in progressive cardiac valve damage.[4,14] Data extrapolated from the Global

	Age-standardised incidence rate (95% UI)	Age-standardised prevalence rate (95% UI)	Age-standardised death rate (95% UI)	Disability-adjusted life years (95% UI)
Global	50·7 (40·1–63·1)	684·2 (540·4–848·9)	4·5 (3·9–5·3)	162·1 (139·1–190·5)
African region	93·7 (72·9–118·0)	1336·7 (1021·2–1691·8)	2·7 (2·4–3·2)	139·1 (110·2–178·9)
Region of the Americas	42·9 (34·8–52·8)	641·2 (521·2–783·5)	0·9 (0·8–1·0)	55·0 (43·4–71·2)
South-East Asia region	44·2 (34·8–55·6)	628·9 (429·1–787·5)	11·2 (9·3–15·1)	346·3 (292·1–439·8)
Eastern Mediterranean region	53·4 (42·1–66·5)	758·7 (601·0–933·1)	6·5 (5·2–8·6)	240·3 (197·1–305·7)
Western Pacific region	35·6 (28·3–44·2)	542·2 (431·3–666·3)	3·3 (2·7–4·1)	97·9 (81·7–117·4)
European region	12·8 (11·0–14·9)	167·6 (145·6–194·7)	1·6 (1·4–1·7)	42·6 (38·9–47·5)

95% UI=95% uncertainty interval. Disability-adjusted life-years are age-standardised. All measures are reported per 100 000 of the population.

Table: **2021 Global Burden of Disease estimates for rheumatic heart disease globally and across WHO regions[4]**

Burden of Diseases, Injuries, and Risk Factors Study (GBD) estimates the RHD prevalence in 2021 at approximately 55 million, representing a 1·7-fold increase from 1990.[4,14] This increase can largely be attributed to population growth, although improved ability to diagnose ARF and RHD are contributing factors. The poorest nations bear the largest RHD burden and ARF likely mirrors this distribution. The table summarises 2021 GBD estimates for RHD across WHO regions, although it is important to note there are marked variations within regions and nations (eg, age-standardised incidence rate in Northern Africa is 49·4 [95% UI 38·0–61·6] per 100 000 and 129·1 [99·2–165·5] per 100 000 in Southern Africa).[4] RHD burden is projected to be as severe in the next decade, remaining highest in low-income and middle-income countries (LMICs), with the fastest increase in Australasia, highlighting the need for urgent interventions.[15]

Risk factors and genetics

The GBD data show an inversely proportional relationship between the RHD burden of a country or region and its sociodemographic index (a composite measure of income, educational attainment, and fertility rate).[3,4,16] Social determinants of health strongly determine the overall risk of GAS infection, subsequent ARF, and its progression to RHD, with modifiable risk factors such as household overcrowding and access to primary care playing a key role (figure 1).[17–20]

The highest incidence of ARF is among school-aged children, consistent with the peak incidence of GAS infections.[2,6] A seasonal variation has been observed, with a higher incidence in winter, highlighting respiratory transmission in closed indoor environments such as schools and household overcrowding as major risk factors.[21,22] The prevalence of RHD is highest among those aged 25–29 years, with an equal gender distribution until adolescence followed by a strong female predominance thereafter.[2,16] Although RHD is a common cause of heart failure globally, it has a greater contribution to the burden among women of childbearing age, with a predicted increase in this gap over the next decade.[15,23] The gender discrepancy in prevalence is higher within low sociodemographic index regions, suggesting an interplay between biological factors and broader social determinants of health. Opportunistic health assessments during antenatal care and pregnancy with increased risk of disease progression during this time could account for increased diagnosis.

Familial aggregation of ARF and RHD cases support a longstanding interaction between predisposing genetic and environmental factors. Within the regions of Oceania and Canada, Indigenous people carry a higher burden of ARF and RHD than non-Indigenous people.[10,24] A case control study in New Zealand (124 cases and 372 controls) found a five-times higher risk of ARF (OR 5·0 [95% CI 2·5–9·8]) among those with a family history, even when social and environmental factors were accounted for, supporting previous twin studies suggesting a 60% genetic heritability estimate.[20,25] Echocardiography of parents and siblings of 70 children with ARF reported the relative risk of RHD to be 2·5 times the background population prevalence in New Zealand (95% CI 1·4–4·4%; p=0·001).[26]

Although human leukocyte antigen (HLA) and non-HLA factors have previously been implicated, genome-wide association studies have led to emergence of stronger data to support genetic susceptibility to RHD in recent years.[27,28] There is clearly not a single gene, but plausible evidence that a genetic risk may be a small part of the pathophysiology. Key genome-wide association studies are summarised in panel 1.

Pathophysiology

The immunomodulatory mechanism that underpins the pathophysiological basis of ARF remains incompletely understood. A process of molecular mimicry, triggered by a superficial GAS infection, is believed to result in clinical manifestations of ARF (figure 2).[33,34]

Among Aboriginal and Torres Strait Islander people in Australasia, where GAS pharyngitis is less common, GAS impetigo is perceived to be the driver of ARF, often precipitated by scabies.[35] Population administrative datasets from New Zealand report markedly higher

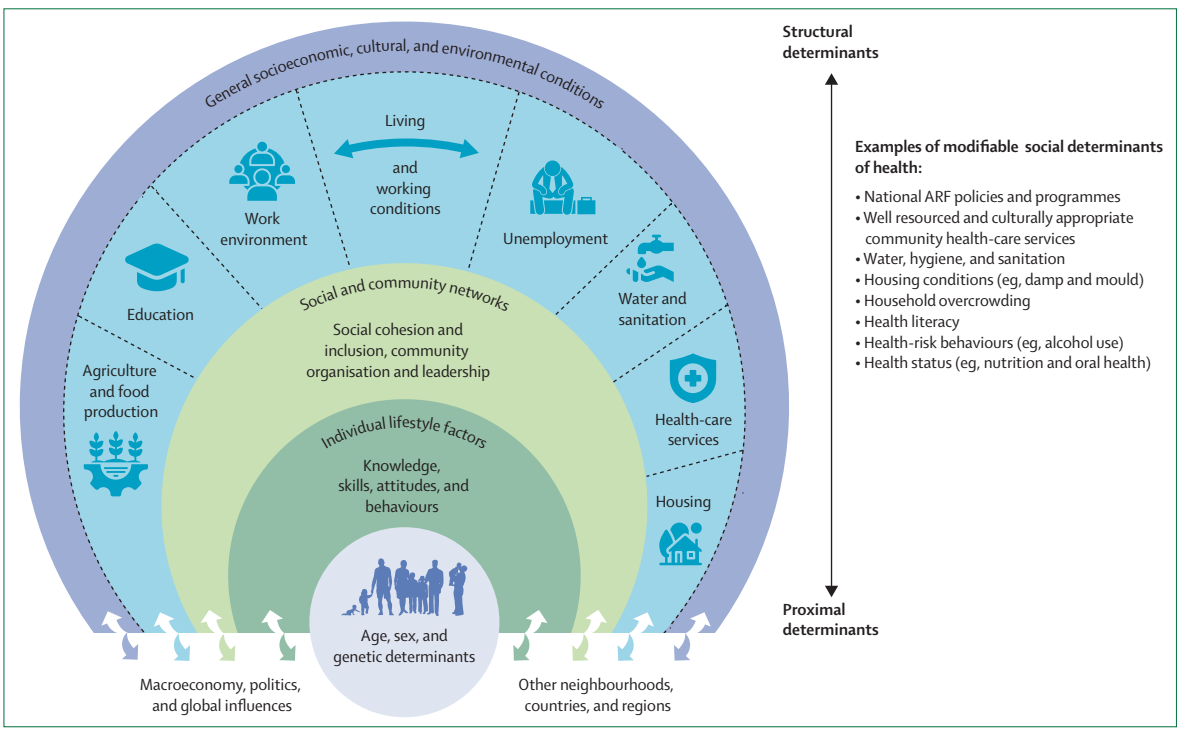

Figure 1: **Social determinants of health**
The Dahlgren and Whitehead model[17–19] depicts social determinants of health that influence the risk of Group A streptococcus infection, acute rheumatic fever, and progression to rheumatic heart disease in a population. Social determinants of health include structural (eg, economic and political systems) and proximal determinants, consisting of components of daily life (eg, family environment, housing, traditional practices), the socioeconomic environment (including macroeconomic measures such as wealth), demography, lifestyle, and behaviour. ARF=acute rheumatic fever.

Panel 1: Key genome-wide association studies supporting genetic susceptibility to rheumatic heart disease

- *IGHV4-61*02*: a susceptibility signal in the immunoglobulin heavy chain locus corresponding to the *IGHV4-61*02* allele has been associated with a 1·4-fold increased risk of rheumatic heart disease among 1016 Indigenous peoples of the South Pacific (399 cases; 617 controls).[29]
- *HLA-DQA1_DQB1*: specific risk (*HLA-DQA1*0101_DQB1*0503*; *HLA-DQA1*0103_DQB1*0601*) and protective (*HLA-DQA1*0301_DQB1*0402*) haplotypes for rheumatic heart disease have been identified with variations in *HLA-DQA1_DQB1* among 1263 Aboriginal Australians (398 RHD cases; 865 controls).[30]
- Class 3 region of the HLA complex: a rheumatic heart disease susceptibility signal in this region has been identified among 1163 South Asians (672 cases; 491 controls) in India and Fiji, and subsequently confirmed with a European Biobank dataset (150 cases; 1309 controls).[31]
- 11q24.1: the genetics of RHD (RHDGen) study, a multi-centred genome-wide association study comprising 4809 participants (2548 rheumatic heart disease cases and 2261 controls) from eight African nations, identified a single rheumatic heart disease susceptibility locus (11q24.1) among Black African individuals.[32]

HLA=human leukocyte antigen. RHD=rheumatic heart disease.

rates of GAS impetigo and ARF incidence among Māori and Pacific Peoples.[36] Additionally, retrospective analysis of administrative data estimated the risk ratio of developing ARF 8–90 days following a GAS-positive throat swab at 4·8 (95% CI 3·6 to 6·4) and GAS-positive skin swab at 5·1 (95% CI 1·8 to 15·0) among this population.[37] Asymptomatic household members with GAS detected from pharyngeal swabs or impetigo have been implicated in transmission networks of GAS supporting a role for subsequent development of ARF; however, the exact pathophysiology remains poorly understood.[38]

Clinical features and diagnostics

2015 Jones Criteria

The diagnosis of ARF is based on a combination of features showing the presence of systemic inflammation variably affecting the joints, heart, brain, skin, and subcutaneous tissues (panel 2), with a fever and evidence of antecedent GAS infection, in the absence of other causes. The Jones Criteria, developed in 1944 with subsequent revisions by the American Heart Association, was last revised in 2015.[39,47,48] The criteria provide a diagnostic framework for ARF by dividing clinical features into major and minor manifestations based on prevalence and specificity (panel 3).[39] Although it is a valuable diagnostic tool for ARF, non-specific features such as arthralgia or elevated erythrocyte sedimentation rate (ESR) can result in misdiagnosis, with unnecessary secondary antibiotic prophylaxis, patient and parental anxiety, and the potential for adverse antibiotic reactions, particularly

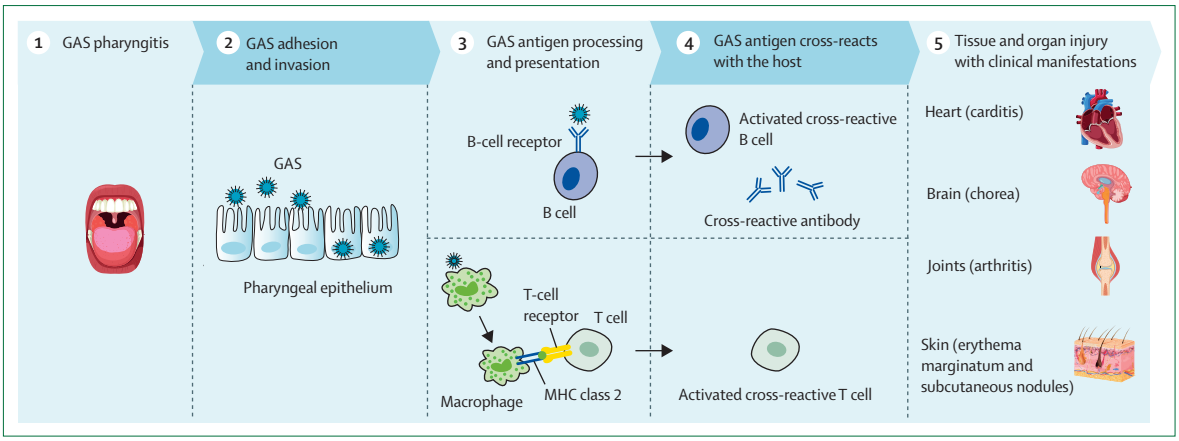

Figure 2: **The process of molecular mimicry in the pathophysiology of acute rheumatic fever**
Following GAS pharyngitis (1), there is adhesion and invasion of the pharyngeal epithelium (2). Presentation of GAS antigens results in activation of B cells and T cells (3). Activated T cells and antibodies produced by activated B cells cross-react with antigenic epitopes (4) in the heart, brain, joints, and skin and subcutaneous tissues resulting in clinical manifestations of acute rheumatic fever (5). Cross-reactive antibodies bind to Group A carbohydrates, triggering increased expression of vascular cell adhesion molecule 1 in the cardiac valve endothelium, causing T-cell infiltration and cytokine-mediated immune damage. Cross-reactive antibodies binding to dopamine receptors and lysogangliosides result in Sydenham's chorea. A delayed hypersensitivity reaction causes the skin and subcutaneous tissue manifestations while immune-complex deposition in the joints results in arthritis. GAS=group A *Streptococcus*. MHC=major histocompatibility complex.

Panel 2: Common clinical features of acute rheumatic fever

Joint manifestations

Joint manifestations occur in approximately 60–80% of ARF cases, commonly presenting as a nonsuppurative, asymmetric, migratory polyarthritis predominantly affecting the large joints (eg, wrist, elbow, ankle, knee).[39] Monoarthritis and polyarthralgia are seen in high-incidence areas. Symptoms are managed with non-steroidal anti-inflammatory drugs and largely resolve spontaneously within 4 weeks. Rarely, Jaccoud arthropathy, a non-erosive arthropathy classically resulting in ulnar deviation of metacarpophalangeal joints, can occur.[40]

Carditis

Endocarditis (valvulitis) involving regurgitation of the mitral valve followed by the aortic valve is the hallmark of rheumatic carditis. Pericarditis can occur and usually resolves without long-term sequelae. Systolic dysfunction from primary myocarditis is uncommon, however can occur in cases of recurrent acute rheumatic fever.[41]

Mitral regurgitation classically presents with a high-pitched, apical, holosystolic murmur radiating to the axilla or a low-pitched mid-diastolic Carey Coombs murmur. A pericardial rub can be heard in the presence of pericarditis. Approximately 12–21% of cases are, however, subclinical.[39] Cardiac rhythm disturbances are often self-limiting and can occur in the absence of valvulitis with approximately half of patients showing prolonged PR intervals. Rarer rhythm disturbances include accelerated junctional tachycardia, premature contractions, and second-degree heart block. QTc prolongation in the early phase of acute rheumatic fever is likely benign, but QT prolonging medications should be used with caution.[42]

Severe cardiac complications such as complete heart block, cardiomegaly, and congestive cardiac failure are relatively uncommon.

Sydenham's chorea

Chorea is a cardinal feature of acute rheumatic fever, occurring in 10–30% of cases with a female predominance and peak incidence in pre-pubertal children.[39] Sydenham's chorea commonly presents with carditis, but can occur in isolation with a latent period of 1–6 months and the absence of serological evidence of Group A streptococcus infection. The typical presentation is purposeless, involuntary movements of the extremities and trunk, which disappear during sleep.[43] Other presenting features include neuropsychiatric disturbance, dysarthria, dysgraphia, and hypotonia.[44,45] Symptoms commonly remit within 6 months, however can persist for up to 2 years, and relapses can occur.

Skin and subcutaneous manifestations

Skin and subcutaneous manifestations are rare (<10%) and consist of erythema marginatum and subcutaneous nodules.[41] Erythema marginatum is a non-pruritic, evanescent, maculopapular, blanching rash with a serpiginous border.[46] The rash manifests on the trunk and limbs, sparing the face, palms, and soles, and might not be evident on dark skin tones. Subcutaneous nodules are small, firm, mobile, and painless nodules occurring over extensor joint surfaces (eg, elbows, knees, and ankles), the occiput, and vertebrae, and are usually associated with carditis.

Panel 3: 2015 Jones Criteria for diagnosis of ARF[39]

For all patient populations with evidence of preceding Group A Streptococcus infection

- Diagnosis of initial ARF: two major manifestations or one major plus two minor manifestations
- Diagnosis of recurrent ARF: two major criteria or one major and two minor criteria or three minor criteria

Major criteria

*Low-risk populations**

- Carditis (clinical or subclinical)†
- Arthritis (polyarthritis only)
- Chorea
- Erythema marginatum
- Subcutaneous nodule

Moderate-risk to high-risk populations

- Carditis (clinical or subclinical)
- Arthritis (monoarthritis or polyarthritis); polyarthralgia‡
- Chorea
- Erythema marginatum
- Subcutaneous nodule

Minor criteria

*Low-risk populations**

- Polyarthralgia
- Fever (>38·5°C)
- ESR greater than 60 mm/h, CRP greater than 3 mg/dL (>30 mg/L), or both§
- Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion)

Moderate-risk to high-risk populations

- Monoarthralgia
- Fever (>38°C)
- ESR greater than 30 mm/h, CRP greater than 3 mg/dL (>30 mg/L), or both§
- Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion)

ARF=acute rheumatic fever. CRP=C-reactive protein. ESR=erythrocyte sedimentation rate. *ARF incidence is less than 2 per 100 000 school-aged children per year or all-age rheumatic heart disease prevalence of less than or equal to 1 per 1000 population per year. †Subclinical carditis indicates echocardiographic valvulitis. ‡Polyarthralgia should only be considered as a major manifestation in moderate-risk to high-risk populations after exclusion of other causes. Joint manifestations can only be considered in either the major or minor categories, but not as both in the same patient. §The CRP value must be greater than the upper limit of normal for the laboratory. Also, because ESR might evolve during ARF, peak ESR values should be used.

within the possible ARF diagnostic category.[49] Numerous clinical syndromes can present with overlapping clinical features (eg, malaria, arboviral infections, septic arthritis), although data from Uganda suggest a reassuringly low risk of false negative diagnosis with use of these criteria.[50] Providing evidence of antecedent GAS infection to support the diagnosis of ARF remains an ongoing challenge. A comprehensive outline of superficial GAS infection, including clinical assessment and conventional diagnostics are provided in the appendix (pp 1–2).

See Online for appendix

Within LMICs, as well as remote regions of HICs, resource limitations and lack of diagnostics can hinder the ability to diagnose GAS and ARF. An epidemiological study conducted in Uganda reported that community health centres largely relied on clinical assessment for diagnoses, district hospitals had basic diagnostics such as electrocardiography and full blood count, whilst conventional GAS diagnostics (eg, C-reactive protein, ESR, and echocardiography) were only available in tertiary referral hospitals.[51] A statistical model with clinical variables predicted ARF with an optimism-corrected area under the curve (c-statistic) at 0·7 in community health settings, 0·8 in district health settings, and 0·9 in tertiary health settings. Logistical barriers, gaps in knowledge related to ARF and RHD, limited awareness of diagnostic guidelines, and absence of clear referral pathways to tertiary referral centres for further diagnostic tests pose further barriers.[51] In contrast, delayed or missed ARF diagnosis in low-endemic settings can result from lack of familiarity with diagnostic criteria and a low index of suspicion, despite the availability of adequate resources.[52]

Advances in GAS point-of-care testing

The successful implementation of rapid molecular diagnostic testing for diagnosis of conditions such as tuberculosis, HIV, and SARS-CoV-2 in recent years has prompted research for molecular GAS point-of-care testing.[53,54] Rapid molecular diagnostic testing has a superior sensitivity compared to rapid antigen detection tests, whilst offering the same advantages of a rapid turnaround time and ease of use by non-laboratory trained health-care providers.[55] A prospective study conducted in Australia comparing the GeneXpert (Cepheid, Sunnyvale, CA, USA) point-of-care test with cultures of throat samples reported a sensitivity of 100% and specificity of 79%, with reported positive predictive values of 49% and negative predictive values of 100%.[56] There was, however, a stronger correlation between GAS serology and molecular point-of-care testing, suggesting the so-called false-positive results could reflect the detection of DNA from GAS after active infection or are below the threshold of culture positivity. This finding suggests the potential value of molecular point-of-care testing in the diagnostic work-up of ARF to identify preceding GAS infection, although further research is warranted in this area. Similarly, a prospective study conducted within a hospital emergency department in New Zealand reported the same GAS GeneXpert molecular test to be highly sensitive with a strong negative predictive value, supporting its use as a point-of-care testing for pharyngitis.[57]

The possibility of a rapid scale-up of GAS molecular point-of-care testing by incorporating the test into the panel of pathogens of already existing GeneXpert platforms is promising, although logistical challenges such as staff training and maintenance costs need to be considered for sustainable implementation.[53,54] The

advent of artificial intelligence (AI) technology and its expanding application for disease diagnosis across various disciplines offers scope to use AI to support GAS diagnosis.[58] Early research into the use of impedimetric biosensors to detect GAS antibodies also provides the prospect of rapid GAS detection.[59]

ARF biomarkers

The absence of an accurate diagnostic test for ARF remains a major impediment towards the reduction of ARF disease burden globally. There is an ongoing search for biomarkers that reliably distinguish ARF from other conditions with similar or overlapping clinical features. The ongoing Searching for a Technology-Driven Acute Rheumatic Fever Test study is the most comprehensive biomarker study being conducted to date, which entails extensive immune profiling of patients with ARF, and age, sex and ethnicity-matched eligible controls across Australasia to generate biomarker signatures for ARF.[60] Global collaborations and donor funding are key to accelerating the progress towards ARF biomarker discovery, as evidenced by the ARF Diagnosis Collaborative Network (comprising experts from six continents), which has been supported with substantial funding from the Leducq Foundation in 2021.

Echocardiography in ARF

Increased availability and technological advances in echocardiography in the last decade have revolutionised the ability to diagnose ARF on the basis of mitral or aortic valvulitis in the absence of clinical findings.[39] In RHD endemic settings, the majority of ARF cases are still missed and present with long-term sequelae of RHD.[61] A recent study in Sudan has shown a substantial burden of ARF that was unmasked by the application of echocardiography among febrile children.[62]

A detailed description of echocardiographic findings in ARF has been reviewed.[39] Valvulitis is the most consistent feature of ARF, and isolated pericarditis or myocarditis should almost never be considered rheumatic in origin. Clinical carditis has been a major manifestation of ARF since the original Jones criteria and continues to be accepted as such in all populations. Echocardiography provides the ability to detect subclinical carditis (ie, pathological valvular regurgitation detected on echocardiography that is not evident clinically), a much-needed addition with more availability of reliable cardiac ultrasound. Thus, the concept of subclinical carditis has become increasingly accepted and incorporated into guidelines as a major manifestation of ARF.[39,63] The major criterion of carditis requires the presence of pathological mitral or aortic regurgitation (or both), as defined by the 2023 World Heart Federation (WHF) guidelines (panel 4).[64] Valvular regurgitation in ARF is secondary to various mechanisms including valvulitis, annular dilatation, leaflet prolapse, and chordal elongation or rupture, all of which can be detected on echocardiography. The typical morphological changes of RHD often develop at a later stage and thus are not required for the diagnosis of acute carditis in the setting of ARF. The study conducted in Sudan by Sulafa and colleagues shows that echocardiography increased the sensitivity of ARF diagnosis, with up to 11% of children having subclinical carditis as their only major manifestation.[62] This finding underscores the need for decentralisation of echocardiography services to improve ARF detection in RHD endemic settings.

In the setting of RHD, differentiation between acute valvulitis and established RHD continues to pose a clinical dilemma. No evidence exists for the use of echocardiography to differentiate between acute-on-chronic valvulitis and chronic RHD. Echocardiography cannot accurately measure when the rheumatic changes occurred, but a comparison with previous echocardiograms to assess the severity and progression of the valve lesions might be useful in determining whether there is acute valve inflammation in an ARF recurrence. Details of the diagnostic criteria, disease staging, and medical management of chronic RHD, which are outside the scope of this seminar, are available in the 2023 WHF guideline document.[64]

ARF recurrences

The natural history of ARF without SAP is recurrence with exposures to new strains of GAS. Panel 3 provides the diagnostic criteria for an ARF recurrence. The risk of recurrent ARF and progression from rheumatic carditis to RHD is highest in the first year after the initial ARF episode.[65] Carditis and congestive cardiac failure are the most common presentation of recurrent ARF, highlighting the value of echocardiography.[66–68]

Panel 4: **Confirmatory criteria for pathological valve dysfunction (2023 World Heart Federation guidelines)[64]**

Pathological mitral regurgitation (at least mild; all criteria must be met)

- Observed in at least two views
- Observed in at least one view, mitral regurgitation jet length measures equal to or greater than 1·5 cm (in individuals weighing equal to or less than 30 kg) or equal to or greater than 2·0 cm (in individuals weighing equal to or greater than 30 kg)
- Velocity equal to or greater than 3·0 m/s for one complete envelope
- Pansystolic jet in at least one envelope

Pathological aortic regurgitation (at least mild; all criteria must be met)

- Observed in at least two views
- Observed in at least one view, aortic regurgitation jet length equal to or greater than 1·0 cm
- Velocity equal to or greater than 3·0 m/s in early diastole
- Pandiastolic jet in at least one envelope

Panel 5: **Symptomatic and supportive therapy of acute rheumatic fever**

Arthritis

Non-steroidal anti-inflammatory drugs are recommended for management of arthritis and arthralgia, with naproxen and ibuprofen replacing aspirin as first-line therapy due to a more favourable safety profile.[69,70] Rapid symptomatic improvement is generally achieved with high-dose therapy which is weaned after 1–2 weeks based on clinical response and decline in inflammatory markers.[71] Resolution occurs in 90% of cases within 12 weeks, although rebound symptoms can occur on withdrawal of therapy warranting medication reintroduction.[72] Alternative diagnoses should be sought in individuals who are not responsive to non-steroidal anti-inflammatory drugs.

Carditis

Almost half of latent rheumatic heart diseases cases resolve within 5 years.[73] Mild to moderate rheumatic carditis is managed conservatively, with pharmacological therapy targeting management of complications such as heart failure (eg, angiotensin-converting enzyme inhibitors, diuretics, and nitrates). Emergency valve replacement surgery is sometimes warranted for chordae tendineae rupture. Although older studies did not suggest the benefit of corticosteroids and intravenous immunoglobulin in preventing subsequent rheumatic heart disease, subsequent smaller studies have shown improvements in laboratory and radiological parameters with the use of corticosteroids in severe carditis.[71,74–76] Screening and treatment of latent infections (eg, strongyloides, tuberculosis) should be performed before commencing immunosuppressive treatment. Hydroxychloroquine has shown the ability to control inflammation and pericarditis in a case series of two patients with protracted rheumatic carditis, with ongoing studies offering potential to provide further insight on its use.[77,78]

Chorea

The management of Sydenham's chorea is geared towards improving daily function and consists of symptomatic and immunomodulatory therapy, although the evidence base is scarce. Dopamine antagonists might provide symptomatic benefit, but their use is limited by extra-pyramidal side-effects. Anti-epileptic agents such as carbamazepine and sodium valproate are used most. Immunomodulatory therapies including corticosteroids, intravenous immunoglobulin, and plasmapheresis are reserved for severe and refractory cases. Recent retrospective studies suggest corticosteroid therapy might provide quicker resolution of chorea and are associated with a lower risk of relapse.[44,79] Randomised controlled trials aim to provide further evidence (eg, NCT06259006).

Additionally, disease progression and outcomes are worse among those with severe disease at presentation, with recurrent ARF being a predictor for valve surgery, highlighting the need for follow-up echocardiography.[65,67]

ARF therapeutics, management, prevention, and control strategies

Hospitalisation, where possible, is recommended for diagnostic confirmation and initial management of ARF, including counselling and education of patients and families. Goals of initial ARF management are supportive management of arthritis, carditis, and chorea (panel 5), and eradicating the inciting GAS infection. Antimicrobial treatment options for GAS pharyngitis and impetigo are outlined in the appendix (p 2). There is no proven immunomodulatory treatment shown to alter the outcome of carditis in the short or long-term, and considerable variation in clinical practice exists regarding the use of steroids, non-steroidal anti-inflammatory drugs, and bedrest for acute ARF. Strategies for prevention and treatment of ARF, GAS, and RHD often overlap across primordial, primary, secondary, and tertiary levels, and are targeted across the individual, interpersonal, institutional, community, and policy levels (figure 3).

Addressing social determinants of health and associated factors

Although modifiable social determinants of health affect a person's exposure to GAS infection (figure 1) and are the core focus of primordial prevention strategies, they influence progression to ARF and RHD, inadvertently playing a role in primary, secondary, and tertiary prevention (figure 3). An improvement in socioeconomic status and reduction in health disparity is associated with a clear decline in RHD burden, emphasising the value of addressing factors such as housing conditions, social overcrowding, hygiene and sanitation, health literacy, and access to health-care services within ARF and RHD control programmes.[80,81] Improving community awareness and health literacy have been identified as integral components of control programmes, including improving adherence of secondary prophylaxis, particularly as ARF and RHD are prevalent within communities with low rates of literacy.[82] Practical implementation of prevention strategies addressing modifiable social determinants of health are, however, costly and require sustained political commitment and community engagement to address broader health and social inequities. Within LMICs where widespread socioeconomic disparity exists, primordial prevention strategies are best implemented at a district or national level to shift ARF and RHD burden, often in conjunction with primary and secondary prevention interventions, or as part of broader health and social strengthening initiatives.[83] Interventions are best guided by local context; however, data related to economic evaluation to guide cost-effective strategies are limited.

Gaps in knowledge relating to GAS burden and transmission dynamics, and the interplay of these factors with social determinants of health remain a barrier to inform primordial and primary prevention strategies. A meta-analysis reported the pooled prevalence of GAS pharyngitis in sore throat programmes at 10% (95% CI 8–12%), as compared to 24% (23–26%) in clinical settings, with a higher asymptomatic GAS carriage prevalence in HICs (10%; 7–16%) compared with LMICs (6%; 4–8%).[84] In contrast, a cross-sectional study in 532 school-aged children in a high ARF-endemic region in Uganda revealed a GAS pharyngitis rate for sore throat at 42% as compared to 16% for asymptomatic carriage.[85] Although school-based sore-throat programmes have shown success in reducing ARF burden in high-endemic settings, consideration of attributing local social determinants of health with evaluation of health and economic benefits of health promotion programs to improve health-seeking behaviours versus active surveillance strategies should be undertaken.[86] An ongoing longitudinal household study

in The Gambia consisting of active surveillance of pharyngitis and impetigo completed a 1-year follow-up of 44 households in September, 2022, and aims to provide further insight into GAS epidemiology, transmission dynamics, and sociodemographic risk factors.[87]

In countries such as Australia and New Zealand, where ARF and RHD are endemic only among Indigenous communities (with GAS impetigo being a primary driver), efforts have been concentrated towards community-based primary and primordial prevention strategies with a focus on promoting healthy skin and treating skin infections, although data relating to downstream effects on ARF prevention are still scarce.[35–38,88,89] A recent community-led programme implemented among 29 families in northern Australia delivered multimodal interventions via trained Aboriginal Community Workers, such as health provider and community education, housing and environmental health support (eg, supporting repairs of showers), and family support for health navigation.[90] There was a decline in potential GAS infections at 3 years that although did not reach statistical significance, likely due to a small sample size, enabled establishment of a community-driven model that could potentially be scaled up.

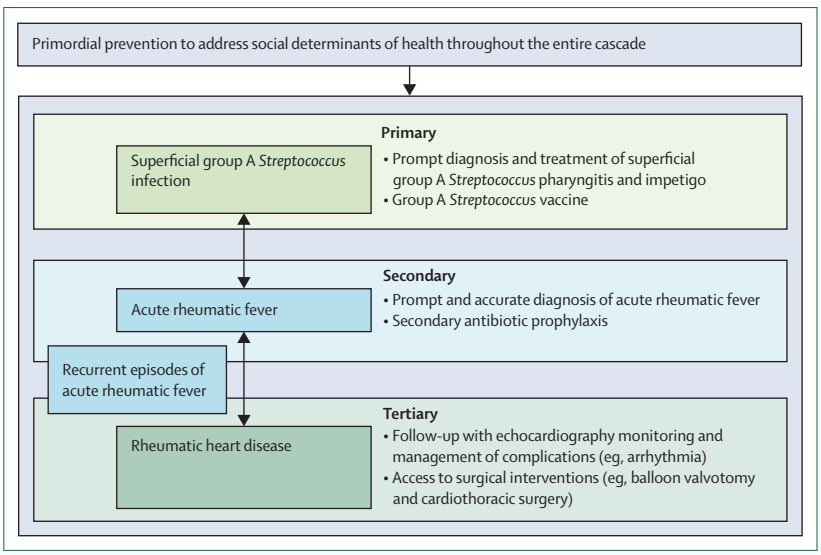

Figure 3: **Opportunities for prevention and treatment of group A *Streptococcus* infection, acute rheumatic fever, and rheumatic heart disease**

Improving diagnostic capacity and health-systems strengthening

Strengthening health-care delivery and ensuring that health-care providers have adequate resources and skills for the diagnosis and appropriate management of GAS infections, ARF, and RHD are an integral aspect of primary and secondary control strategies. Digital education modalities for health-care providers (eg, mobile apps, online learning packages) to support decision making have been found to be feasible and acceptable, but still require a level of clinical expertise, emphasising the need to consolidate training on ARF and RHD into core health education curricula.[91] Formalised in-person training for health-care workers can improve ARF knowledge, however the need for refresher training for long-term knowledge retention is required for sustainability.[92,93] Better availability of point-of-care diagnostic tools for GAS, including AI modalities to aid clinical assessment, integration of molecular point-of-care testing into existing platforms, and the search for ARF biomarkers, offer the potential to revolutionise diagnosis in the future.[53,54] Innovations in digital health interventions such as AI-assisted echocardiography and telemedicine have shown positive outcomes and offer viable solutions towards bridging gaps in health equity from ARF and RHD globally.[94] Handheld echocardiography by non-experts offers the possibility of a cost-effective approach for diagnosis of RHD and ARF with reasonable sensitivity and specificity.[95,96] The WHF 2023 criteria support this notion of task-shifting by providing simplified echocardiographic screening criteria.[64] Factors such as initial and ongoing staff training, logistical support, and safe pathways to deal with false positive results, however, require consideration.[95]

Innovations in secondary antibiotic prophylaxis

Administration of intramuscular benzathine penicillin G (BPG) every 3–4 weeks to prevent ARF recurrences remains well established practice and is the cornerstone of secondary prevention of ARF and RHD.[97] The duration of SAP varies based on age, the presence of carditis or valve disease, and the risk of ARF recurrences, with a minimum recommended duration of 5 years. The value of SAP has been further demonstrated for latent RHD, with an RCT conducted among 916 Ugandan children and adolescents reporting significantly reduced risk of disease progression at 2 years among those receiving SAP compared to the control group.[98] The risk of ARF recurrence does not decline until approximately 40% of BPG doses are administered and receiving under 80% of doses is still associated with a four-fold increase in the odds of ARF recurrence, supporting the target of at least 80% adherence.[99] Despite this, poor adherence to SAP continues to result in cardiac mortality and morbidity across both LMICs and HICs, with factors such as accessibility to health-care services, culturally appropriate health-care provision, socioeconomic vulnerabilities, and poor health literacy being contributing causes, in addition to intrinsic factors such as pain from intramuscular injections and health-risk behaviours such as alcohol use.[99–101] Strategies to improve adherence to SAP—such as recall systems and reminders for BPG injections and delivery of injections through community outreach—have been shown to offer benefits; however, high staff turnover and difficulties in tracking transient patients are still problematic.[68,100]

Panel 6: GAS vaccine pipeline

M protein vaccine candidates

The M protein is encoded by the *emm* gene and consists of a coiled-coil structure with a hypervariable N-terminal, central domain, and conserved C-terminal region. There are currently four M protein-based candidate GAS vaccines on a product development track.[114-116] The most advanced is StreptNova, a 30-valent vaccine comprised of four recombinant proteins containing N-terminal peptides.[117] The vaccine has reported to be well tolerated, immunogenic, and safe, with no evidence of cross-reactivity or clinical autoimmunity among 23 healthy adult volunteers in a phase 1a trial completed in 2020.[117] The J8/S2 combivax and P*17/S2 combivax incorporate peptides from the conserved C-terminal region and also include non-M peptides into their formulation.[118] Animal studies have shown immunogenicity with no clinical toxicity and the candidates have progressed to clinical trials in 2022. StrepInCor, which consists of a 55-amino acid peptide from the derived from C-terminal region, has shown safety and efficacy in animal studies and is due to progress to clinical trial.[119,120]

Non-M protein vaccine candidates

Non-M protein-based vaccines target highly conserved factors across GAS isolates (eg, *Streptococcus pyogenes* adhesion and division protein [SpyAD], streptolysin O, C5a peptidase) and have shown promising results in preclinical trials.[114-116] These consist of subsets of protein antigens such as the Combo5 and Teevax vaccines. Some candidates also feature GAC, which is a surface polysaccharide present across all GAS isolates (eg, Combo4 and VAX-A1).[121] Experimental evidence has, however, shown autoantibodies to GlcNAc, an immunodominant side chain in GAC, which can cross-react with cardiac and brain tissue raising theoretical safety concerns. VAX-A1 consists of a modified version of GAC in which the GlcNAc side chains are removed and conjugated to SpyAD. Animal studies have shown VAX-A1 to be immunogenic with no evidence of cross-reactivity to cardiac or brain tissue.[122] There is ongoing research to explore novel technologies that feature modified GAC subunits with the goal for a universal GAS vaccine.[121]

GAC=Group A carbohydrate. GAS=Group A streptococcus. GlcNac=N-acetylglucosamine.

Strategies that focus on medically driven models of care have resulted in little shift in long-term adherence to SAP, highlighting the need to incorporate measures that address health-system and individual barriers into registry-based programmes to enable active surveillance and recall of patients.[102,103] The ongoing Active Case Detection and Decentralized Dynamic Registry to Improve the Uptake of Rheumatic Heart Disease Secondary Prevention study in northern Uganda aims to address these factors through the phased decentralisation of ARF and RHD care from tertiary to district sites, with active engagement of stakeholders to address barriers to care.[104] Multimodal interventions include the implementation of a mobile digital registry that serves as a medical record, provides information to guide diagnosis and management to support clinicians, functions as a database for public health surveillance, and tracks medication supplies. Capacity building at local sites through initial and ongoing health provider education and selection of site champions offer the prospect of long-term sustainability and national scale-up.

Over recent years there have been increasing efforts to improve modes of penicillin delivery that can be administered at a lower frequency with less discomfort, whilst remaining cost-effective and independent of cold-chain storage to enable improved adherence and equitable access globally.[105] BPG administered subcutaneously has been shown to be safe and less painful compared to intramuscular administration, resulting in substantially delayed penicillin absorption and allowing a longer gap between treatments.[106,107] The standard adult dose of 1·2 million units (MU) of BPG fails to maintain the conventionally accepted target concentration of 20 ng/mL beyond 9 days, however a subsequent pharmacokinetic study showed that a higher subcutaneous dose of 10·4MU can maintain a level above the target concentration for 57 days, highlighting the possibility of three-monthly subcutaneous BPG injections.[108] Sustained release implant systems have been successfully developed in various fields (eg, contraceptives) and are being actively explored for penicillin delivery.

Although there have been long-standing assumptions that plasma benzylpenicillin concentrations above 20 ng/mL are required to achieve adequate prophylaxis, this concentration has not been correlated to clinical outcome and is likely not achieved between doses of intramuscular BPG.[109,110] The ongoing Controlled Human Infection for Penicillin G Against *Streptococcus* Pyogenes trial is a double-blind, placebo-controlled, randomised experimental human infection study that aims to determine the minimum concentration required to prevent GAS pharyngitis.[111] It is hoped that this study will provide further insights to accelerate the development of long-acting penicillin delivery.[111] Although historical studies show intramuscular penicillin to be superior to oral penicillin prophylaxis, there is also need for novel research to establish the effectiveness of modern oral formulations with improved bioavailability as they continue to remain an option in many guidelines.[112] The Intramuscular Versus Enteral Penicillin Prophylaxis to Prevent Progression of Latent RHD Trial in Uganda is an ongoing RCT developed to provide evidence on the efficacy of oral penicillin compared with intramuscular BPG (NCT05693545).

GAS vaccine development

In 2019, WHO published a roadmap to provide a framework for research and development and preferred product characteristics for a GAS vaccine.[113] Within the same year, establishment of the Strep A Vaccine Global Consortium and the Australian Strep A Vaccine Initiative has accelerated efforts towards this mission by promoting awareness, financial commitment, and collaborative partnerships globally.

The antigenic targets of GAS within the current vaccine pipelines are either M protein or non-M protein-based candidates. Panel 6 summarises key candidate vaccines currently on a product development track. A major safety concern related to GAS vaccines is the risk of triggering an autoimmune response, including ARF, from

autoantibodies produced to antigenic epitopes. Several M proteins and non-M antigens have been identified that can result in antibody cross-reactivity with cardiac proteins.[123,124] Gaps relating to ARF pathogenesis and lack of animal models of ARF and RHD remain a major limitation towards the development of a safe vaccine, although there has been some early success towards the development of a GAS human challenge model.[125]

WHO preferred product characteristics recommend at least 90% of the current disease-causing isolates from the region targeted for use are prevented by a GAS vaccine.[113] However, a major challenge in developing a universal GAS vaccine is the extensive genomic heterogeneity of the global GAS population due to frequent genetic recombination events and the lack of comprehensive epidemiological data on GAS strain distribution. An analysis of a database consisting of over 2000 GAS strains identified over 290 clinically associated genomic phylogroups across 22 countries, with only 13 antigen genes conserved in over 99% of isolates.[126] GAS diversity was reported to greatly vary between regions globally—molecular characterisation of strains within LMICs, which have the highest GAS burden, remain scarce.[21] This genomic heterogeneity is further reflected by a systematic review and meta-analysis encompassing 25 studies conducted in Africa that observed a pooled prevalence of GAS pharyngitis at 21% (95% CI 17–26%), with 88 different *emm* strains identified, corresponding to a vaccine coverage of 28–65%, although this is likely to still be a gross underestimate.[127] Furthermore, there can be substantial diversity in GAS strains within a population, as highlighted by recent data from New Zealand where 65 distinct sequence clusters spanning 49 *emm* strains were identified among 468 children in Auckland, with evidence of multiple global introductions and local clonal expansion.[128]

Generating national and global priorities for action

Within LMICs and remote regions in HICs, constrained resources, including human resources, remain as major barriers to the diagnosis and management of GAS and ARF. Shortages of antibiotics, including penicillin, poses a challenge to global health security (particularly within LMICs) and contributes towards the emergence and spread of antimicrobial resistance globally.[129] Addressing these core issues at a government level, with collaborative regional and global partnerships, are crucial to achieve global targets of universal health coverage.[112]

In 2018, WHO adopted a Global Resolution on ARF and RHD at the World Health Assembly in Geneva, Switzerland, placing this as a global priority and providing specific actions and recommendations.[130] There has since been increasing global advocacy to reduce the burden of ARF and RHD. The American Heart Association has renewed its commitment towards this goal, outlining a framework with key strategies.[83] In 2021, the National Heart, Lung, and Blood Institute convened a global stakeholders' workshop supporting the development of primordial, primary, secondary, and tertiary care working groups, culminating in a series of publications outlining key research priorities with a call to establish a RHD research network.[35,81,112,115,131] In November, 2023, the WHF hosted the first World Congress on Rheumatic Heart Disease in Abu Dhabi, United Arab Emirates, bringing together global experts and advocates, including those with lived experience, to promote engagement and streamline efforts, with ongoing biannual meetings planned.

To achieve broad and sustainable declines in ARF burden, governments need to place this as a priority on the national agenda and scale-up primordial, primary, and secondary interventions at a macro level. To date, several successes have been achieved with integration of disease prevention and control programmes into country health-care systems; HIV is an ideal example where integration with maternal and child health, tuberculosis, and sexual and reproductive health services in LMICs have shown improvement in health and health-system outcomes.[132] Although there have been efforts to partly integrate ARF and RHD programmes into country health-care systems, to date none are fully integrated.[133] Within HICs, integration within national immunisation programmes, with specific relevance to delivery of BPG, has been postulated.[134]

Multilevel national interventions consisting of community health promotion, health professional education, and strengthened surveillance have shown to be cost-effective and lead to a decline in the burden of ARF and RHD (as shown by the 10-year programmes launched previously in Martinique and Guadeloupe in 1981 and Cuba in 1986), however, few countries have followed suit.[135,136] Many countries have, however, established national ARF and RHD registries leading to more accurate estimates on national burden and improved surveillance to monitor the effectiveness of interventions and facilitate better care, such as the delivery of SAP.[137–139] National collaborative approaches have also been adopted to streamline efforts, as evidenced by the RHD Endgame Strategy (developed by researchers, Aboriginal and Torres Strait Islander leaders, communities, and people with lived experience), which sets out a comprehensive approach to eliminate RHD in Australia by 2031.[140] Funding constraints, however, remain a major limitation in LMICs, with conflicting priorities for resource allocation. An RHD programme established in Nepal in 2007 as a joint initiative between the Government of Nepal and the Nepal Heart Foundation, with a plan for multi-level interventions and a focus in SAP, was halted due to lack of funds and a prioritisation towards conducting cardiac surgery.[141] International collaborations and strong political leadership have shown to be key in overcoming these barriers in other countries. The WHF Colour to Save Hearts programme in Mozambique has led to the successful implementation of

multi-level national interventions, including school-based health-promotion and sore-throat screening, community engagement, and health-systems strengthening.[142] In 2012, the Government of Sudan adopted a RHD programme implemented through non-governmental organizations using non-conventional funding resources that has continued to strengthen.[13] Advocating a framework of surveillance, integration, communication, awareness, advocacy, and training, the Sudanese RHD programme serves as a model for other LMICs.

There is a need for evaluation of cost-effectiveness of intervention programmes to help countries prioritise intervention strategies. A modelling study in India concluded that although scaling up primary, secondary, and tertiary interventions results in the highest reduction in clinical RHD (54%) and severe RHD cases (76%), a combination of secondary and tertiary prevention were the most cost-effective than a combination of all three (incremental cost effectiveness ratio per quality-adjusted life year US$30 *vs* $71205).[143] Similarly, a modelling study in the African Union also reported combined secondary and tertiary prevention to be cost-effective to avert short-term mortality and morbidity as compared to primary prevention, although the benefits of the later were predicted to accrue over a longer time.[144] Gaps in epidemiological data remain a barrier to accurate estimates, with differences in the type and scale of delivery strategies influencing the effects.

The Sustainable Development Goals intersect with ARF and RHD through targets for non-communicable diseases (NCDs) including the reduction of premature NCD mortality by one-third, achieving universal health coverage, and supporting the research and development of vaccines and medicines for NCDs that primarily affect developing countries.[145] There are, however, substantial barriers towards these goals, including widespread regional disparities in accessibility, availability, and affordability of appropriate services, lack of social inclusion, gender inequality, and disruptions resulting from the COVID-19 pandemic.[146] Despite the progress in the last several years, attention and investment in ARF and RHD remains small relative to the global burden.[147] In addition to exploring the nature of the disease and how to address it, political will to drive leadership and governance, and commitment, collaboration, and advocacy from national and international organisations remain essential to facilitate progress towards achieving prevention and control of ARF and RHD.[146]

Conclusion

There have been considerable advances in ARF in the last several years, with major progress in the search for GAS point-of-care testing, ARF biomarkers, GAS vaccine development, SAP, innovations in AI, and development of decentralised health-care services to better serve affected populations. Further research to better understand the pathophysiology and global distribution of ARF and GAS is required to move these initiatives forward. The huge disparity in funding as compared to the global scale of disease burden remains problematic, but increasing global advocacy with ongoing efforts to strengthen international collaborations and streamline national efforts has potential in pushing primordial, primary, and secondary prevention strategies to reduce the morbidity and mortality resulting from GAS infections, ARF, and RHD.

Contributors

ABo and KH conceptualised the outline of the manuscript. KH wrote the first draft of all the sections, and subsequent revisions. JR contributed extensively to the write-up of the echocardiography in the ARF section. JR, RW, ABe, JK, JC, and ABo provided critical feedback and helped shape the manuscript. All authors reviewed and approved the final version of the manuscript.

Declaration of interests

We declare no competing interests.

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