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Persisting burden and challenges of rheumatic heart disease

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Rheumatic heart disease (RHD) is the result of episodes of acute rheumatic fever with valvular (and other cardiac) damage caused by an abnormal immune response to group A streptococcal infections, usually during childhood and adolescence. As a result of improved living conditions and the introduction of penicillin, RHD was almost eradicated in the developed world by the 1980s. However, being a disease of poverty, its burden remains disproportionately high in the developing world, despite being a fundamentally preventable disease. Rheumatic heart disease generates relatively little attention from the medical and science communities, in contrast to other common infectious problems (such as malaria, HIV, tuberculosis), despite the major cardiovascular morbidity/mortality burden imposed by RHD. This relative neglect and paucity of funding have probably contributed to limited fundamental medical advances in this field for over 50 years. Given the importance of prevention before the onset of major valvular damage, the main challenges for RHD prevention are improving social circumstances, early diagnosis, and effective delivery of antibiotic prophylaxis. Early identification through ultrasound of silent, subclinical rheumatic valve lesions could provide an opportunity for early intervention. Simple echocardiographic diagnostic criteria and appropriately trained personnel can be valuable aids in large-scale public health efforts. In addition, a better understanding of the immunogenic determinants of the disease may provide potential routes to vaccine development and other novel therapies.

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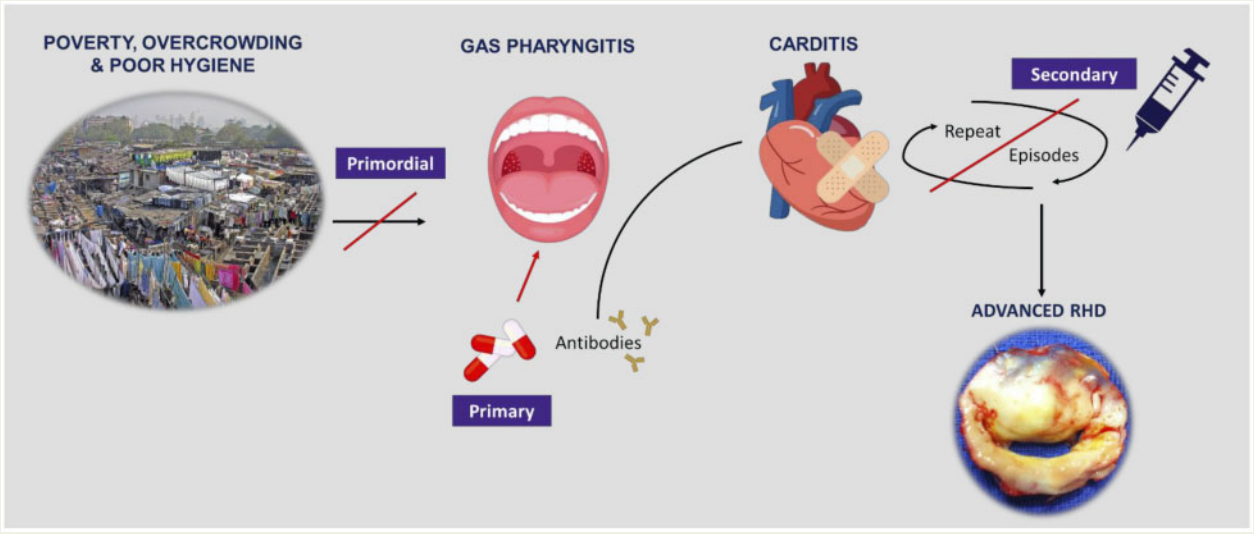
Graphical Abstract



Levels of rheumatic heart disease prevention.

Keywords Rheumatic heart disease • Acute rheumatic fever • Global health • Prevention • Global burden of diseases • Cardiology

Introduction

Acute rheumatic fever (ARF) and rheumatic heart disease (RHD) are unique among infectious diseases in primarily being the focus of cardiologists rather than infectious disease specialists, by virtue of their capability to cause major valvular damage and significant cardiac morbidity and premature mortality. Rheumatic heart disease is a disease of poverty, overcrowding, and poor hygiene, with the result that it has largely disappeared from developed nations and indeed from the 'radar' of most cardiologists and researchers in the Western world. There, the new generation of younger cardiologists is especially unlikely to have encountered even a single case of ARF.

The recent Global Burden of Diseases (GBD) report on RHD served as a timely reminder of the marked global heterogeneity in RHD burden,[1] with near-zero prevalence in developed countries sharply contrasting with significant prevalence and mortality in developing areas.[2–4] While the near eradication of RHD from the developed world is certainly a welcome achievement, an unfortunate downside has been the dwindling attention given to RHD from the scientific and medical communities, reflected by the low number of publications, conference presentations, and poor media coverage of this subject. This relative neglect and poor funding for RHD is in sharp contrast to the global engagement with other infectious diseases such as malaria, HIV, and tuberculosis, despite the fact that the morbidity, mortality, and economic burden imposed by RHD is as great if not greater.[5] Subsequently, there has been no major scientific advance over the last few decades in terms of pathophysiology, mechanisms, or disease-modifying therapy. This has been further compounded by the withdrawal of funding for large screening programmes, once recommended by the World Health Organization. This is especially unfortunate given the importance of prevention before the onset of major valvular damage.

Pathophysiology of acute rheumatic fever/rheumatic heart disease

Immune cross-reactivity and valvular damage

Acute rheumatic fever is caused by an abnormal immune response to group A streptococcal infections, usually occurring in childhood.[6,7] Rheumatic heart disease is the result of valvular damage following repeated episodes of ARF.[6,7] The basis of ARF is thought to be molecular similarity (mimicry) between the streptococcal M protein and a number of cardiac proteins (cardiac myosin, tropomyosin, keratin, laminin, and vimentin) due to which immune-mediated damage to cardiac tissue occurs. Antigenic similarity to other tissues such as synovium (joints) and neurologic tissue is responsible for the non-cardiac manifestations of ARF. The pathophysiological basis for RHD is thus the confluence of rheumatogenic group A Streptococcus (GAS) strains, genetically susceptible individuals, and an aberrant host immune response.[8–10]

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Clinical course—acute rheumatic fever with carditis

Acute rheumatic fever follows exposure to Streptococcus pyogenes, most usually following a throat infection, although occurrence after skin infection has also been described. Rheumatic heart disease most often results from cumulative valve damage due to recurrent ARF episodes over several years.[6,10] Classically, ARF manifests ~3 weeks after streptococcal pharyngitis (which may be pauci- or asymptomatic and therefore not apparent on clinical history). Cardinal features include polyarthritis, carditis, chorea, erythema marginatum, and subcutaneous nodules, although all features are almost never encountered together, with the first two being the most common. Clinical criteria to diagnose ARF were first described by Jones in 1944 and have been subsequently modified/revised four times, becoming more stringent, with the most recent criteria also including subclinical carditis by echocardiography, given the expanding knowledge related to it (detailed below).[11,12]

Acute rheumatic fever most commonly affects children, adolescents, and young adults, with a peak incidence between 5 and 14 years. Arthritis is the most common feature of the disease, present in 60–80% of patients. Arthritis is classically very painful, transient, and migratory (described as 'flitting and fleeting'), moving from one joint to another, mainly affecting medium and large joints and exquisitely responsive to anti-inflammatory drugs such as non-steroidal anti-inflammatory drugs. Carditis is the second most common feature, seen in ~50% of ARF, typically a pancarditis (involving all three layers of the heart). This usually presents as valvulitis, sometimes combined with pericarditis or (more contentiously) myocarditis. The mitral valve is most commonly involved in valvulitis followed by the aortic valve. Myocarditis in ARF often manifests as sinus tachycardia (particularly its persistence at night). Pericarditis is common and characterized by chest pain, a transient pericardial friction rub and a small pericardial effusion. The neurological manifestation of chorea is uncommon and unique in being more delayed (usually several months) after the GAS pharyngitis episode.

Chronic sequelae—rheumatic heart disease

Established RHD develops gradually and usually manifests between the 2nd and 4th decade of life; however, much more rapid progression has been documented in tropical countries. Although the previous history of ARF may be present, RHD is often newly diagnosed in individuals with no prior cardiac or rheumatic history. A higher prevalence of RHD has been noted among women of childbearing age[6,13]; the reasons for this female predominance have not been fully elucidated. Hypotheses include social factors, such as a greater role in childcare, resulting in repeated GAS exposure, less access to health care and genetically mediated immunological factors that may predispose to auto-immune diseases in general.

Advanced RHD also most commonly involves the mitral valve, with a classical combination of morphological changes including leaflet thickening, sub-valvular apparatus thickening, shortened chordae, commissural fusion, calcification, and restricted leaflet motion.[14,15] Mitral valve incompetence is the most common valvular lesion in patients with RHD in the early stages of the disease (subclinical RHD). Mitral stenosis usually develops later, as a result of persistent or recurrent valvulitis with bicommissural fusion.

Aortic valve involvement is next common, usually seen later than mitral valve disease, and presents with thickened cusps with rolled edges. Aortic regurgitation is seldom isolated but may be severe. Tricuspid valve involvement is uncommon in the rheumatic process. Tricuspid stenosis if seen, almost always occurs alongside mitral stenosis. Tricuspid regurgitation is more common, but usually functional, secondary to pulmonary artery hypertension and consequent right ventricular dilatation as a consequence of mitral valve disease. Isolated pulmonary valve involvement has not been described in RHD. Rheumatic heart disease may also initially present through complications such as atrial arrhythmias, embolic events, acute heart failure, or infective endocarditis. The natural history of progressive valvular disease is heart failure (in the absence of appropriate intervention). In very advanced stages of the disease, even surgery may become difficult, if there is also advanced myocardial dysfunction. Unfortunately, many patients present too late, especially in remote areas, due to a combination of limited awareness and lack of ready access to healthcare.

Persisting rheumatic heart disease burden

Major heterogeneity in rheumatic heart disease prevalence

The current epidemiology of RHD has been most recently described in the GBD project,[1] showing marked variation in RHD burden, with near-zero prevalence in developed countries sharply contrasting with high prevalence and substantial mortality in developing areas. The highest prevalence is in sub-Saharan Africa and among indigenous Australians. However, the GBD project importantly highlights the scarcity of accurately measured data in many locations, especially in areas of the highest prevalence (such as sub-Saharan Africa). Modelling methods used by the GBD 2015 authors to overcome this gap have wide confidence intervals; their estimate of disease prevalence (33.4 million) is more than twice that calculated in 2005; the 2015 estimate used a systematic evaluation of literature, originating from surveys of school children in whom the diagnosis was based on clinical assessment with subsequent echocardiographic confirmation.[16] The GBD study estimates that 10 persons per 1000 population in South Asia and central sub-Saharan Africa, and 15 persons per 1000 population in Oceania, respectively, were afflicted with RHD in 2015. Concerted efforts to obtain actual prevalence data from remote areas are urgently needed to know the true burden.

With an estimate of ~375 000 deaths each year in 1990 vs. 320 000 in 2015,[1] RHD therefore continues to remain the major cause of cardiovascular mortality in children and young adults in developing countries.

Subclinical rheumatic heart disease: the 'hidden' problem?

The recent use of cardiac ultrasound for the detection of subclinical cases challenges traditional epidemiological data on RHD prevalence (*Figure 1*). The concept of echocardiographic identification of silent,

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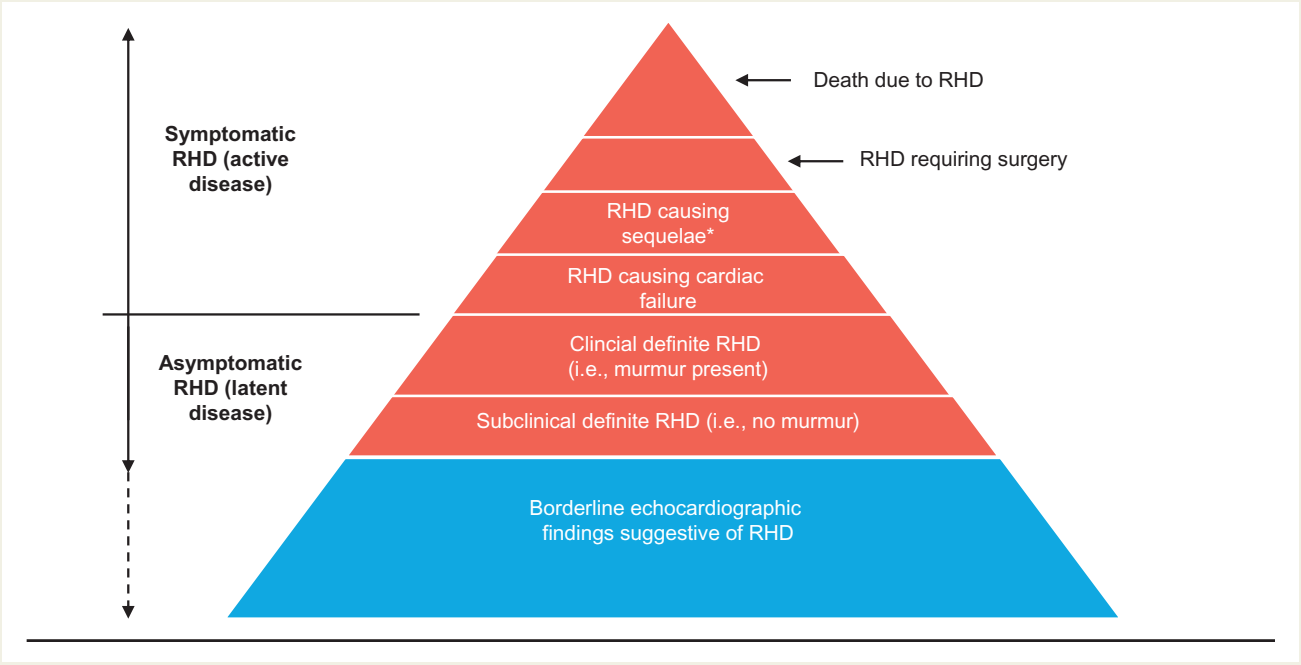

Figure 1 The spectrum of rheumatic heart disease. This model illustrates the distinctions between symptomatic and asymptomatic (or latent) disease and between definite and borderline rheumatic heart disease. *Sequelae of rheumatic heart disease include heart failure, atrial fibrillation/stroke, and infective endocarditis, among others. Reprinted from Ref.[17]

early rheumatic valve lesions have emerged over the last two decades.[18–20] This in turn has led to the proposition that the true RHD 'burden' may be much higher than currently estimated, with subclinical cases representing the submerged part of the 'RHD iceberg' (*Figure 1*). A significant number of patients with no murmur have echocardiographic findings consistent with pathological mitral regurgitation when compared with controls.[21]

This issue is of importance because there is emerging evidence that subclinical RHD may progress to clinical disease, which could be preventable.[22] Although optimal management of subclinical RHD is yet to be defined, preliminary experience suggests that this could be an opportunity for early intervention. Simple echocardiographic diagnostic criteria and appropriately trained personnel can be valuable aids in large-scale public health efforts.

Challenges for reducing rheumatic heart disease burden

Primordial prevention

Acute rheumatic fever and RHD have been attributed to overcrowding and unhygienic living related to low socioeconomic status, which results in persistent GAS in the environment and allows cross-infection from person to person by droplet dissemination (*Graphical abstract*). Improvement of social conditions and increasing access to primary health care have thus been associated with dramatic fall in the incidence of rheumatic fever, even before the advent of antibiotics. Primordial prevention requires avoidance of 'risk factors' for infection in the community, consisting of (i) improving the socioeconomic status, (ii) preventing overcrowding, (iii) improving nutritional status, (iv) making prompt medical care available, and (v) educating the public regarding the risk of ARF from sore throat.[23]

Although important, economic improvement does not provide complete protection against RHD, as demonstrated by relatively recent disease outbreaks in children in 'developed' nations such as the USA and Northern Italy.[24] 'Success stories' in developing nations have generally involved comprehensive strategies including a combined approach of advocacy, primordial, primary, and secondary prophylaxis.[25,26]

Primary prevention

Antibiotic treatment of proven or presumed GAS pharyngitis with intramuscular penicillin constitutes the main approach to primary prevention. Although eradication of GAS from the upper respiratory tract can usually be achieved by a 10-day course of oral penicillin, this may not be completely effective, as ARF occurred in 15–48% of children given oral penicillin for 10 days in an earlier epidemic in USA.[27]

While theoretically feasible, primary prevention is difficult to achieve, as it requires identification of GAS sore throat and correct use of penicillin to eradicate it. Potential barriers to the effectiveness of primary prevention of rheumatic fever solely with antibiotic therapy of GAS pharyngitis is the fact that as many as one-third of patients who develop rheumatic fever do not recall any symptoms of pharyngitis, and that in outbreaks symptoms of pharyngitis are absent in up to 58% of those infected. Thus, additional activities for primary prevention should include public awareness regarding the danger of ARF from sore throat and identification of sore throat as being due to GAS infection.

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Table 1 Recommended durations of secondary prophylaxis according to international guidelines

Guideline	Secondary prophylaxis duration recommended
American (AHA 2009)[33]	ARF with carditis and residual heart disease: until age 40 years or for 10 years after last ARF (whichever is longer); lifetime prophylaxis may be needed
	ARF with carditis but no residual heart disease: until age 21 years or for 10 years after last ARF (whichever is longer)
	ARF without carditis: until age 21 years or for 5 years after last ARF (whichever is longer)
WHO Expert Consultation Geneva (2004)[34]	Lifelong if severe valvular disease or after valve surgery
	For 10 years after the last ARF or until age 25 years in patients with the previous diagnosis of carditis
	For 5 years after the last ARF or until age 18 years in patients without proven carditis
Indian (2008)[35]	Lifelong in severe disease or post-intervention patients; may opt for secondary prophylaxis until age 40 years
	ARF with healed, mild, or moderate carditis: until age 25 years or for 10 years after last ARF (whichever is longer)
	ARF without carditis: until age 18 years or for 5 years after last ARF (whichever is longer)
New Zealand (2014)[36]	After definite/probable ARF, continue prophylaxis for at least 10 years; consider 5 years of prophylaxis after ARF in patients with mild or no carditis >21 years of age or in patients with ARF classified as 'possible'
	Severe RHD generally until age 40 years, with review at age 30 years
	Moderate RHD until age 30 years
	Mild RHD or ARF without RHD diagnosis, until age 21 years or for 10 years after last ARF (whichever is longer)
Australian (2021)[37]	Possible ARF: 12 months
	Probable or definite ARF without carditis: minimum of 5 years or until age 21 years (whichever is longer)
	Borderline RHD: not usually recommended but can be considered for 1–3 years based on risk factors
	Mild RHD:
	If documented history of ARF, then a minimum of 10 years after the most recent episode of ARF or until age 21 years (whichever is longer)
	If no documented history of ARF and aged <35 years, then a minimum of 5 years after diagnosis of RHD or until age 21 years (whichever is longer)
	Moderate RHD:
	If documented history of ARF, then a minimum of 10 years after the most recent episode of ARF or until age 35 years (whichever is longer)
	If no documented history of ARF and aged <35 years, then a minimum of 5 years after diagnosis of RHD or until age 35 years (whichever is longer)
	Severe RHD:
	If documented history of ARF, then a minimum of 10 years after the most recent episode of ARF or until age 40 years (whichever is longer)
	If no documented history of ARF, then a minimum of 5 years after diagnosis of RHD or until age 40 years (whichever is longer)

Adapted from Kumar *et al.*[75]
AHA, American Heart Association; ARF, acute rheumatic fever; RHD, rheumatic heart disease; WHO, World Health Organization.

A systematic review on primary prevention showed an overall benefit by preventing one ARF case for 53 sore throats treated,[28] confirmed by a later meta-analysis.[29] However, the only available randomized controlled trial conducted in New Zealand and including 22 000 children, failed to demonstrate a benefit of this strategy, in terms of reducing ARF incidence.[30] Two other fundamental limitations of primary prevention strategies include asymptomatic GAS throat and the possibility of other sites of pathogenic GAS infection (such as skin).

Secondary prevention

Preventing ARF recurrences with penicillin G prophylaxis has well-established efficacy and safety and should theoretically enable near-complete eradication of advanced RHD, when combined with broader changes such as improved living conditions, education, and awareness.[26,31,32]

Secondary prevention and active surveillance programmes

Since advanced RHD is the consequence of repeated ARF episodes, secondary prevention is based on preventing recurrent GAS infections through antibiotic prophylaxis. Striking a balance between efficacy and compliance has led to recommendations for 3–4 weekly intramuscular injections of benzathine penicillin G, rather than daily oral therapy in patients after an ARF episode (*Table 1*).[33–37] The duration of secondary prophylaxis depends on the patient's age, date of the last ARF attack, and most importantly, the presence and severity of RHD (*Table 1*). In some highly endemic regions, patients are at higher risk of recurrence and long-term prophylaxis in the presence

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Table 2 World Heart Federation Criteria for the diagnosis of rheumatic heart disease

Definite RHD (A, B, C, D) Age ≤ 20 years	**Definite RHD (A, B, C, D) Age >20 years**
A. Pathological MR and at least two morphological features of RHD of the MV	A. Pathological MR and at least two morphological features of RHD of the MV
B. MS mean gradient ≥ 4 mmHg[a]	B. MS with mean gradient ≥ 4 mm Hg[a]
C. Pathological AR and at least two morphological features of RHD of the AV	C. Pathological AR and at least two morphological features of RHD of the AV in those age <35 years
D. Borderline disease of both the AV and MV	D. Pathological AR and at least two morphological features of RHD of the MV
Borderline RHD (A, B, C)	**Borderline not applicable to those aged >20 years**
A. At least two morphological features of RHD of the MV without pathological MR or MS	
B. Pathological MR	
C. Pathological AR	
Pathological mitral regurgitation	**Pathological aortic regurgitation**
Seen in two views	Seen in two views
In at least one view, jet length ≥2 cm[b]	In at least one view, jet length ≥1 cm[b]
Velocity ≥3 m/s for one complete envelope	Velocity ≥3 m/s fin early diastole
Pan-systolic jet in at least one envelope	Pan-diastolic jet in at least one envelope
Mitral valve	**Aortic valve**
AMVL thickening ≥3 mm (age 20 years)	Irregular or focal thickening
≥4 mm (age 21 to 40 years)	Coaptation defect
≥5 mm (age > 40 years)	Restricted leaflet motion
Chordal thickening	Prolapse
Restricted leaflet motion	
Excessive leaflet tip motion during systole	

AMVL, anterior mitral valve leaflet; AR, aortic regurgitation; AV, aortic valve; MR, mitral regurgitation; MS, mitral stenosis; MV, mitral valve; RHD, rheumatic heart disease.
[a]Must rule out congenital anomalies of the mitral and aortic valve.
[b]Jet to be measured from the vena contracta to the last pixel of colour. Modified with permission from Remenyi *et al.*[40]

of severe RHD or previous valvular surgery has been recommended, including lifelong prophylaxis in some recent guidelines (*Table 1*).[33]

Secondary prophylaxis is thought to be the most cost-effective of interventions. It has been proven to be more efficiently delivered within community-based registry programmes. Poor compliance with secondary prophylaxis has been an issue in several programmes, being as low as 50% in different campaigns, mainly due to the target population's mobility, understaffing, and remote settings. Education, involvement of health workers with strong local community links, integration into the already existing primary care networks, and simple measures to decrease injection-related pain are paramount to improve the efficacy of a community-based secondary prevention programme.

Echocardiography and secondary prevention

The rationale for active surveillance is not only to provide the most accurate epidemiological data of RHD but also to offer early treatment to those affected, especially the large proportion of asymptomatic patients who may subsequently develop advanced RHD. For example, in a community-based clinical and echocardiography-confirmed screening of 1848 children in Sri Lanka, only 12% of those found to have RHD were on secondary prophylaxis at the time of screening.[38] The Council of Europe and the World Health Organization (WHO) recommend screening programmes in the setting of preventable diseases.[39] Under the auspices of the WHO, ~15 million children were screened for RHD across 16 countries. Unfortunately, the emergence of HIV and its devastating consequences may have diverted local priorities in many developing nations and led to the discontinuation of funding for many RHD programmes.

Echocardiography has emerged as a valuable tool to detect RHD, with standardized criteria now defined by an international group of experts (*Table 2*),[40] despite the absence of a 'gold standard'.[41] In large comparative surveys of school-aged children in Cambodia and in Mozambique,[42] we found a case detection rate by echocardiography which was ~10-fold greater than that achieved by careful clinical examination alone. Echocardiographic criteria included Doppler and morphological valve features as identified by three independent and experienced readers, with good reproducibility (*Figure 2*). Similar results were observed by other groups with slightly different echocardiographic criteria for subclinical RHD.[44–52]

Preliminary experience supports the notion that detection of subclinical RHD could be an opportunity for early intervention.

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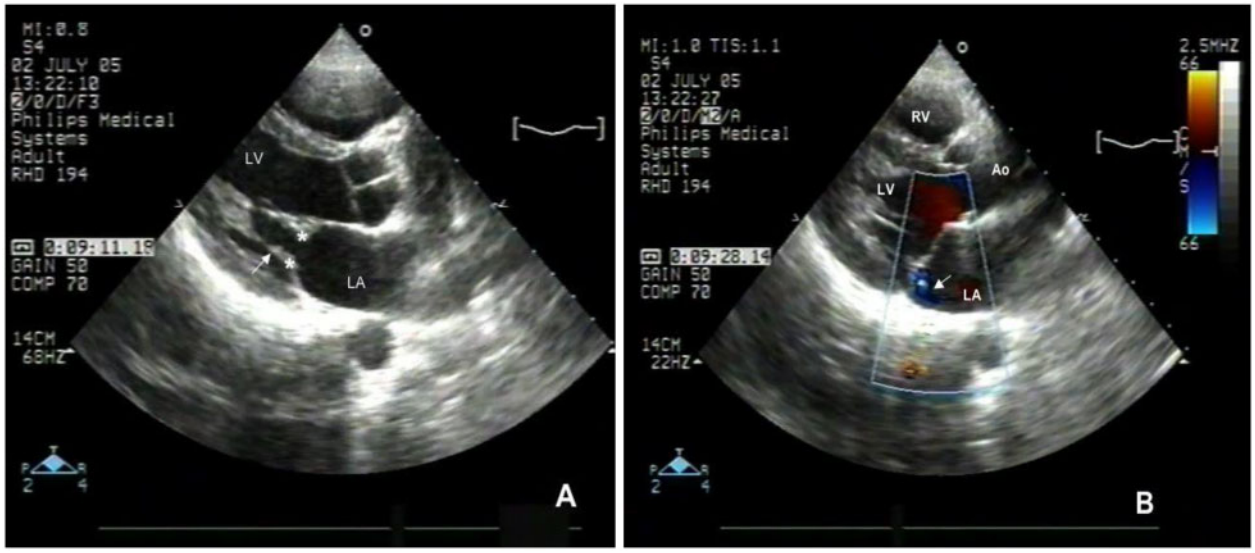

Figure 2 Echo in subclinical rheumatic heart disease. Echocardiographic findings (left parasternal long-axis view) of subclinical rheumatic heart disease with the criteria used in the study carried out by Marijon *et al.*[42,43] in Mozambique. (*A*) Evidence of morphological features for rheumatic heart disease—valvular thickening predominantly at the tip of both leaflets (*) and sub-valvular apparatus thickening (arrow)—with minimal mitral regurgitation visible as a blue jet (*B*). Ao, aorta; LA, laft atria; LV, left ventricule; RV, right ventricule.

Simplified echocardiographic diagnostic criteria and appropriately trained semi-skilled personnel such as nurses or technicians can be valuable aids in large-scale public health screening efforts.[53–55] Since the first reported echocardiography screening study was conducted, further major technological improvements have been achieved with respect to 'field' echocardiography equipment, including miniaturization and long-lasting portable batteries. Although echocardiography machines may become even more accessible, large-scale implementation of such programmes in resource-limited settings remains a logistical challenge.

Echocardiography is a valuable tool for detecting cases at an early stage; however, several uncertainties remain with respect to the relevance of echo-based screening.[56,57] A recently published cluster randomized comparison in 35 Nepalese schools, involving 3973 children, compared a strategy of echocardiographic screening and antibiotic prophylaxis with a 'control' of no screening.[19] The study suggested that a strategy of screening for early detection and timely institution of antibiotic prophylaxis has the potential to prevent disease progression and reduce the burden of clinical RHD over time. More such prospective studies with careful longitudinal follow-up are needed to fully delineate the natural history of subclinical RHD and the impact and cost-effectiveness of timely antibiotic prophylaxis.[58]

Early, subclinical valvular lesions of RHD have been shown to be reversible.[44] Prospective cohort studies in Uganda and Malawi have shown regression or remission after approximate follow-up durations of 2 years.[44,47] School-based systematic echocardiographic screening represents a pragmatic approach to detect children with the early-stage disease in low-resource settings, with the initiation of secondary antibiotic prophylaxis before valvular pathologies become irreversible. Ultimately randomized controlled trials are the ideal way to prove this concept. The randomized, GwokO Adunu pa Lutino (GOAL) trial, which is currently recruiting to achieve a target sample size of 916 children, is designed to determine the impact of secondary penicillin prophylaxis on the course of latent RHD.[59]

Vaccines

Since there are no methods to definitively identify the 3–5% of individuals with genetic susceptibility to ARF, a safe, effective, and affordable vaccine designed to prevent GAS infections could have a major impact on the health of millions of people at risk of developing ARF/RHD. The development of vaccines started in the early 1960s with crude cell wall to purified M proteins. However, several factors contribute to slow progression towards a protective vaccine, namely: widespread diversity of Streptococcus pyogenes strains (more than 250 *emm* types, corresponding to gene encoding M protein), cross-reactivity between streptococcal and host proteins, and lack of relevant animal models for studying the pathogenesis of RHD.[60]

There are currently three major types of vaccines in development: (i) based on cell surface proteins: M protein, C5a peptidase, fibronectin-binding proteins (serum opacity factor and streptococcal haemoprotein receptor), Streptococcus pyogenes cell envelop protein, R28, Streptococcus protective antigen, and Streptococcal immunoglobulin binding protein; (ii) based on secreted proteins, which are most effective for systemic and invasive diseases, and directed to pyrogenic exotoxins[61] known to play an important role in causing scarlet fever, streptococcal toxic shock-like syndrome, and necrotizing fasciitis, but not extensively tested for RHD; and finally (iii) based on carbohydrates, which are of potentially less interest because they are recognized by the cross-reactive auto-antibodies (*Figure 3*).[62]

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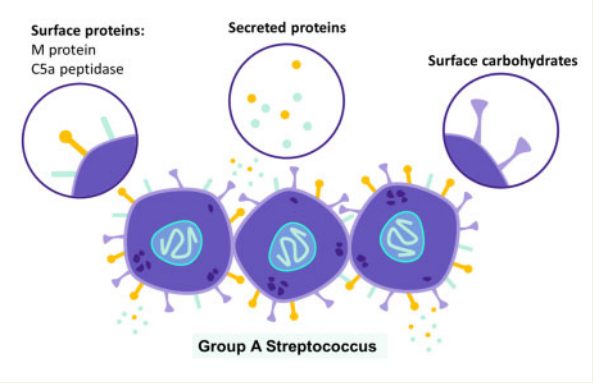

Figure 3 Possible rheumatic heart disease vaccine targets.

The epidemiology of the M protein *emm* clusters from GAS infections in high-burden areas is mandatory to inform vaccine development. Considering an *emm* cluster-based vaccine strategy that assumes cross-protection within clusters, two M protein-based vaccines—the 26-valent[63] and a more effective 30-valent M[64]—would cover most *emm* types in high-income countries, providing good coverage in North America, Europe, Asia, and Middle East. However, they would have limited coverage in the Africa and Pacific regions. The 30-valent vaccine would provide hypothetical coverage to 80.3% of isolates in Africa, where the most predominant GAS *emm* cluster is E6 followed by E3, E4, and D4.[65] There are equally concerns regarding its efficacy in Australia.[66]

The StreptInCor vaccine candidate—containing 55 synthetic amino acid residues of the M protein C-terminal region—is also promising as it was safe and did not induce harmful effects on different tissues and organs of minipigs.[67] A phase I/II clinical trial is planned for a near future, with four groups consisting of healthy adults in Brazil.[67]

The current obstacles to vaccine development could likely be overcome through global collaborative efforts to identify key activities required and secure financial resources to accelerate the process; this could lead to the successful introduction of a safe and effective, widely applicable vaccine. The unprecedented pace of development and introduction of COVID-19 vaccines in the past year stands as a testament to what co-ordinated, worldwide efforts can achieve.

Treating advanced rheumatic valvular disease

General considerations

In its advanced stages, RHD can lead to considerable morbidity and premature mortality. Major challenges exist for the management of damaged valves in developing countries, including case identification, preoperative assessment, choice of procedure, and postoperative care. In practice, the decision to perform valve repair or replacement is determined not only according to the age group and valve affected, but also to gender, socioeconomic, and geographic factors that might influence follow-up, particularly access to anticoagulation and adherence to long-term prophylaxis. Although some children/adolescents undergo mitral valve repair, many undergo valve replacement, especially in environments where the skills for mitral valve repair are not available or if time is a limiting factor. Often, the results of valve repair in developing countries have not been encouraging; on the other hand, the choice between bioprosthetic and mechanical valve is also challenging in young patients with barriers to adequate anticoagulation. In Jamaica, 19% of mitral valves repaired needed re-operation; the average time between initial surgery and re-operation was 1.2 years and bioprosthetic valves were used in 11% of patients undergoing mitral valve replacement.[68]

Stress testing (upright treadmill or supine bicycle or dobutamine stress echocardiography) can be particularly clinically useful allowing an objective measure of exercise performance as well as a comprehensive assessment of change in transmitral gradient and pulmonary artery pressure, and mitral valve area. The patient should be tested without withdrawal of his or her medical treatment, including digoxin and beta-blocker. It is indicated in patients with no symptoms or symptoms equivocal or discordant with the severity of mitral stenosis. Exercise echocardiography may provide additional objective information by assessing changes in mitral gradient and pulmonary artery pressure.[69] A simplified algorithm for the evaluation and treatment of symptomatic mitral stenosis has recently been published in the 2017 ESC guidelines on valvular heart disease.[70]

In summary, the principles of management of advanced RHD and its complications depend greatly on the context of the individual patient, the main factors being age, the nature of the pathology (ongoing active inflammation vs. 'burnt out' disease), and geographic location. The location is critical because it determines the healthcare infrastructure and expertise available (for catheter-based and/or surgical interventions). Many relevant aspects have been recently covered in the 2020 ACC/AHA guideline for the management of patients with valvular heart disease.[71]

Medical therapies

Although the evidence base specifically for the treatment of RHD is often incomplete, most of the treatments for heart failure and atrial fibrillation in this context are relatively inexpensive. The cornerstones of medical therapy for rheumatic mitral stenosis include diuretics and beta-blockers to avoid tachycardia. For mitral and aortic valve regurgitation, vasodilator therapy with angiotensin-converting enzyme inhibitors is often useful. Digoxin can be useful for rate control in atrial fibrillation. Anticoagulation is often indicated for RHD-related valve problems complicated by atrial fibrillation, although monitoring and compliance are often problematic in developing world settings. The advent of non-vitamin K antagonist oral anticoagulants (NOACs) may be helpful in this regard with the latest guidelines recommending them even in valvular disease with the notable exception of mitral stenosis and mechanical valves, although specific experience with RHD and NOACs is lacking. A trial investigating this issue is currently underway, due to complete in late 2022 (INVICTUS-VKA, ClinicalTrials.gov ID NCT02832544).

Pulmonary hypertension (PH) often complicates RHD in the left heart, especially mitral stenosis; however, PH-specific medications (such as endothelin receptor antagonists or phosphodiesterase-5 inhibitors) are contraindicated in such cases, as they can lead to pulmonary oedema and have not been shown to improve outcomes.[72]

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The treatment of choice, for PH in such situations, is relief of the causative valvular abnormality.

Catheter-based interventions

Notwithstanding the issues related to cost and the availability of facilities such as surgical backup, catheter-based procedures such as balloon mitral valvuloplasty (BMV) have been very successful in the treatment of advanced rheumatic valve disease. Detailed information on patient selection and procedural aspects and limitations have been published recently.[73,74] Balloon mitral valvuloplasty for severe isolated rheumatic mitral stenosis has relatively low cost and can usually be performed quickly and relatively safely.[75,76] Scoring systems for suitability have been published recently.[67] Long-term outcomes are similar to those achievable by surgical mitral commissurotomy and BMV has therefore largely replaced surgery in this specific regard.[77,78] The procedure can also be performed more than once for those with recurrent mitral stenosis after previous successful balloon treatment and can even be performed in those with up to mild concomitant mitral regurgitation. Nevertheless, urgent surgery is required after 2–5% of such procedures and so surgical backup in the same institution needs to be available.[75]

Newer procedures may be feasible in RHD, although much less well studied than for degenerative or functional valve abnormalities. There has been a case report of successful MitraClip for severe rheumatic mitral regurgitation.[79] This case had severe mal-coaptation of the mitral valve leaflets as the main abnormality. Transcatheter aortic valve replacement has also been described for rheumatic aortic stenosis,[80] although this is rarely likely to be suitable in rheumatic aortic stenosis because of the excessive calcification to allow for secure device anchoring.

Novel tricuspid valve techniques, such as clipping or balloon spacing devices, may in future be suitable for treating functional tricuspid regurgitation that complicates rheumatic left-sided valve disease, although the use of these has not been described in RHD to date.

Surgical management

Although traditional dogma holds that mitral valve repair is very difficult in rheumatic mitral regurgitation, because of extensive fibrosis and distortion of the valve leaflets and sub-valve apparatus, experienced operators have reported success for repair in up of 75% of cases of rheumatic mitral regurgitation.[81] Specialized techniques include leaflet extension with the autologous pericardium, neochordal replacement, and/or chordal shortening/resection, occasionally commissurotomy or papillary muscle splitting and the stabilization of repairs with annuloplasty rings. In experienced hands, such procedures can have good short- and mid-term outcomes with low re-intervention rates, and reasonably durable results.[82,83] Well-performed valve repair has important advantages over traditional valve replacement, especially with regard to avoiding anticoagulation, which may be crucial with the preponderance of disease in women of childbearing age. Valve repair for RHD is limited to few described series so far, likely related to the need for specific training and expertise to do these difficult procedures. Relatively longer theatre time required may also pose obstacles in busy practices and less administrative freedom for the surgeon to attempt complex cases in resource-constrained settings. Greater awareness and encouragement for surgeons to develop these techniques are needed to optimally manage young patients potentially facing a lifetime of anticoagulation with its attendant problems. Tricuspid valve repair is also recommended at the time of mitral valve surgery, in the presence of moderate or worse tricuspid regurgitation.[84]

Mitral valve replacement for RHD is often required but there are important clinical considerations. Bioprosthetic valves tend to degenerate faster in younger than in old patients, particularly those with ongoing inflammatory processes. Outcomes with mechanical valve replacement are often adversely influenced by poorly managed postoperative anticoagulation. Thus, surgical decision-making for advanced RHD must take into account the individual, the stage of the disease process, the severity of the problem, the geographic location, and the educational level of the patient, amongst other factors.

Minimally invasive surgery (MIS) should also be considered, as it is generally safe, rapid, cost-effective, more comfortable, and cosmetic for the patients, and has been used for both mitral regurgitation and stenosis.[85] Results of MIS for rheumatic mitral regurgitation in Vietnam also suggest that it can be safely and effectively performed with few perioperative complications and good short and midterm results; among 142 patients with mean age 42.6 ± 9.6 years the 30-day mortality was 0.7%, two patients had to be converted to conventional sternotomy, and the overall survival rate was 98.6%.[86] Finally, among 3238 consecutive patients who underwent mitral valve surgery in East China between July 2009 and June 2019, the proportions of MIS grew from 0.7% in the first 3 years to 30.2% in the last three, while the spectrum of mitral valve disease experienced a trend towards more degenerative valve lesions and less rheumatic valve lesions.[87] Unfortunately, there are major disparities in usage of MIS and these results should be interpreted with caution. The great majority of patients from the most highly endemic areas in Africa are much younger, have long-term complications such as atrial fibrillation, and patients present with the multivalve disease. Additionally, health system weaknesses determine low numbers of cardiac surgeries, making it difficult for local surgeons to acquire the needed experience to perform MIS.[88]

In patients with atrial fibrillation, valve surgery should also be utilized as an opportunity to perform a concomitant Maze procedure in order to try and achieve/maintain sinus rhythm in the long run. A combination of valve repair and sinus rhythm can be valuable in efforts to avoid anticoagulation in the long run. Again, awareness and sensitization among operating surgeons with regard to this issue are important.

Pregnancy and rheumatic heart disease

Reproductive health issues are important in managing young RHD patients, especially with female predominance in most clinical series. Pregnancy in advanced RHD poses high risks for both mother and foetus, particularly in the setting of severe uncorrected valvular obstruction or significant pulmonary artery hypertension. In developing regions, there is often poor usage of contraception, cultural barriers to family planning, and low availability of appropriate medicines to be used during pregnancy and lactation.[89] In the international prospective Registry of Pregnancy and Cardiac Disease[90]—in which 75% of the 390 women came from emerging countries—maternal death occurred during pregnancy in one patient with severe mitral RHD, and three more deaths occurred over 6-month follow-up postpartum (which was available for half of the cohort). Heart failure was the

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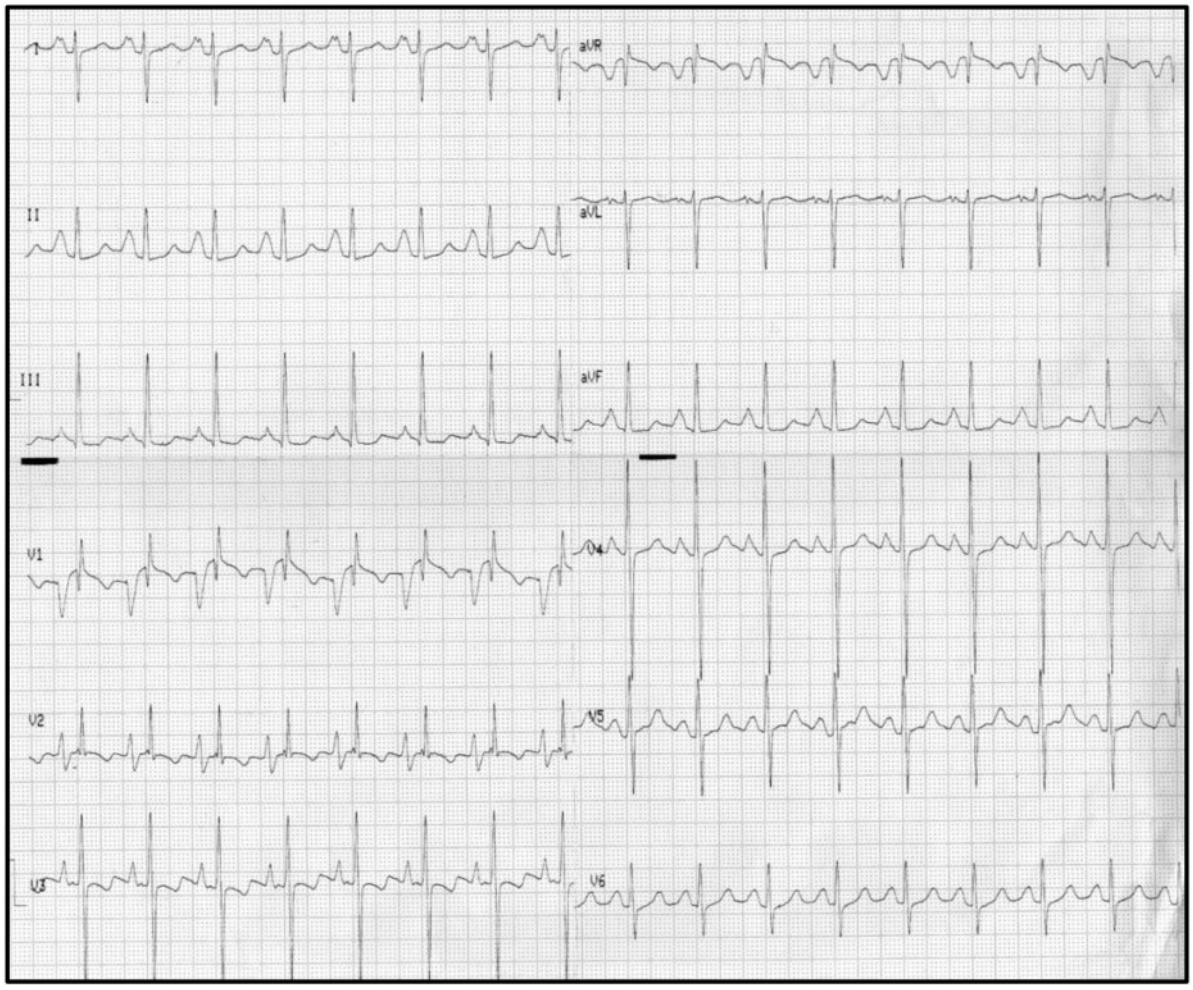

Figure 4 A 29-year-old woman, dyspnoea New York Class Association class IV, before percutaneous mitral balloon valvotomy for severe mitral valve stenosis with high pulmonary pressure. Significant bilateral enlargement on ECG. Reprinted from Ref.[91] ECG, electrocardiogram.

main reason for hospitalization in both mitral stenosis and regurgitation, and 16 women needed intervention during pregnancy (14 percutaneous balloon mitral commissurotomy and 2 surgical valve replacements).[90] An example is shown in *Figure 4*. Delayed detection of RHD late in pregnancy is often an important reason for adverse outcomes, due to a combination of lack of awareness, socioeconomic constraints, and inadequate access to healthcare in remote settings. Whether systematic echocardiographic screening programmes in pregnant women (in early pregnancy) and even in late adolescence in girls, in endemic regions could help in this regard deserves investigation.

Future challenges and possibilities

Challenges/costs in developing countries to manage advanced rheumatic heart disease

Poverty, poor health literacy of the communities, low awareness of health professionals, lack of trained personnel, and weak health systems, all constitute major barriers at individual, societal, and health systems' levels, hampering early diagnosis, continuum of care, comprehensive assessment for eligibility for surgical intervention, and postoperative follow-up.

The management cascade for RHD is complex and includes a set of interventions that demand multidisciplinary approaches to care, and involves not only health professionals from different backgrounds—paediatricians, internists, gynaecologists, psychologists, surgeons, dentists, etc.—but also interventions outside the health sector.[92] Patients with advanced disease are less able to attend clinics, have more costs related to their care (medicines, laboratory tests, invasive interventions, and surgery), and therefore are at higher risk of poor access to care and reduced compliance to full therapy, needing community-based support systems not always available in these settings. Under-resourced health systems are unable to ensure integrated and interdependent services for secondary prevention, severe heart disease management, catheter-based interventions, and valve surgery. Heat maps of retention and adherence to secondary prophylaxis usually suggest geographic disparities in treatment

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and postoperative follow-up, with limited number of patients coming from more remote districts.[93]

Despite progress made in improving access to surgery in recent years, there are still major unmet needs,[94,95] particularly regarding long-term postoperative care. This results in poor long-term outcomes in sub-Saharan Africa and South Asia, with 2-year case fatality rate as high as 17%, and the median age at death being 28.7 years.[96] The ratio of cardiac surgery centres per million inhabitants in sub-Saharan Africa is 1:33 (when excluding South Africa).[97] To give another example, in Uganda, a country with no local cardiac surgery facilities, patients were diagnosed by visiting cardiologists with symptomatic rheumatic or congenital heart disease. The intervention was scheduled in 38 patients with RHD (86%) [median age 19 years (IQR 12–31)] and in 36 patients (88%) with congenital heart disease [median age 4 years (IQR 1–5)]. Twenty-seven (32%) patients were eventually operated on overseas, with a median waiting time of 10 months (IQR 6–21).[98]

Given the above realities, it is likely that worldwide, millions of young patients with RHD are denied treatment every year. Cardiac surgery is a complex area that needs infrastructure and expertise of a multidisciplinary team. Surgical non-government organizations providing interventions overseas, or on-site with visiting teams have attempted to help. It is important that efforts focus not only on tertiary-level intervention but on comprehensive programmes that include prevention (especially in the setting of highly prevalent RHD), implementation of high standards of medical therapy (such as proper use of oral anticoagulants), and sustainability. Importantly, visiting teams can allow capacity building locally. The resources used to treat a minority of patients overseas should be more efficiently utilized for knowledge transfer, for the development of techniques applicable in low-resource settings and for the enhancement of local collaborations, with the aim of establishing national or regional referral centres. In countries such as Ghana and Namibia, government funding has contributed to a local cardiac surgery programme after an initial partnership with visiting teams. Political will and interest from 'big funders' are needed urgently to address the lack of cardiac surgical/interventional facilities in developing countries.

Scientific advances are needed

Advances at a basic level in RHD have the potential to drastically alter our understanding and approach to disease prevention and management. A better understanding of the immunogenic determinants of the disease, for example, may provide a potential route to identify relevant bacterial antigens and aid novel developments in streptococcal vaccines, as above.[99] Newer tools such as genome-wide association studies may aid the identification of vulnerable individuals, allowing targeted therapies.[100] Case-control association studies using a fine-resolution genome-wide approach should be informative for the identification of genetic variants affecting individual susceptibility to RHD. In the area of screening/disease detection, improvements in mobile technology and telecommunications open up the possibility of making echocardiographic screening more efficient/accurate through on-field image acquisition and 'remote' diagnosis by experts. Exciting developments in the field of artificial intelligence and machine learning may enable partial or complete automation of echocardiographic recognition of both subclinical and advanced RHD, with significant implications with respect to reduced need for trained personnel.[101]

Mass communication and education programmes through rapidly expanding social media and other novel avenues may help enhance awareness in both physicians and patients, especially for compliance with prophylaxis, anticoagulation, etc. Lastly, innovative ways have to be sought to expand population screening approaches, not only by leveraging newer technology but also through efficient integration with locally existing public health programmes targeting other diseases such as tuberculosis, HIV, and leprosy, which broadly afflict similar populations as RHD.

Conclusions

Given the major burden imposed by RHD, especially on young and economically productive people, it is clear that the scientific community at large can no longer afford to ignore the disease. The time for renewed interest and a sustained global effort towards eradicating RHD is now. Indeed the continued existence of RHD in the 21st century is in a sense a barometer of global inequalities which should no longer be acceptable. Multidisciplinary approaches involving basic scientists, cardiologists, immunologists, and public health experts, in meaningful collaboration with local governments are the need of the hour to make a dent on the RHD behemoth. Ultrasound-based screening represents a promising avenue through which large-scale public health efforts can be directed. Persistent endeavours will be needed to address existing barriers for both screening and delivery of prophylaxis at a community-wide level. However, medical history is replete with major public health victories against other infectious diseases in the past which should inspire physicians and researchers to work with determination towards the goal of eliminating RHD from the global map, by the end of this century.

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