During the early part of the 20th century, rheumatic fever (RF) and rheumatic heart disease were considered the “most deadly enemy of youth.” Although RF has almost disappeared in developed countries, it remains rampant in regions of the world characterized by poverty, overcrowding, and lack of adequate health care.

Progress in the field of rheumatic heart disease (RHD) has been slow, in part, because the disease has largely been eradicated from the developed world, but more importantly, because human immunodeficiency virus (HIV) and tuberculosis (TB) now occupy the center stage of disease in the developing world. Although the global annual mortality for HIV is 1.5 million and the global annual mortality for TB is 1.3 million, that for RHD is not insignificant at an estimated 233,000. The fact is that, at a fraction of the cost of treating HIV/TB, but with concerted effort, we have the potential to all but eliminate the burden of RHD.

Although there are many unresolved questions around RF and chronic RHD, we have chosen to address those that we believe are germane to promoting a better understanding of the changing epidemiology, diagnostic methods, prevention, and treatment of the disease.

The Rise, Fall, and Resurgence of RF
There has been a profound decline in RF in Europe and North America beginning around the middle of the last century. Until recently, the incidence of RF was so low that it was thought to have all but disappeared in the United States. The inappropriateness of a complacent approach was highlighted by a sharp rise in the incidence of RF in geographically distinct regions of the United States, starting in Utah in 1985. A surge in the incidence of RF has been noted elsewhere as well. With the collapse of the USSR, the incidence of RF has increased dramatically in emerging market economies such as India, the incidence of RF has decreased from >100/100,000 in the Aborigines of Australia. In some emerging market economies such as India, the incidence of RF has decreased from >100/100,000 in the 1970s to 20 to 40/100,000 presently.

Understanding the reasons for the wide fluctuations of RF and RHD within societies and between regions is crucial not only for containing the current epidemic, but also, more importantly, for preventing further recrudescence in populations presently at low risk. As with most diseases, factors responsible for the occurrence of RF may pertain to the host, the environment, or the pathogen. Although genetic predisposition, based on association of RHD with certain haplotypes such as HLA DR2, DR4, DR1, and DRw6 has been previously documented, this association is not nearly as strong as that noted with other autoimmune disorders. Other evidence for a genetic predisposition comes from a meta-analysis of twin studies showing a concordance risk for RF of 44% in monozygotic and 12% in dizygotic twins.

The obvious association of RF with conditions of living, and the widely disparate frequency in the same geographical region between the more and less privileged strata of society, as seen in South Africa, Asia, and Australasia, can only lead to the conclusion that the frequency and severity of rheumatogenic group A streptococcus (GAS) infection and the lack of prompt antibiotic treatment is the preeminent cause of RF and chronic RHD. Nevertheless, at a more fundamental level, variation in the frequency of RF has to be related to the epidemiology of GAS pharyngitis, in general, and infection with rheumatogenic subtypes, in particular, although this observation has only been confirmed in previous epidemics occurring in Europe and North America.

There is ample evidence that the epidemiology of GAS in the United States is changing. Before the 1900s, scarlet fever was epidemic with a mortality of 30%. In the first part of the 20th century, RF became the most serious manifestation of GAS pharyngitis, and today invasive syndromes such as toxic shock are prominent. Remarkably, despite the fact that GAS has continued to constitute ≥30% of all pharyngitis seen in children over the past 5 decades, the occurrence of RF in industrialized countries has fallen spectacularly. Several lines of evidence suggest that the decline in RF may be intrinsically linked to a transition in the epidemiology of GAS pharyngitis with a shift from rheumatogenic to nonrheumatogenic strains. A comparison of GAS M-type distribution in a large cohort of children with pharyngitis in Chicago showed the prevalence of rheumatogenic subtypes in 49.7% in the years between 1961 and 1968 and only 10.6% for the period 2000 to 2004. Furthermore, most, but not all, of the more recent outbreaks of RF in the USA were characterized by isolates of rheumatogenic GAS M-types.
A detailed understanding of the frequency of GAS, prevalence of M-types associated with RF, attack rate of streptococcal pharyngitis, and antibiotic resistance are crucial for implementing appropriate and cost-effective preventative and therapeutic strategies in developing countries. Evidence that the microbiology of endemic RF may not be the same as in the previous epidemics in Europe and North America comes from the Aboriginal population of the Northern Territories in whom pyoderma rather than pharyngitis,17 and group C and G streptococci rather than GAS,18 are thought to play an important role. Furthermore, the analysis of emm type distribution shows variation in the molecular epidemiology of GAS infections in Africa and the Pacific in comparison with that observed in high-income countries.19,20

**Echocardiography to Define Structural and Functional Abnormality in Acute RF and Chronic RHD**

Previous descriptions of cardiac involvement in RF and RHD relied on postmortem studies and observations made during surgery. Although these methods were useful, both were limited by the fact that the heart was examined in a flaccid nonbeating state. With its unique ability to view intracardiac anatomy in detail combined with its noninvasive nature, echocardiography has provided insights into many aspects of RF and RHD, laying to rest some long-held dogmas, but at the same time generating new controversies.

**Acute Rheumatic Fever**

A long-held belief that heart failure and death during an episode of RF were the result of myocarditis was perpetuated by clinical observation of tachycardia and a gallop rhythm, little macroscopic abnormality of the mitral valve at postmortem, and evidence of inflammation on histology. Echocardiography in these patients, however, confirmed an almost uniform presence of severe mitral or aortic regurgitation, normal left ventricular contractile function, and amelioration of heart failure with successful valve surgery.21,22 Echocardiography thus played a crucial role in developing the concept that the appropriate management of heart failure during RF was not corticosteroid therapy but urgent surgery to restore competence of the mitral and aortic valve.

Although mitral regurgitation is the hallmark of acute RF and forms the clinical benchmark by which rheumatic carditis is diagnosed, the appearance of the mitral valve on echocardiography is somewhat more controversial. Varying echocardiographic morphologies have been described, and, although this must in the main be related to differences in severity of carditis and whether the index episode represents the first event or recurrence, other factors related to differences in the host or organism are possible. In series reported from South Africa characterized by young age and severe mitral regurgitation often requiring operative intervention, the anatomic hallmark has been anterior leaflet prolapse confirmed both on echocardiography (Figure 1) and during surgery.23–26 Support for this mechanism also comes from a carefully performed study from Lembo and colleagues in San Antonio, TX, who studied 30 patients with an apical systolic murmur and well-documented history of rheumatic fever.27 Echocardiography demonstrated mitral valve prolapse in 80% of patients. Detailed evaluation by Marcus et al28 showed that mitral valve prolapse, often severe, was due to a combination of annular dilatation and chordal elongation. However, not all published series have been able to confirm these findings. The most frequent finding in a report of 108 clinically confirmed cases of RF from India were leaflet thickening and focal nodules suggestive of verrucous vegetations with anterior mitral leaflet prolapse in the minority.28

Much less is known about the nature of aortic valve involvement in RF and the mechanism of regurgitation. There is some evidence that the stretching of the cusps associated with inflammation and consequent prolapse (Figure 2) may play a role, but this is by no means definite.29

**Progression from Acute RF to Chronic RHD**

The appearance of the mitral valve during episodes of acute RF or early in the course of the disease is strikingly at odds with the appearance as the disease enters the chronic phase. The factors that determine this progression are not clearly understood but probably include the severity of the initial episode of carditis, magnitude of the host immune response, recurrent episodes of RF, success of prophylactic penicillin regimens against GAS pharyngitis, and local hemodynamic factors that could potentially perpetuate valve injury (Figure 3). Even more intriguing is the question of why some patients, mainly female, go on to develop predominant mitral stenosis, others develop pure mitral regurgitation, and yet others develop mixed mitral valve disease. Prospective longitudinal echocardiographic studies of patients with acute

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**Figure 1.** Echocardiography (parasternal long-axis view) in a patient with acute rheumatic fever and mitral regurgitation. A, Mildly thickened mitral valve with prolapse of the anterior mitral leaflet. B, Color Doppler showing significant mitral regurgitation. Reprinted from Crawford et al29 with permission from the publisher. Copyright © 2009, Elsevier.
RF with extended follow-up could potentially provide some insights but are unlikely to be performed. Nevertheless, based on our observations and a detailed clinical, echocardiographic, hemodynamic, and surgical analysis of 714 patients, it is likely that all patients begin with mitral regurgitation of variable severity. Those with severe mitral regurgitation are likely to remain with this lesion or develop some degree of stenosis due to commissural fusion, leaflet thickening, and subvalvular disease. These features are consonant with the fact that pure or predominant mitral regurgitation is a lesion seen predominantly in the young. Pure or predominant mitral stenosis, on the other hand, may have its roots in milder episodes of carditis with less severe mitral regurgitation, a slower evolution, and a greater predisposition to commissural fusion, although this is unproven. The fact that mitral stenosis is a lesion of older patients, with fewer having a history of RF or evidence of active carditis would support this argument.

Chronic Rheumatic Valvular Disease

Although the echocardiographic features of advanced chronic rheumatic valvular disease are quite obvious, the recognition of milder disease and differentiation from nonpathological regurgitation, valvulopathy associated with inflammatory diseases, endocarditis, and functional mitral regurgitation may be more challenging. Clearly, the valvular pathology in a younger individual from a high-prevalence rheumatic population could be little else, providing congenital or obvious myxomatous disease have been excluded. In older patients, differentiation from degenerative mitral or aortic valve disease may sometimes be difficult. Clues to the presence of rheumatic disease include leaflet doming suggestive of commissural fusion, thickening of the tips of the leaflets, subvalvular disease, and, in younger patients, rigidity of the posterior mitral leaflet.

Should Echocardiography Be Included in the Jones Criteria for the Diagnosis of Acute RF?

The original Duckett Jones criteria were published in 1944 as a clinical guideline for the diagnosis of RF. Successive revisions thereafter progressively reduced sensitivity and increased specificity, but even the last modification published in 2002 while acknowledging the advantages, discourages the use of echocardiography for the diagnosis of carditis. The extent of disagreement in this area is evident from the position of the World Health Organization (WHO) writing committee that cautiously encourages the use of echocardiography compared with the Australian and New Zealand guidelines that strongly endorse echocardiography and even include it as a major diagnostic criterion in high-risk groups. Because valvulitis is the only significant complication of rheumatic carditis, the detection of mitral or aortic regurgitation by auscultation formed a cornerstone of evaluation both from a diagnostic and prognostic point of view. The superiority of echocardiography for evaluating cardiac structure and function, together with the declining clinical skills of modern physicians, has led to proposals that echocardiographically detected regurgitation with or without morphological valvular abnormality be cautiously considered or definitely included in the Jones criteria. Echocardiography has much to commend it, but is there sufficient evidence to allow making a compelling case for its inclusion as a diagnostic criterion in RF? The health consequences of a strategy incorporating echocardiography for the diagnosis of RF should be judged by its accuracy, whether it results in a substantial change in treatment, impact on long-term outcomes, and cost.

Accuracy of Echocardiography

In the modern era, there is no doubt that properly performed Doppler echocardiography is more accurate than clinical auscultation. Furthermore, in the setting of RF with tachycardia and anemia, murmurs may either be missed or alternatively, physiological murmurs wrongly interpreted as indicating disease. In a patient with a murmur, the high sensitivity of echocardiography means that the absence of regurgitation on color Doppler would effectively exclude carditis. Also, murmurs occurring as a result of myxomatous mitral valve disease, congenital abnormalities, or endocarditis are readily detected by...
Echocardiography. A study of 333 patients with possible clinical carditis showed that the Jones criteria and echocardiography were concordant (both positive or both negative) 83% of the time.42 Controversy arises in the group of patients with so-called subclinical carditis or silent carditis in whom the clinical examination is negative but echocardiography reveals features suggestive of valvulitis.43,44 In the Utah outbreak, carditis could only be detected by echocardiography in 14 of 74 (19%) of patients.8 A meta-analysis that included 1700 patients showed a prevalence of subclinical carditis of 17%.45 Marked heterogeneity between studies is a reflection mainly of nonuniform echocardiographic criteria for the diagnosis of carditis. The WHO criteria37 include (1) regurgitant jet length > 1 cm, (2) regurgitant jet visualized in at least 2 planes, (3) mosaic jet with peak velocity > 2.5 m/s, and (4) pansystolic mitral or pendiastolic aortic regurgitation, but some have recommended that the minimum jet length of the mitral or aortic regurgitation be increased to 2 cm to increase specificity,43 and yet others require additional morphological valvular abnormality42 to reduce overdiagnosis of carditis. Although echocardiography is able to detect valvular abnormality more frequently than the clinical examination, the true sensitivity and specificity of the test for the diagnosis of rheumatic carditis is unknown, because there is no gold standard against which to compare.

**Does Subclinical Carditis Have the Same Implication as Clinically Detected Carditis?**

This is a pivotal issue, and a definitive answer would provide substantial justification for the routine use of echocardiography. Unfortunately, the data are sparse and of poor quality. In the Carapeti meta-analysis, follow-up data after 3 to 23 months was available in only 99 patients with a weighted pool average of persistence or progression of carditis of 44.7%.45 This is similar to the occurrence of progression of mild clinically detected carditis, but the data are deficient with lack of uniform follow-up echocardiography, information on recurrent carditis, or adequacy of penicillin prophylaxis. Since the publication of this meta-analysis, Araujo and colleagues reviewed their experience in 462 well-characterized patients with RF, all of whom met the modified Jones criteria, had baseline echocardiography according to WHO recommendations, and were followed both clinically and echocardiographically for a mean of almost 14 years.46 The prevalence of subclinical carditis was 16%, the clinical examination consistently underestimated the severity of carditis, and echocardiography was a far better predictor for progression to chronic RHD. Interestingly, the predictive value of echocardiography for disease progression was most evident in patients judged to have mild carditis clinically, and had no incremental value in those with more severe disease. Looked at in a slightly different way, 1 in 4 patients with acute RF and no carditis based only on a clinical examination went on to chronic RHD versus only 1 in 25 patients who had no evidence of valvulitis on echocardiography. These data strongly support the case for routine echocardiography to be included in the Jones criteria, but many would argue that more information is needed.

Additionally, echocardiography has many other advantages in the setting of acute RF, including quantification of severity of valve disease and requirement for surgery, assessment of left and right ventricular function and hemodynamics, detection of concomitant endocarditis, measurement of pulmonary artery pressure, and diagnosis of pericardial effusion. It is inconceivable, we believe, that echocardiography would not be regarded as a routine investigation in any other setting of valvular disease. The assertion by many regarding cost and availability, although valid, should be countered by a position statement that, although echocardiography is not essential, its use as an instrument to confirm the major criterion of carditis is acceptable, if not desirable. This position should of course be contingent on defining a strict set of echocardiographic criteria which we think should include both valve regurgitation and morphology. It should be emphasized that the use of echocardiography should not result in laxity of any of the other criteria for a diagnosis of acute RF.

**Echocardiography as a Screening Tool for Subclinical RHD**

Screening echocardiography is predicated on the fact that many studies have demonstrated a much higher prevalence of RHD by using Doppler echocardiography than by auscultation alone.47–55 Using portable echocardiography to screen 3677 school children in Cambodia and 2170 in Mozambique, Marijon and coworkers noted a 10-fold higher prevalence of RHD with echocardiography in comparison with auscultation by experienced clinicians.48 Although these publications have been useful in highlighting the burden of RHD in developing countries, and no doubt would benefit health organizations to plan and allocate resources, the call by some to substitute the stethoscope in favor of ultrasound for RHD screening49 and by others that the clinical examination is not only not useful, but may even weaken the strategy of routine echocardiographic screening55 is premature.

Like all early detection strategies, screening echocardiography for RHD involves trade-offs. If physicians practicing in developing countries are to truly embrace mass screening programs for RHD, they need further clarification of many pressing issues ranging from purely scientific to socioeconomic ones. These include questions pertaining to the predictive value of screening echocardiography, who should screening be targeted toward, how and by whom, how often, which diagnostic echocardiographic criteria to use, the significance and prognosis of latent RHD, whether early identification and intervention could alter the natural history of RHD, the economic cost of screening echocardiography, and the more difficult but equally important ethical judgment of how and where to best allocate limited resources in developing countries.

**Predictive Value of Screening Echocardiography**

In diagnostic testing, the gold standard is the single best test that is considered the preferred method for confirming a disease. In the case of RHD, we have no gold standard,57,58 making the calculation of sensitivity, specificity, and positive and negative predictive value difficult. Even if we considered the expert opinion of 3 experienced physicians interpreting an echocardiogram performed on a state-of-the-art machine under optimal conditions as the gold standard, then this has to be undertaken in the entire sample population under investigation.
together with the technique against which it is being compared. In most echocardiographic screening studies published to date, a secondary review (gold standard) was only performed in the patient with an abnormal field echocardiogram. There is therefore uncertainty whether the normal screening echocardiogram represents a true negative or a false negative. These issues aside, although the sensitivity of screening echocardiography is important, some studies have reported low positive predictive values ranging from 53% to 56%, meaning that if we were to rely solely on echocardiography, many patients would be treated unnecessarily for many years and also be impacted by the stigma of having been labeled with a disease. Furthermore, referral of all patients with a positive screening echocardiogram to tertiary centers for confirmation would overburden hospitals already stretched to capacity. Even then, such a strategy may be useful if it were inexpensive and convenient, neither of which is the case for screening echocardiography.

Who Should Be Targeted With Screening Echocardiography?

Since the predictive value of a test is highest when the prevalence of the disease, or the pretest probability, in the population being tested is high, it is logical to target echocardiographic screening to children and young adults residing in RHD endemic areas. The reduced diagnostic yield in low-risk populations was clearly demonstrated in a study comparing screening echocardiography in high-risk rural Indigenous children in northern Australia with low-risk non-Indigenous urban children. With the exception of the study from Nicaragua that randomly selected children and adults from an urban and rural community, almost all other publications have included only children attending school. While a school-based approach may be convenient, the true prevalence may be underestimated, because school attendance in disadvantaged areas is frequently <70%. Furthermore, RHD prevalence in adults may be higher than in children, and the disease may be more advanced because of greater chronicity. In the study from Nicaragua, the prevalence of echocardiographically detected RHD in adults aged 20 to 35 years, although lower than children, was still significant at 22/1000. These data would suggest that a screening strategy confined to school children only may be insufficient to identify the true prevalence of RHD.

Screening Echocardiography: How, by Whom, and How Often?

While screening echocardiography in the setting of clinical trials may appear quite straightforward, the task may be much more daunting in the real world. Issues ranging from organizational structure, sufficient support from tertiary facilities, quality control, data storage and review, effective communication between frontline teams and supporting cardiologists, transportation, and large migrant populations with high communicable disease burden all represent substantial impediments to implementing an effective echocardiographic screening program in the rural locations of low-income countries. When one considers that the ratio of cardiologists to population in many of these countries is <1 per million, the challenge appears even more formidable. To overcome the gross shortage of skilled cardiac ultrasound personnel, the use of trained nurses is being investigated and may be promising.

Most strategies for primary screening with echocardiography require confirmation by a secondary study at a more advanced level. Because a few studies have shown regression of disease in up to one-third of patients on subsequent evaluation, some have argued the case for routine follow-up echocardiography in subclinical or borderline cases so as not to administer unnecessary prophylactic penicillin. Finally, because the risk for GAS infection and RF is more or less ongoing, should mass screening echocardiography be performed annually or perhaps even more often?

What Are the Optimal Echocardiographic Criteria for Confirming RHD?

Although echocardiography has become a routine in standard clinical practice, its unsupervised use without detailed attention to clinical data, patient characteristics, device settings, and operator experience may lead to erroneous conclusions even in the controlled environment of a hospital setting. Greater vigilance would be required in a less sophisticated environment, as would be the case when performing screening echocardiography for RHD. On the 1 hand, echocardiography may be useful to exclude physiological murmurs, but a significant concern is that it may overdiagnose valvular abnormality because of its high sensitivity. The difficulty in striking the right balance between sensitivity and specificity is reflected in the large number of echocardiographic criteria ranging from simple to complex, the evaluation of regurgitant flow only to the inclusion of valve morphology, and a variety of categorizations including definite, probable or possible, or borderline. In the study by Marjion and colleagues, application of 2 different sets of criteria in the same population resulted in an almost 4-fold difference in the calculated prevalence of RHD, emphasizing the importance of echocardiographic definition. The most recent guideline proposed by the World Heart Federation is a useful attempt to formulate a consensus document based on evidence-based medicine, but already has been criticized for being too complex for application in developing countries or too stringent and lacking sensitivity.

The Significance of Subclinical RHD

The natural history of subclinical RHD is a crucial issue when deciding on the clinical utility of screening echocardiography. Confirmation that subclinical RHD may be the forerunner of progressive valve deformity with regurgitation or stenosis, development of symptoms, and eventually heart failure and death, would strengthen the argument for screening echocardiography. Because none of the guidelines for the echocardiographic diagnosis of RHD require quantification of the severity of valvular disease, it is difficult to appreciate the spectrum of disease severity when analyzing studies using screening echocardiography. What is evident, however, is that the majority of patients are asymptomatic and fall into the category of mild or borderline disease. From detailed clinical observations made in the last century, we know that patients with mild disease have an excellent long-term prognosis anyway. If mild clinically evident disease had a good prognosis, then subclinical echocardiographically detected disease...
that is mild should have an even better outcome. The results of 3 studies confirm that this is the case. On average, after a follow-up from 6 to 24 months, lesions remained unchanged in two-thirds, improved or resolved in one-third with deterioration in 0% to 9.5% in settings with either no penicillin prophylaxis or with poor compliance with prophylaxis.

**Would Any Intervention Significantly Alter the Natural Progression of Subclinical RHD?**

The hypothesis that early echocardiographic identification of subclinical RHD would enable the initiation of effective secondary prophylactic therapy with penicillin has not been tested, with widely divergent views on how to manage this issue. It is unclear whether penicillin should be administered to everybody with subclinical RHD by any criterion, only to those with valve regurgitation, or to those with isolated valve thickening if there has been a history of acute RF. The WHO has suggested that in endemic areas echocardiographically detected subclinical disease be treated as RHD until proven otherwise. What is clear, however, is that the use of secondary prophylaxis, even in clinically diagnosed RF and RHD is poor worldwide, averaging only ≈30% of patients eligible for penicillin. It is therefore incumbent on proponents of mass echocardiographic screening for RHD to conduct prospective randomized controlled studies to provide the burden of proof that this strategy would result in superior clinical outcomes, although some have pointed out that the logistics and ethics make this an unlikely proposition.

**Can Screening Echocardiography for RHD in Developing Countries Be Cost-Effective?**

Health and the provision of health care are complex issues in most developing countries. Faced by epidemics of communicable diseases including HIV, TB, and malaria, many populations are in a transition phase with rising tides of noncommunicable diseases such as hypertension, diabetes mellitus, cardiovascular disease, stroke, cancer, and neuropsychiatric illness. Lack of an efficient and well-developed primary healthcare system, a paucity of trained specialists, and overburdened tertiary hospital systems with competing demands on an already constrained economy make it unlikely that screening echocardiography could be incorporated into health delivery systems other than as a research tool. Analysis of the WHO global health observatory data repository shows that the per capita government expenditure on health for 2011 in Uganda, Mozambique, India, and Togo ranged from 11 to 23 USD per year, with, on average, 1 doctor per 100 000 population. Although there have been some studies evaluating different strategies aimed at reducing the cost of echocardiographic screening, including the use of hand-held devices and trained nurses, the overall expense incurred may not be justified in the context of developing economies.

**Preventative Strategies Against RF and RHD**

Clinical interventions to prevent the occurrence of RF and RHD in susceptible individuals following pharyngeal infection with GAS may be instituted at different stages of the illness (Figure 4) with varying efficacy and cost. Several levels of intervention have been defined, including primordial, primary, secondary, and tertiary prevention, but there is ongoing controversy on the optimal strategy. None would argue that primordial prevention—societal and community interventions to raise the standard of living, improve access to health care, and education to increase awareness of sore throats, in general, and cardiac symptoms, in particular—is an essential component of any preventative strategy. Secondary prevention is the most commonly practiced strategy, because asymptomatic GAS pharyngitis is common, it targets individuals with confirmed RF, is effective in preventing recurrences, is the most cost-effective, and has been recommended by the WHO. However, some have argued that secondary prevention fails to prevent RF in the first instance and have provided evidence instead that primary prevention by initiating penicillin during the initial pharyngitis episode is essential to reduce the burden of RF. Because pharyngitis in young children is extremely common, but only one-third of the cases are associated with GAS, this strategy must either include microbiological testing for GAS, which itself is costly, or alternatively include a clinical algorithm whose accuracy is controversial. Nevertheless, using a Markov model to test the cost-effectiveness of treatment with intramuscular penicillin based on various permutations of a clinical algorithm and throat cultures, Irlam et al concluded that treating all patients with pharyngitis is the least costly, but that a strategy of using a clinical decision rule without culturing is the preferred approach. Tertiary prevention entails therapies to improve the symptoms of RHD, prevention and treatment of heart failure, control of atrial fibrillation, anticoagulation, and percutaneous or surgical intervention where appropriate.

**Conclusion and Future Direction**

RF and chronic RHD unfortunately represent an unholy alliance that combines the worst of an acute infectious disease and a chronic disorder, striking at impoverished communities least capable of shouldering this additional burden. Developing countries can take hope from the fact that Western nations lived through similar hardship, but, with the collective efforts of government, physicians, advocacy groups, and national associations, have successfully eradicated the disease. Similar efforts launched in South Africa such as the Drakensberg declaration and the Awareness, Surveillance, Advocacy and Prevention Programme are laudable and need to be implemented in all regions where RF and RHD are endemic. Large multicenter studies designed to address important aspects of the epidemiology, microbiology, clinical outcomes, and preventative strategies such as the Rationale and Design of a Global Rheumatic Heart Registry (REMEDY) study will be critical to informing decision making in RF and RHD. The resurgence of RF in small pockets of the world characterized as high income should serve...
to remind us that RF may yet rear its ugly head, and that the need to continue basic science research to understand fundamental aspects of the disease remains. This will require resolve and commitment from industrialized nations on a scale much greater than at present, and the lead taken by the World Heart Federation is appropriate. A fraction of the recent commitment of the UK and US governments of >15 billion USD toward the Global Fund to Fight HIV/AIDS and malaria would go a long way to reducing the burden of RF and RHD. There are many questions that need to be answered ranging from the pathogenesis of RF, the development of a vaccine, and the mechanisms of implementing effective treatment and prevention strategies in endemic areas. In the words of Carapetis and colleagues, “we now stand at a critical juncture for RF and RHD control” and only if we combine our efforts will we be able to improve the lives of the millions living with this disease.

Disclosures

None.

References


21. Essop MR, Wisn但实际上，再将以下的文本转换为自然语言的更详细形式：

