REVIEW ARTICLE

Rheumatic heart disease screening: Current concepts and challenges

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ABSTRACT

Rheumatic heart disease (RHD) is a disease of poverty, is almost entirely preventable, and is the most common cardiovascular disease worldwide in those under 25 years. RHD is caused by acute rheumatic fever (ARF) which typically results in cumulative valvular lesions that may present clinically after a number of years of subclinical disease. Therapeutic interventions, therefore, typically focus on preventing subsequent ARF episodes (with penicillin prophylaxis). However, not all patients with ARF develop symptoms and not all symptomatic cases present to a physician or are correctly diagnosed. Therefore, if we hope to control ARF and RHD at the population level, we need a more reliable discriminator of subclinical disease. Recent studies have examined the utility of echocardiographic screening, which is far superior to auscultation at detecting RHD. However, there are many concerns surrounding this approach. Despite the introduction of the World Heart Federation diagnostic criteria in 2012, we still do not really know what constitutes the most subtle changes of RHD by echocardiography. This poses serious problems regarding whom to treat and what to do with the rest, both important decisions with widespread implications for already stretched health-care systems. In addition, issues ranging from improving the uptake of penicillin prophylaxis in ARF/RHD-positive patients, improving portable echocardiographic equipment, understanding the natural history of subclinical RHD and how it might respond to penicillin, and developing simplified diagnostic criteria that can be applied by nonexperts, all need to be effectively tackled before routine widespread screening for RHD can be endorsed.

Keywords: Acute rheumatic fever, rheumatic heart disease, screening

INTRODUCTION

Rheumatic heart disease (RHD) remains one of the most preventable causes of heart disease in children and young adults worldwide and is the most common cardiovascular disease in those aged under 25 years.[1] In low- and middle-income nations, and in marginalized people of some wealthy countries, RHD poses a major public health challenge and inflicts severe disability and premature death on many of those affected. As a physical manifestation of poverty, children are particularly vulnerable and hard hit. Worldwide, more than three-quarters of those aged 15 years and younger live in high-prevalence regions,[2] with RHD accounting for the greatest cardiovascular-related loss of disability-adjusted life-years among 10–14-year olds (516.6/100,000 individuals) and the second highest number among children aged 5–9 years old (362/100,000 individuals).[3]

The purpose of this review article is to examine the rationale and issues concerning screening for RHD as a means of reducing the burden of both acute rheumatic fever (ARF) and RHD in endemic areas.

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SEARCH STRATEGY

We searched PubMed in English with the search terms "acute rheumatic fever," "rheumatic heart disease ± screening," and "subclinical rheumatic heart disease" for papers mostly published in the past 20 years until August 2016. We also relied on our familiarity with key literature. Pertinent review articles, book chapters, proceedings, and papers older than 20 years were used when judged important.

EPIDEMIOLOGY AND PATHOGENESIS

The Global Burden of Disease Estimates in 2013 implied that there are 33 million prevalent cases of RHD worldwide causing 275,000 deaths annually.[4] However, many echocardiographic screening studies put the prevalence of RHD at 8–57 out of 1000 children meaning that the true prevalence may rest closer to 62–78 million individuals worldwide with up to 1.4 million deaths each year.[5,6] By comparison, HIV and tuberculosis, both of which benefit from more intensive research and better funding, each results in 1.5 million deaths annually.[7]

RHD is the only long-term sequela of ARF which, in turn, results from an autoimmune reaction to pharyngeal (and possibly skin)[8,9] infection with *Streptococcus pyogenes*, the only known Group A *Streptococcus* (GAS). ARF typically affects children of school-going age with a peak prevalence in the 5–14 years age group, and significant valvular damage is thought to accrue due to repeated episodes of ARF.[10,11] The pathognomonic lesion of RHD (due to its specificity) is commissural fusion leading to mitral stenosis in severe cases. However, nonspecific functional lesions such as mitral regurgitation (MR) and aortic regurgitation (AR) are frequently seen. Given the cumulative nature of valvular damage, classical thinking has been that a substantial period of disease latency of up to 20–30 years needs to be present from the initial ARF episode to clinically symptomatic RHD.[12] However, comprehensive registry data from Australia recently found that 35% of children with ARF had developed RHD by 1 year, and in those who progressed to RHD, 14% developed heart failure within a year of diagnosis, increasing to 27% at 5 years.[13] This shorter latency is also frequently seen in Africa where significant morbidity and mortality is often present in adolescence and young adulthood, possibly through a high burden of ARF recurrences.[14-17]

RATIONALE FOR RHEUMATIC HEART DISEASE SCREENING

Although there is compelling epidemiological evidence linking GAS pharyngitis, ARF, and RHD, the pathogenesis of these diseases is incompletely understood with potentially more questions than answers.[7] For example, we do not know why only two-thirds of patients with ARF will report a preceding sore throat, why only 40%–60% of ARF cases progress to RHD,[18] and why up to 75% of children with RHD have no memory of symptoms consistent with previous ARF.[19] Therefore, most cases of RHD are not necessarily typified by the classic sequence of GAS pharyngitis resulting in symptomatic ARF with progression to RHD,[7] suggesting that rheumatic carditis frequently occurs at a subclinical level.

This is exemplified by the fact that RHD often presents with moderate-to-severe multivalvular disease (63.9%), heart failure (33.4%), pulmonary hypertension (28.8%), atrial fibrillation (21.8%), stroke (7.1%), and infective endocarditis (4%).[6] In the context of the developing world, such late presentations leave few options for intervention given that surgical and catheter-based treatments are limited by cost and lack of access.[20]

Therefore, treating sore throats with penicillin to prevent ARF (primary prophylaxis) and treating episodes of ARF with long-term penicillin (2–4 weekly intramuscular benzathine penicillin G, [BPG]) to prevent further episodes of ARF (secondary prophylaxis) may not be reliable approaches to disease control on a population scale. Primordial prophylaxis (strategies to avoid GAS infection, e.g., improve housing)[21] and a GAS vaccine that would prevent ARF[22] are potential options too but with significant barriers.

A strategy of secondary prevention relies entirely on case detection and a successful therapeutic strategy. Therefore, if we hope to bridge the gap between the large number of incident RHD cases and the smaller number of patients who present with ARF (there is a 10-fold difference in endemic areas),[7] we need a more robust strategy for detecting early RHD.

Auscultation for a pathological murmur has been the traditional approach to screening school-aged children for RHD. However, it is neither sensitive[23] nor specific[24,25] as demonstrated in the seminal paper by Marijon *et al.* in 2007, who showed that ten times more cases of RHD were detected using echocardiography compared with auscultation.[23] Subsequent studies have also shown a significant (5–50-fold) increase in RHD detection by echocardiography versus auscultation.[24,26-31]

The advent of echocardiography thus heralded a new era, revolutionizing RHD screening in the process. The high sensitivity of echocardiography meant researchers were discovering early morphological valvular changes before any clinically detectable functional lesion had developed and the term "subclinical RHD" (or latent RHD) subsequently emerged, recognizing that RHD could be clinically silent.[32] Given the cumulative nature of RHD, this was potentially significant because one would predict

that younger patients with early-stage disease have the most to gain from an earlier diagnosis and institution of secondary prophylaxis.

THE WORLD HEART FEDERATION CRITERIA

In 2005, a working group supported by the World Health Organization (WHO) and the National Institutes of Health established case consensus definitions for RHD.[33] These guidelines were not evidence based and the definition of definite RHD required the presence of a heart murmur consistent with MR or AR and echocardiographic evidence of rheumatic valvular damage (or previous history of definite/probable ARF with no echocardiogram having been performed).

Furthermore, these guidelines were not universally accepted and many countries used alternative (sometimes local) guidelines for RHD diagnosis,[24,26,27,34-37] inadvertently resulting in a diagnostic potpourri that seriously undermined the validity and interchangeability of data from different countries. Inevitably, concerns began to emerge regarding diagnostic specificity:[30] For example, a study retrospectively scoring one sample population with different echocardiographic criteria resulted in an almost 6-fold alteration in disease prevalence.[35]

The push for an evidence-based consensus for echocardiographic diagnostic guidelines started to gain momentum. The 2012 World Heart Federation (WHF) criteria[38] [Box 1] were written to meet these needs and defined the lower limit of what constitutes RHD by echocardiography (although this is highly debatable-see later). Auscultation is no longer required, and the guidelines are intended for screening patients with no history of ARF who live in endemic regions.[38] However, the introduction of the WHF criteria did not solve all problems relating to RHD diagnosis and screening (nor did they intend to) and simultaneously raised additional issues that must be tackled (e.g., borderline RHD).

Box 1: The abridged World Heart Federation diagnostic screening criteria for rheumatic heart disease[38]

- Echocardiographic criteria for RHD in individuals ≤20 years
  - For definite RHD (either A, B, C, or D)
    - A: Pathological MR and ≥2 morphological features of RHD of the MV
    - B: MS (mean gradient ≥4 mmHg)
    - C: Pathological AR and ≥2 morphological features of RHD of the AV
    - D: Borderline disease of both the MV and AV
  - For borderline RHD (either A, B, or C)
    - A: ≥2 morphological features of RHD of the MV without pathological MR or MS
    - B: Pathological MR
    - C: Pathological AR
- Echocardiographic criteria for pathological regurgitation
  - Doppler echocardiographic criteria for MR (all 4 must be met)
    - Seen in 2 views
    - In at least 1 view, jet length ≥2 cm
    - Velocity ≥3 m/s for 1 complete envelope
    - Pan-systolic jet in at least 1 envelope
  - Doppler echocardiographic criteria for AR (all 4 must be met)
    - Seen in 2 views
    - In at least 1 view, jet length ≥1 cm
    - Velocity ≥3 m/s in early diastole
    - Pan-diastolic jet in at least one envelope
- Echocardiographic criteria for morphological features of RHD
  - Features in the MV
    - AMVL thickening ≥3 mm (≥4 mm if aged 21-40 years, ≥5 mm if aged over 40 years)
    - Chordal thickening
    - Restricted leaflet motion
    - Excessive leaflet tip motion during systole
  - Features in the AV
    - Irregular or focal thickening
    - Coaptation defect
    - Restricted leaflet motion
    - Prolapse

RHD: Rheumatic heat disease, MR: Mitral regurgitation, AR: Aortic regurgitation, MV: Mitral valve, AV: Atrioventricular, AMVL: Anterior mitral valve leaflet, MS: Mitral stenosis

Box 2: Council of Europe criteria for population screening[39]

- Evidence of an obvious burden of the disease in question
- Initial latent stage of the disease
- A suitable test for disease detection
- Disease can be treated by adequate therapy
- Prove that intervention at an early stage can improve prognosis

PROBLEMS WITH ECHOCARDIOGRAPHIC SCREENING FOR RHEUMATIC HEART DISEASE

The WHO has recommended echocardiographic screening for RHD in endemic areas since 2004. However, RHD only partially meets the Council of Europe (CoE) criteria for population screening[39] [Box 2]. The first two CoE criteria are met unequivocally: there is a significant burden of disease (CoE criterion 1) with a latent stage (CoE criterion 2). The gaps in our current state of knowledge and how this relates to the remaining three criteria are discussed here.

Some general questions, such as the ideal screening age, also remain unanswered and lack concensus in the literature. It has been suggested that screening older age groups to include young adults and pregnant woman would increase pick-up rates of RHD and improve echocardiographic detection of disease.[40,41] At-risk individuals in older age groups, all else being equal, would have had more time to contract ARF and recurrences thereof and are therefore likely to have a higher prevalence of worse valvular involvement, the latter also aiding an already difficult echocardiographic assessment.

However, it is important to remember that RHD screening in its current form with echocardiographic case detection and the institution of secondary prophylaxis aims to prevent ARF recurrences rather than diagnose RHD *per se*. This explains the rationale for screening children rather than adults as the rate of ARF recurrence in the latter group is very low. Most guidelines support this point of view with recommendations to stop prophylaxis at the age of 18–21 years in individuals with mild valve involvement (and without excessive risk). The ideal timing for screening has to carefully balance picking up more cases (by screening later) with picking up less cases by screening as early as possible to allow maximal time for prophylaxis to make a difference. Unfortunately, the added convenience of screening school children comes at a price as school attendance in poor areas can be <70%,[42] risking underestimating the prevalence of disease in those most likely to be worst affected.

Cost-effectiveness of RHD screening

It remains to be determined if echocardiography screening is cost-effective.[5,43,44] A study by Manji *et al.*[43] using Markov modeling suggested that primary prophylaxis may be less cost-effective than echocardiographic screening and treatment of early RHD using secondary prophylaxis. The decisions regarding how and where limited resources should be focused in developing countries is an important ethical question[45] and the decision regarding whether to invest in echocardiographic RHD screening programs at the expense of other, possibly more robust evidence-based interventions for other conditions, warrants due consideration.

The use and delivery of secondary prophylaxis

Secondary penicillin prophylaxis (intramuscular BPG is superior to oral penicillin) plays an important role in preventing ARF recurrences[46] and in doing so reduces the severity of RHD by slowing, stopping, or regressing valvular disease[47,48] (CoE criterion 4). In those with mild disease treated with penicillin prophylaxis, for example, the vast majority will have no detectable disease 5–10 years later.[49,50] However, this specific criterion does not necessarily apply to the screened population. The long-term outcome of secondary prophylaxis as a strategy in patients with borderline RHD and definite RHD diagnosed in the absence of a history of ARF (i.e., those diagnoses found on echocardiographic screening) may be different compared to more "traditionally" diagnosed RHD;[30,51,52] there is no evidence that BPG actually slows or halts RHD progression in these conditions. It has also yet to be proven that diagnosing subclinical RHD and instituting prophylaxis through a screening program will lead to better outcomes compared with intervention when the disease becomes clinically symptomatic (CoE criterion 5).[53]

There is still no reported evidence of GAS resistance to penicillin,[54] and the most cost-effective approach is the delivery of secondary prophylaxis within a register-based RHD control program.[55,56] However, the delivery of high-quality secondary prophylaxis remains a significant global challenge in RHD control:[57] adherence is low in many countries including certain parts of Australia,[58] Egypt,[59] Taiwan,[60] Brazil,[61] Uganda,[62] and South Africa,[63] with worldwide use of penicillin in clinically diagnosed ARF and RHD averaging only around 30%.[64,65] Modifying this trend is a difficult task despite significant research and investment, with efforts thus far only really improving patients from poor to moderate adherence.[66]

Reasons for lack of adherence appear to be multifactorial and include factors such as a lack of awareness or understanding of disease and distance to travel for receiving prophylaxis.[67] An important barrier to adherence also relates to BPG itself, i.e., painful injections and frequent administration (prompting some authors to call for a reformulated BPG with an ideal dosing interval of 3–6 months).[66]

Therefore, before embarking on widespread RHD screening programs, more work needs to be done on how best to mobilize initiatives that improve the availability, delivery, uptake, and maintenance of secondary prophylaxis, despite widely divergent views on how to achieve this.[45]

Improving the portability and cost of echocardiographic machines

Standard portable echocardiography (STAND) machines are an overt barrier to the implementation of widespread screening programs in poor regions: They are expensive, cumbersome to transport, and have limited battery capacity. Handheld (HAND) devices help address these issues although their limited functionality (e.g., lacking continuous wave Doppler) means that they are a work in progress. It is now possible to attach probes to smart devices which should help improve portability and reduce costs. The performance of HAND and STAND devices within screening studies is discussed later.

There is no perfect diagnostic test for rheumatic heart disease

Although echocardiography has become the gold standard for RHD diagnosis, it relies on criteria that must balance sensitivity and specificity and as such invariably remains imperfect at diagnostic categorization (CoE criterion 3). In particular, detecting early valvular lesions that have no diagnostic or prognostic precedent raises many questions including that we still do not truly know what constitutes the lower limit of RHD (the earliest or slightest changes recognizable as being due to RHD) by echocardiography. Part of the problem here is that RHD encompasses pathological changes that exist on a continuum, and delineating the transition point that separates mild disease from a normal variant can be very difficult. Although echocardiography is presently the

most discriminating tool, a deeper understanding of the disease mechanisms that underlie morphological changes will no doubt facilitate a more rational diagnostic criteria.[68]

In a disease like RHD, accurate diagnosis is a particularly critical issue: A false-positive diagnosis will expose the patient to inappropriate and lengthy treatment (usually 10 years or longer), potentially create psychological harm and stigmatization by association with a disease (there is even evidence that echocardiographic RHD screening alone lowers quality of life scores for both the caregiver and screened child),[69] and unnecessarily add to the financial and manpower burden of the already stretched healthcare systems of many developing countries. Conversely, a false-negative result risks missing the opportunity to prevent a potentially fatal disease.

The significance of borderline rheumatic heart disease

Understanding the natural history of borderline RHD in particular is crucial because screening studies tend to uncover a burden of disease that is double (or more) that of definite RHD.[42,70] If borderline RHD is indeed confirmed to be associated with an increased risk for ARF recurrences or progression to definite RHD, then this may more than triple the number of individuals who might benefit from secondary prophylaxis and screening programs.[52] Notwithstanding these considerations, however, we do know that patients with mild, clinically evident RHD have an excellent long-term prognosis (even without regular penicillin prophylaxis)[71] and it should follow then that subclinical disease detected by echocardiography might have a potentially even better outcome.[45]

Longitudinal follow-up studies of patients diagnosed with borderline RHD have provided some clues on natural history, but no firm conclusions. Rémond *et al.*[72] examined Australian children using the WHF criteria in a prospective follow-up study after 2.5–5 years and found that individuals with borderline RHD were 8.8 times more likely to develop ARF, over eight times more likely to experience echocardiographic progression of valve lesions, and that 1 in 6 progressed to definite RHD. However, one-third of these children were receiving secondary prophylaxis, which may have altered the natural course of the disease.

They also demonstrated that patients with nonspecific valvular abnormalities (e.g., one morphological feature of RHD of the mitral valve (MV) and/or aortic valve without pathological MR or AR) were at increased risk of progression to definite RHD, with 1 in 10 progressing. These findings again bring into focus the questions regarding the definition of what constitutes the lower limit of RHD by echocardiography and also raises the issue of how best to manage these patients, whether to treat with secondary prophylaxis, opt for enhanced surveillance or repeat echocardiography, decisions that will have potentially significant implications for already stretched health-care systems.

Another recent study,[73] again using WHF criteria, re-examined 44 South African patients with borderline or definite RHD around 5 years after the initial diagnosis. Half of the participants (52.3%) improved to either borderline RHD or normal status, one-third (31.8%) did not show any change, and 15.9% worsened to definite RHD. In this series, only two patients (4.6%) were on secondary prophylaxis.

Slightly earlier studies from Nicaragua,[27] India,[28,74] Uganda,[75] and New Caledonia[76] also detail the natural history of borderline RHD. Outcomes after 5–43 months from diagnosis were that 49%–69% of possible or borderline RHD (different terminology owing to nonstandard criteria) remained stable, 21%–42% showed disease regression, and 4%–12% showed disease progression. However, the studies from Nicaragua and India used nonstandardized diagnostic criteria (which are associated with widely varying estimates of the prevalence of RHD) and many of these studies reported variable use of secondary prophylaxis, again potentially altering the course of the disease.

One has to question the mechanism of improvement of rheumatic involvement in all these studies and more work is undoubtedly required to tease out true disease improvement from the known measurement variability of mild or subclinical disease. This is an issue because borderline RHD often encompasses minor heart valve abnormalities that are open to subjective assessment (e.g., chordal thickness, anterior MV leaflet thickness, and mild leaflet motion abnormalities). Indeed, one study[77] examining variability in echocardiographic interpretation with serial testing within a 12-month period (and therefore less likely to represent natural progression/regression) demonstrated that there is a large inter-observer and inter-study variability when it comes to the diagnosis of borderline RHD.

Finally, researchers who screened low- and high-risk Australian children for RHD found that high-risk Australians were 3.4 times more likely to have borderline RHD.[42] This shows that almost certainly some cases of borderline RHD represent mild RHD but, as discussed, we have yet to uncover echocardiographically what distinguishes these cases from the normal variants (or alternative pathologies) that also form a significant proportion of the borderline RHD group.

Simplifying the World Heart Federation criteria for rheumatic heart disease screening programs

Implementing the WHF criteria is time-consuming, potentially complex, requires highly trained operators,[38,53]

and may be impractical for in-field application.[30,78] Screening programs to date have employed a two-stage process with suspected RHD confirmed following expert review, something which cannot be maintained if we hope to implement large-volume screening given the paucity of expert reviewers and the extra cost this would entail. Therefore, the development of a uniform, simplified criteria with acceptable sensitivity and specificity that allows for a single-stage screening process by nonexperts using HAND, and which can be implemented within a preexisting health care program would significantly improve feasibility.[53] However, some middle-income countries may not be as restricted in terms of budget and might be able to justify using experienced cardiologists to participate more directly in the screening process. This may circumvent some of the criticism regarding simplification of the criteria and echocardiographic interpretation.

Removing the morphological criteria entirely and simplifying the functional criteria (usually measuring MR jet length only) is a strategy that researchers have recently begun to employ, with HAND devices being increasingly used for this purpose. A minimally defined jet length is used as a marker of pathological MR and by extension presence of RHD. A reasonable but unproven assumption here is the rationale that criteria-defined pathological MR found during screening of high-risk RHD populations is more likely to represent RHD than either normal variants or other pathologies.

Possible problems with this simplified approach are that MR has many causes and we are removing the morphological features meant to add specificity, hoping that from a screening perspective, we maintain enough sensitivity to include all possible RHD cases. It is, however, unclear at this stage that the group with isolated morphological change is insignificant and can be ignored.[68] The original WHO Doppler-only criteria were derived from criteria designed to diagnose acute rheumatic carditis during episodes of ARF by differentiating functional from pathological regurgitation and ignored morphological valvular changes that characterize more chronic rheumatic cardiac involvement.[35,79,80] Marijon *et al.* exposed the lack of sensitivity and specificity of these original criteria by adding important morphological criteria indicative of chronic rheumatic valve involvement and degrading the importance of differentiating functional from pathological valvular regurgitation, although retaining some functional deficits (Marijon Combined Criteria).[35] This study demonstrated the importance of the morphological features or at least getting the balance of morphological and functional features right which may caution against oversimplifying things.

Since 2012, several studies[70,81-83] have examined the performance of MR jet length as the single echocardiographic criterion against a reference approach [Table 1]. The definition of pathological MR varied (≥1.5–2.0 cm) between different studies and some included the presence of any degree of AR as a marker of RHD. Sensitivity for all disease (i.e., borderline plus define RHD) varied from 73% to 78.9% and specificity 82.4%–87.3%. Sensitivity for definite RHD was much better, ranging between 97.8% and 97.9% between studies.

One has to be mindful of the figures in all these studies looking at MR as a single criterion. The gold standard WHF criteria used to define what constitutes RHD in these studies required significant MR as an important diagnostic ingredient for the most common lesion. This risks introducing an important bias into these analyses which become a self-fulfilling prophecy.

However, jet length measurement is quick and reproducible, which suits the requirements of large-volume screening programs and thus remains an important avenue to explore. Cardiology practice guidelines place more importance on the proximal jet width assessment (vena contracta) than length assessment when assessing MR severity. The latter, as a measured marker of MR severity, has all but disappeared from recent guidelines due to its known variability with technical factors (e.g., color scale) and anatomical (e.g., atrial size).[87] However, these guidelines, tasked with shaping patient management, have maximal utility in differentiating moderate from severe lesions,[88] but in the screened population of RHD patients (with mild or very mild MR), the use of MR jet length appears to be quite reasonable as a discriminator of MR severity as long as operators remain mindful of the technical pitfalls when comparing studies.

However, with suboptimal specificity rates, this single criterion may require modification or risk over-treatment. Alternatively, a HAND-positive patient could undergo confirmatory testing with STAND which, although not a flawless approach, will still reduce the number of in-depth echocardiograms that need to be performed. Moreover, when compared to auscultation alone, the case for HAND is very powerful, even if it missed almost one-third of borderline RHD in the Godown study: In developing countries ravaged by disease, some intervention, one could argue, is better than none.

The obvious problem here is that all isolated morphological deficits, even if relatively gross, would be missed by necessity. This again addresses the less obvious sensitivity issues with such a simplified approach. Take the example of a patient with a valve area reduced by half due to rheumatic commissural fusion. Such a valve area may still be above the 2.5 cm^2 cutoff for the earliest guideline definition of mitral stenosis[89] but is a clear departure from the normal 5–7 cm^2 and even if isolated

Table 1: Summary of recent screening studies examining the sensitivity and specificity of simplified diagnostic criteria when compared to the reference approach (images obtained using standard portable echocardiography and interpreted by experienced cardiologists with expertise in rheumatic heart disease using the full 2012 World Heart Federation criteria)

Country and year	Population, mean age (SD), % male	Sample size	Diagnostic equipment	Image interpretation	Simplified diagnostic criteria	Sensitivity (all disease)[a]	Specificity (all disease)[a]	Sensitivity (definite RHD)
Mozambique (Mirabel *et al.*, 2012[81])*	Schoolchildren, 10.6 years (2.5), 47.5%	2170	STAND	Experienced cardiologists	MR jet length ≥2 cm	73%	Not recorded (PPV 92%)	Not recorded
Uganda (Beaton *et al.*, 2015[82])	Schoolchildren 10.8 years (2.6), 47%	1420	HAND	Pediatric cardiologists	WHF criteria minus CW Doppler	78.9%	87.2%	97.9%
Uganda (Lu *et al.*, 2015[83])	Schoolchildren, 10.8 years (2.6), 47%	1439	HAND	Pediatric cardiologists	MR jet length ≥1.5 cm or any AR	73.3%	82.4%	97.9%
Uganda (Godown *et al.*, 2015[70])	Schoolchildren, 10.8 years (2.6), 46%	1317	HAND	Experienced cardiologists	WHF criteria minus CW	78.4%	87.3%	97.8%
Fiji (Colquhoun *et al.*, 2013[84])¶	Schoolchildren (age/sex not recorded)	50	STAND	Nurses (scanning and interpretation)	MR jet length ≥1.5 cm	100% 83%[b]	67.4% 79%[b]	Not recorded
New Caledonia (Mirabel *et al.*, 2015[85])	Schoolchildren, 9.6 years (0.5), 49.6%	1217	HAND	Nurses (scanning and interpretation)	MR jet length ≥2 cm or any AR	83.7% 77.6%[b]	90.9% 92.0%[b]	93.3% 86.7%
Uganda (Ploutz *et al.*, 2016[86])	Schoolchildren, 11.1 years (2.5), 42.1%	956	HAND	Nurses (scanning and interpretation)	MR jet length ≥1.5 cm or any AR	74.4%	78.8%	90.9%

Two studies used different diagnostic criteria given that they predated the WHF criteria. [a]All disease: Borderline RHD + definite RHD. Owing to nonstandard criteria, this does not apply to the studies by Mirabel *et al.* (2012) and Colquhoun *et al.* (2013), [b]Both studies compared the performance of two nurses using HAND on the same population, therefore there are two separate values for sensitivity and specificity (the study by Ploutz *et al.* (2016) compared the performance of two nurses using HAND on two different populations), *Diagnostic criteria: 2001 WHO Doppler criteria plus morphological criteria (≥2 of leaflet thickening, restricted leaflet mobility, and thickened, shortened chordae),[81] ¶Diagnostic criteria: WHO and NIH RHD working party diagnostic guidelines.[33] SD: Standard deviation, RHD: Rheumatic heart disease, STAND: Standard portable echocardiography, HAND: Handheld echocardiography, MR: Mitral regurgitation, AR: Aortic regurgitation, PPV: Positive predictive value, CW: Continuous wave Doppler, WHF: World Heart Federation, WHO: World Health Organization, NIH: National Institutes of Health

in terms of not being associated with MR could constitute an important missed group of patients with isolated, milder forms of commissural fusion. The importance of functional versus morphological aspects of the criteria must be weighed carefully and future recommendations based on study evidence.

Task-shifting in rheumatic heart disease screening

Task-shifting (i.e., delegation of clinical tasks to less specialized health workers) is absolutely vital to the success of any potential RHD screening program in developing nations. However, while reducing costs and freeing physicians to perform other tasks,[90] it may actually require additional resources for successful implementation, particularly in the short term.

Studies examining task-shifting using nurses, having previously received focused echocardiographic training, were first conducted in 2013 [Table 1]. Overall sensitivity for all disease ranged from 74.4% to 100% and specificity was 67.4%–92%. Again, sensitivity for definite RHD was high at 86.7%-93.3%.[84-86]

These studies demonstrate that nurses, having received brief and focused training, can follow a simplified screening algorithm using STAND or HAND and achieve reasonable sensitivity and specificity. However, the amount of echocardiographic experience of the nurses (before training for the studies) varied significantly in some cases. Medical students may also make suitable candidates for task-shifting in some developing countries.[91,92] More studies using standardized, high-quality training programs and standardized diagnostic criteria are needed to build a clearer picture of the role of HAND by nonexperts employing simplified criteria.

One possible option for standardized training is an international team of trainers that could act as accredited instructors, implementing these training protocols with competency testing. A cheaper alternative (and which may reach a wider audience) is web-based learning that is open to everyone such as that devised by Engelman *et al.*,[78] who published their successful training protocol online, which was initially tested on-site (http://www.wiredhealthresources.net/EchoProject/). The WHO guidelines also recommend continuous monitoring and evaluation as vital components of the task-shifting process.[93] In addition, results will vary depending on the skill and motivation of the workers, as well as ability to retain these individuals.[94]

CONCLUSION

The recent proliferation of echocardiographic RHD studies has heralded a much-needed reinvigoration into the study and advancement of this neglected disease, but much work lies ahead. Effective strategies that encourage the regular uptake of secondary prophylaxis, a deeper understanding of the natural history of subclinical RHD and its response to penicillin prophylaxis, advancements in portable echocardiography, and a simplified criteria that is based on disease mechanisms, that can be applied by nonexperts, and adequately balances sensitivity and specificity, are desperately needed. Until then, routine widespread screening for RHD cannot be endorsed.

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Conflicts of interest

There are no conflicts of interest.

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