Editorial

Echocardiographic screening for rheumatic heart disease—some answers, but questions remain

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Abstract: Despite being preventable, rheumatic heart disease (RHD) remains a significant global cause of cardiovascular disease. Echocardiographic screening for early detection of RHD has the potential to enable timely commencement of treatment (secondary prophylaxis) to halt progression to severe valvular disease. However, a number of issues remain to be addressed regarding its feasibility. The natural history of Definite RHD without a prior history of acute rheumatic fever (ARF) and Borderline RHD are both unclear. Even if they are variants of RHD it is not known whether secondary antibiotic prophylaxis will prevent disease progression as it does in "traditionally" diagnosed RHD. False positives can also have a detrimental impact on individuals and their families as well as place substantial burdens on health care systems. Recent research suggests that handheld echocardiography (HAND) may offer a cheaper and more convenient alternative to standard portable echocardiography (STAND) in RHD screening. However, while HAND is sensitive for the detection of Definite RHD, it is less sensitive for Borderline RHD and is relatively poor at detecting mitral stenosis (MS). Given its attendant limited specificity, potential cases detected with HAND would require re-examination by standard echocardiography. For now, echocardiographic screening for RHD should remain a subject of research rather than routine health care.

Keywords: Rheumatic heart disease (RHD); echocardiography; screening; prophylaxis

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Despite being preventable, rheumatic heart disease (RHD) remains a significant global cause of cardiovascular morbidity and mortality (1). This is true not only in developing countries but also in some high income countries where a significant rate of acute rheumatic fever (ARF) and prevalence of RHD persist. For example, Australia's Aboriginal and Torres Strait Islander populations have amongst the highest reported rates of RHD in the world (2-4) and RHD remains a significant public health issue in Māori and Pacific Islander populations in New Zealand (5).

Classically RHD develops as a sequela of carditis associated with ARF that in turn is precipitated by prior group A streptococcal (GAS)-mediated infection. The valvular damage associated with RHD is more likely to develop and worsen with cumulative episodes of ARF (6,7). Hence one approach to the management of patients with a previous episode of ARF, or who have already developed early evidence of RHD, is to provide regular secondary antibiotic prophylaxis to prevent further GAS infection and recurrent ARF.

Recent modifications to the American Heart Association's criteria for ARF diagnosis are likely to increase the sensitivity of what is essentially a syndromic diagnosis. Nonetheless, even with such increasingly sensitive tools many people with RHD continue to first present with advanced RHD without an attendant history of ARF (8-11). In such a setting, relying on a diagnosis of ARF to identify all individuals at risk of RHD will necessarily fail to detect a substantial number of patients who may benefit from secondary antibiotic prophylaxis. This was emphasized in a recent Australian school-based RHD echocardiographic screening study which revealed that for every detected case

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of Definite RHD that was already known to the health system, another previously undetected/unreported case of Definite RHD without a clinical history of ARF was uncovered (3). Such findings suggest that a significant proportion of individuals who have post-GAS associated carditis may not experience the classical symptoms of ARF, do not seek clinical review, or are not diagnosed with ARF even if they do receive health care. Indeed a recent study from Ethiopia revealed that up to 75% of children with RHD could not remember ever having symptoms consistent with ARF (12).

If relying on a history of ARF can 'miss' three quarters of people with RHD then how might secondary antibiotic prophylaxis be better directed? One option of increasing research interest has been to explore the utility of echocardiographic screening for the early detection of RHD prior to the development of symptoms associated with severe valvular disease. The existence of subclinical valve disease, undetectable by auscultation, raised debate as to whether prior auscultation-based screening programs had significantly underestimated RHD prevalence (13,14). One of the first reported studies of echocardiographic screening was undertaken by Marijon and colleagues in Cambodia and Mozambique commencing in 2001 (15). Based on the findings of Marijon and colleagues almost ten times as many children with RHD were detected using portable echocardiography-based screening compared with auscultatory screening (15). Since this study, numerous further echocardiographic prevalence studies have been undertaken in a wide variety of settings including Australia (3), India (16), New Zealand (17), Tonga (18), New Caledonia (19), Nicaragua (20), Senegal (21), and Uganda (22) and have been systematically reviewed by Rothenbühler *et al.* (23).

One of the issues surrounding the feasibility of screening for early RHD is that, until recently, there have been no agreed criteria for the diagnosis of RHD based on echocardiographic findings alone. Many of the RHD screening studies cited above utilised conflicting and/or unclear diagnostic criteria for assessing echocardiograms. In an attempt to address this problem, and standardise RHD diagnosis, in 2012 the World Heart Federation (WHF) published a guideline for the echocardiographic diagnosis of RHD (24). This provides clear diagnostic criteria based on the morphology and function of the mitral and aortic valves. Furthermore, it includes a category of "Borderline RHD" which encompasses those individuals with morphological or functional heart valve abnormalities that do not satisfy criteria for Definite RHD but which are of potential significance. These guidelines have precipitated further research regarding the feasibility of RHD echocardiographic screening and enabled more robust investigation of novel screening methodologies.

In a recent study, Godown and colleagues investigated how handheld echocardiography (HAND) may have a role in RHD screening comparing it both to auscultation and standard portable echocardiography (STAND) (25). The potential advantages of HAND relate not only to reduced equipment costs but also to the potential to develop simpler screening protocols that may incorporate non-specialist health care providers. Such a strategy is likely to be particularly appealing in resource-limited settings where existing health care systems are often stretched both in terms of funding and staff.

Results from this cross-sectional study of 4,773 Ugandan school children who underwent STAND revealed that 52 (1.1%) had Definite RHD while 140 (2.9%) had Borderline RHD. Such findings highlight the importance of determining the exact significance of Borderline RHD which, if shown to be associated with a subsequent increased risk of ARF or Definite RHD, may more than triple the pool of screened individuals who might benefit from later follow-up or secondary antibiotic prophylaxis.

Of the 1,317 children selected to undergo HAND and auscultation (10% random selection of all children plus any with STAND-detected functional valve lesions) 45 (3.4%) had Definite RHD, 126 (9.6%) had Borderline RHD, and 1,146 (87%) had normal findings on STAND. The researchers found that, when using a slightly modified version of WHF criteria (limited by the inability to perform continuous-wave Doppler), HAND had high sensitivity for Definite RHD (97.8%) and, to a lesser extent, Borderline RHD (71.4%) compared with auscultation (22.2% and 14.3% respectively). This latter finding concurs with other studies which have shown that auscultation is largely ineffective for the screening-based detection of RHD in asymptomatic individuals and should not be advocated (15,26).

So where are we now in determining the utility and feasibility of echocardiographic screening for RHD? Godown and colleagues have provided useful evidence that HAND may be a cheaper and potentially more accessible adjunct to traditional portable echocardiography for RHD screening. Nonetheless, a number of issues and questions still remain to be tackled before it can be said that the case for handheld-based echocardiographic screening for RHD

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specifically, and echocardiographic screening for RHD more generally, can be advocated.

In the Godown study, while HAND identified 44 out of 45 cases of Definite RHD it missed almost one third of cases of Borderline RHD. Whilst evidence regarding the clinical significance of Borderline RHD remains unclear, recent studies would suggest such findings on screening echocardiography cannot be ignored (27). If Borderline RHD does indeed represent the earliest stages of RHD then it would be difficult to support a technology that failed to identify 30% of individuals who might potentially have benefited from follow-up and secondary antibiotic prophylaxis. The particular inability of HAND to perform continuous-wave Doppler is likely to have contributed to its relatively poor detection of mitral stenosis (MS) (sensitivity 60%). Whilst MS was rare in this paediatric sample, HAND's suboptimal sensitivity for MS should nonetheless caution extending the findings of this study to other populations where screening, particularly in pregnant women, might be considered. In this scenario, a similar under-detection of MS, a treatable condition with significant implications to both mother and child, could have major implications. The combined specificity of HAND for Definite or Borderline RHD was 87% indicating an ongoing need for STAND to confirm diagnoses. Given that the appeal of HAND is its affordability, then the fact that many individuals may need to be retested with STAND to avoid unnecessary treatment would tend to negate any initial cost savings through the use of this potentially more affordable technology.

The feasibility of echocardiographic RHD screening must also necessarily take account of the broader issues relating to any screening program, its risks and benefits and impact on the health care system more generally. The natural history of Definite RHD without a prior history of ARF and Borderline RHD are both unclear. Even if such conditions are shown to represent variants of RHD it is not known whether secondary antibiotic prophylaxis will prevent progression as it does in "traditionally" diagnosed RHD. The impact of screening on populations and health service providers must also be considered. False positives can have a significant detrimental impact on individuals and their families as well as place substantial burdens on health care staff and systems in ensuring long-term follow-up of positive cases (28,29). There is little point in screening for RHD if there are inadequate systems and resources to provide follow-up and treatment. Secondary antibiotic prophylaxis, relatively inexpensive in terms of medication costs, requires many years of treatment and hence consumes valuable health care resources while being inconvenient, painful and possibly expensive to consumers.

Finally, the vexed question remains as to why echocardiographic screening tends to reveal a high proportion of undetected RHD with no prior history of ARF? Are these individuals simply not seeking health care when they have ARF, are they being misdiagnosed when presenting to health services, is there an unseen epidemic of asymptomatic or mild ARF that leaves little chance to implement early secondary prevention initiatives to prevent the development of RHD, or is this a variant of RHD with a different natural history and/or response to secondary antibiotic prophylaxis? We are well on the way to determining the potential role of echocardiographic screening for RHD. Whilst studies such as that of Godown and colleagues discussed here provide some answers, questions still remain to be answered before we can advocate for echocardiography-based screening for RHD as an effective means of RHD prevention.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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