Background—Historically, sub-Saharan Africa has had the highest prevalence rates of clinically detected rheumatic heart disease (RHD). Echocardiography-based screening improves detection of RHD in endemic regions. The newest screening guidelines (2006 World Health Organization/National Institutes of Health) have been tested across India and the Pacific Islands, but application in sub-Saharan Africa has, thus far, been limited to Mozambique. We used these guidelines to determine RHD prevalence in a large cohort of Ugandan schoolchildren, to identify risk factors for occult disease, and to assess the value of laboratory testing.

Methods and Results—Auscultation and portable echocardiography were used to screen randomly selected schoolchildren, 5 to 16 years of age, in Kampala, Uganda. Disease likelihood was defined as definite, probable, or possible in accordance with the 2006 National Institutes of Health/World Health Organization guidelines. Ninety-seven percent of eligible students received screening (4869 of 5006). Among them, 130 children (2.7%) had abnormal screening echocardiograms. Of those 130, secondary evaluation showed 72 (55.4%) with possible, probable, or definite RHD; 18 (13.8%) with congenital heart disease; and 40 (30.8%) with no disease. Echocardiography detected 3 times as many cases of RHD as auscultation: 72 (1.5%) versus 23 (0.5%; \(P < 0.001\)). Children with RHD were older (10.1 versus 9.3 years; \(P = 0.002\)). Most cases (98%) involved only the mitral valve. Lower socioeconomic groups had more RHD (2.7% versus 1.4%; \(P = 0.036\)) and more advanced disease (64% versus 26%; \(P < 0.001\)). Antistreptolysin O titers were elevated in children with definite RHD.

Conclusions—This is one of the largest single-country childhood RHD prevalence studies and the first to be conducted in sub-Saharan Africa. Our data support inclusion of echocardiography in screening protocols, even in the most resource-constrained settings, and identify lower socioeconomic groups as most vulnerable. Longitudinal follow-up of children with echocardiographically diagnosed subclinical RHD is needed. (Circulation, 2012;125:3127-3132.)

Key Words: cardiology ■ echocardiography ■ pediatrics ■ rheumatic heart disease

Rheumatic heart disease (RHD) is the world’s most common acquired cardiovascular disease.1 It afflicts >15 million people, leaving hundreds of thousands with debilitating heart disease and 233 000 people dead each year.2 Historically, RHD disproportionately affects children living in poor, unsanitary, and overcrowded conditions.3–7 Practically eradicated in wealthy countries, RHD remains endemic in Asia, the Pacific Islands, and Africa—home to the largest number of victims.1,2,8 In sub-Saharan Africa, the hardest-hit area, >1 million children suffer from RHD; few receive the medical or surgical care needed to survive and lead normal lives.9

Editorial see p 3060

Clinical Perspective on p 3132

If RHD is detected early, monthly penicillin injections (secondary prevention) are a cost-effective and clinically effective means of preventing more advanced cardiac disease.2 Recently, screening protocols that include primary echocardiography have been shown to have a higher sensitivity for the detection of subclinical RHD, with prevalence rates up to 10 times higher than clinical examination alone.10–13

In recent studies using the consensus World Health Organization/National Institutes of Health (WHO/NIH) guidelines,14 echocardiographic screening has shown a high prevalence of subclinical RHD in India15 and the Pacific Islands.13 Although historical data identify sub-Saharan Africa as the area with the greatest prevalence of clinically detectable disease,6 the search for subclinical disease in this region has, thus far, been limited to Mozambique.

In the largest single-population study in Africa, we used clinical examination and echocardiography to screen almost 5000 Ugandan schoolchildren. We compared the yield of echocardiography screening and auscultation, evaluated the prevalence of RHD by sociodemographic criteria, and assessed the usefulness of laboratory data.
Cardiac auscultation was performed with the patient in the upright position, and the examiner noted the presence or absence of a heart murmur consistent with any combination of mitral regurgitation or aortic regurgitation. A heart murmur was defined as a heart murmur consistent with any combination of mitral regurgitation or aortic regurgitation.

**Methods**

**Setting and Survey**

A cross-sectional population-based study was conducted in Ugandan primary schools. Children between August and November 2010. Approval was obtained from the institutional review boards of the Children’s National Medical Center (Washington, DC), Makerere University (Kampala, Uganda), and the Ugandan Ministries of Health and Education. Letters inviting participation went to 21 randomly selected schools. Schools were assigned to a socioeconomic cohort, taking into account the location, tuition, and estimated average household income. Ten schools responded, and 6 were selected to obtain a socioeconomic balance. Permission was obtained from the headmaster for pupil participation. Letters went home with all students providing parental notification about the study and their opt-out right.

A physician, research nurse, and research coordinator visited each school. All schoolchildren 5 to 16 years of age were included. Absentees were noted and revisits were arranged to maximize coverage. For each child, we obtained demographic information, recorded height and weight, conducted a clinical cardiac examination, and performed a screening echocardiogram (General Electric Vivid I, Milwaukee, WI; Philips Optiq, Andover, MA). Any child with mitral or aortic valve thickening or regurgitation or evidence of congenital heart disease was identified as an abnormal screening echocardiogram and referred to Mulago Hospital for follow-up echocardiography (Philips CX50 or General Electric Vivid 7) and clinical evaluation (history, physical examination, and laboratory values). Images were recorded for later analysis by 3 independent physicians blinded to all clinical data. Children were classified as having no, possible, probable, or definite RHD according to the WHO/NIH joint criteria (Table 1). Complete blood count, erythrocyte sedimentation rate, C-reactive protein, and antistreptolysin O (ASO) titers were obtained at follow-up visits. In cases when a child did not present for follow-up, diagnosis was made by school screening echocardiogram and clinical evaluation.

Children designated as having definite or probable RHD were prescribed penicillin prophylaxis every 4 weeks. Clinicians had the option to begin antibiotic prophylaxis in possible RHD patients according to the local standard of care. All positive cases were enrolled in a program for medical surveillance every 6 months, including clinical and echocardiographic review, initiation of antibiotic prophylaxis for advancing lesions, and attempted placement for surgical intervention when necessary.

**Clinical and Echocardiographic Definitions**

Cardiac auscultation was performed with the patient in the upright and left lateral decubitus positions. Children in whom the presence of a heart murmur consistent with any combination of mitral regurgitation or aortic regurgitation was seen and in whom RHD was confirmed echocardiographically were classified as having clinically detected RHD. Echocardiographic criteria were taken directly from the 2006 WHO/NIH expert consensus statement (Table 1). Only left-sided valves were examined for features of RHD; mild tricuspid regurgitation and mild pulmonary regurgitation were frequently noted but not regarded as indicating RHD. Significant mitral regurgitation was defined as a regurgitant jet at least 2 cm away from the coaptation point of valve leaflets, seen in 2 planes, mosaic in quality (high velocity), and persistent throughout systole. Significant aortic regurgitation was defined as a regurgitant jet at least 1 cm away from the coaptation point of the valve leaflets, seen in 2 planes, and mosaic in quality (high velocity).

**Statistical Analysis**

Contingency table analyses were used to compare the prevalence of positive RHD screens detected by auscultation with those identified by portable echocardiography and to evaluate sociodemographic differences. The weighted κ statistic was computed to evaluate the reliability (interrater agreement) with respect to the certainty of diagnosis.

**Results**

Our study included 4869 of 5006 of eligible students (97%) enrolled in 6 schools over a 4-month period. Despite multiple visits, not all enrolled students were available; no parent, however, refused participation. We screened, on average, 3 days a week. Each school-based screening took ~2 minutes to complete, giving us the ability to screen 200 to 250 children with 1 ultrasonographer in 1 day. Our team consisted of 3 members. Despite having 2 trained echocardiographers on the team, it proved more efficient to have 1 echocardiographer continuously scanning, supported by the 2 other staff members who served as organizers and data tabulators.

Of the 4869 children examined, 130 (2.7%) had abnormal screening echocardiograms. One hundred sixteen children (89%) presented to Mulago Hospital for repeat screening. Of the 130 children, 72 were classified as having definite, probable, or possible RHD, resulting in a prevalence rate of 14.8 cases per 1000 children (95% confidence interval, 7.3–22.3). The positive predictive value of school-based screening echocardiograms was 56%. Eighteen of the 58 children who did not have RHD were found to have congenital heart disease, and 40 were diagnosed as having physiological mitral regurgitation (Figure 1). No child with congenital heart disease also fell into any subcategory of RHD classification. On clinical evaluation alone, only 23 of these children met the criteria for a diagnosis of RHD, corresponding to a prevalence of 4.9 cases per 1000 children (95% confidence interval, 0.9–9.2). Thus, 47 children were found by echocardiography to have findings suspicious for clinically silent RHD. Most cases (97.8%) involved only the mitral valve. There was good agreement among the 3 physician-reviewers on assigned diagnostic category (weighted κ = 0.75).

There was no difference in the prevalence of possible, probable, and definite RHD by sex, body mass index, or boarding status. Children found to have possible, probable, and definite RHD were older than their RHD-negative peers (10.1 versus 9.3 years; P = 0.002; Table 2). The prevalence rate of all possible, probable, and definite RHD remained...
<1% in children <9 years of age and increased to >2% in children 10 to 13 years of age (Figure 2). In addition, the rates of subclinical disease also increased significantly after 9 years of age, with a prevalence of <1% in children 6 to 9 years of age and >1.5% in children >10 years of age (Figure 2). Children who attended schools in a lower socioeconomic cohort had significantly higher rates of possible, probable, and definite RHD (2.7% versus 1.4%; \( P = 0.036 \)) and were more likely to have more probable or definite RHD (64% versus 40%; \( P < 0.001 \); Table 3). No children or families were able to recall a history of acute rheumatic fever.

No group differences were observed in white blood cell count, C-reactive protein, or erythrocyte sedimentation rate. ASO titers were elevated (≥267 IU/mL)\(^{16} \) in 3 of 7 definite cases (43%), 1 of 12 probable cases (8%), 6 of 31 possible cases (19%), and 3 of 12 children with no disease (25%). ASO titers were significantly higher in children with definite RHD compared with children with both probable and possible disease (302 IU/mL [95% confidence interval, 199–424] versus 153 IU/mL [95% confidence interval, 92–147]) and children with physiological mitral regurgitation (147 IU/mL; 95% confidence interval, 92–147).

All children with definite or probable RHD began antibiotic prophylaxis. Four of 49 children with possible RHD began antibiotic prophylaxis. All 4 had both significant valvular regurgitation and morphological valve changes on their echocardiograms but lacked a murmur.

By applying the observed prevalence in our sample of 4869 children to the whole population of children 5 to 16 years of age in Kampala, Uganda (368 643),\(^ {17} \) we estimate that 1806 cases of possible, probable, and definite RHD would be detected by citywide clinical screening compared with 5455 from echocardiographic screening. If expanded to the entire Ugandan population (an estimated 18 million children 5–16 years of age),\(^ {17} \) 266 400 children would be detected by echocardiography, whereas only 88 200 would be found by clinical examination alone.

**Discussion**

In 2004, the WHO recommended that echocardiography be used to diagnose “silent but significant rheumatic carditis.” Since then, there has been much debate on which echocardiography protocol does the best job of diagnosing subclinical patients. In 2006, a working group put together by the NIH and WHO developed consensus guidelines for the echocardiographic diagnosis of possible, probable, and definite RHD.\(^ {14} \) Only recently have the results of large-scale screenings using these guidelines begun to emerge. Although tested in India and the Pacific Islands, no data using these criteria are available for sub-Saharan Africa, the region of the world long thought to have the greatest prevalence. Our study attempts to fill that gap. In this, one of the largest single-population childhood RHD prevalence studies to date, we confirm a much higher rate of possible, probable, and definite RHD identified by echocardiography than by clinical examination alone—a 400% increase. Our data also provide further evidence that to maximize case detection, screening programs should focus on lower socioeconomic groups and a slightly older age cohort. Finally, this study highlights the shortcomings of the WHO/NIH criteria and the difficulty with their practical application.

**Table 2. Demographic Characteristics**

<table>
<thead>
<tr>
<th>RHD Positive</th>
<th>RHD Negative</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>10.1 (9.67–10.62)</td>
<td>9.38 (9.31–9.45)</td>
</tr>
<tr>
<td>Mean BMI, kg/m(^2)</td>
<td>16.51 (15.95–17.07)</td>
<td>16.53 (16.45–16.61)</td>
</tr>
<tr>
<td>Male, %</td>
<td>40</td>
<td>48</td>
</tr>
<tr>
<td>Boarding, %</td>
<td>17.5</td>
<td>17</td>
</tr>
</tbody>
</table>

RHD indicates rheumatic heart disease; BMI, body mass index. Numerical data are shown as means (95% confidence intervals).

**Table 3. Socioeconomic Characteristics**

<table>
<thead>
<tr>
<th>Low SES</th>
<th>Middle SES</th>
<th>High SES</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total students, n</td>
<td>501</td>
<td>2560</td>
<td>1808</td>
</tr>
<tr>
<td>RHD positive, n (%)</td>
<td>14 (2.79)</td>
<td>32 (1.25)</td>
<td>26 (1.44)</td>
</tr>
<tr>
<td>Probable/definite, n (%)</td>
<td>9 (64)</td>
<td>5 (16)</td>
<td>11 (42)</td>
</tr>
</tbody>
</table>

SES indicates socioeconomic status; RHD, rheumatic heart disease.

* \( P \) values compare children in the low SES tertile with children in the middle and high SES tertiles.
Historically, sub-Saharan Africa has had the greatest prevalence of clinically detected RHD. Before 2000, cross-sectional surveys were undertaken in Kenya, the former Congo, Ethiopia, and Sudan using primary auscultation followed by echocardiography in suspicious cases. Clinical detection rates were low in otherwise healthy schoolchildren, ranging from 2.4 to 10.2 per 1000. In the last decade, echocardiography has proven to be more sensitive for RHD detection. Only 1 reported study used echocardiography-based screening and included sub-Saharan Africa, and it was performed before the availability of any published echocardiography-based guidelines. Between 2001 and 2002, Marijon et al found a much higher burden of disease (30.4 cases per 1000) in 2170 otherwise healthy schoolchildren in Mozambique. Our data from Uganda showed a lower burden of disease, with 15 cases per 1000, although still much higher than studies using auscultation alone.

Initial laboratory results were obtained on all children who presented for a follow-up examination at Mulago Hospital. A significant elevation of ASO titer was found in children categorized as definite RHD. An elevated ASO titer generally reflects exposure to streptococcus in the past 6 months. Thus, these results indicate a tendency toward repeat streptococcal exposures in children with the most severe disease. We believe that currently available laboratory tests are not likely to be helpful adjuncts to screening protocols. The development of biomarkers with better specificity and sensitivity for detecting RHD is an important area of future research.

RHD is a disease of cumulative exposure; a single negative screening does not guarantee a healthy outcome. It is also not practical, given limited resources and time, to screen every school-aged child annually. We show that children in schools with lower average socioeconomic representation were 200% more likely to have any category of RHD and 25% more likely to have possible or definite RHD. The ideal screening age that would optimize detection of children who will ultimately develop clinically significant RHD but are still in the subclinical phase is unclear. We speculate that the prime detection age of subclinical RHD is likely 10 years as indicated by our findings. Beginning at 10 years of age, children were significantly more likely to meet any of the WHO/NIH criteria for RHD as well as being more likely to fall in the probable and definite RHD categories. This suggests that in a resource-limited setting, the target population should be 9- to 10-year-old children, especially those in the lowest tertile of socioeconomic representation.

Our study reinforces the need for a 2-staged approach for RHD detection: an initial screening echocardiography followed by comprehensive follow-up for positive screens. School-based echocardiograms are just that: a screening tool. As with any good screening test, the goal is high sensitivity with the inevitable tradeoff of reduced specificity. It would be impractical and prohibitively expensive to evaluate all children with negative school screens more completely. To deal with this issue, screening protocols are purposely designed to optimize sensitivity and to have a nearly 100% negative predictive value. The tradeoff is a lower positive predictive value. Our rate of false-positive screening echocardiograms was 30%. Marijon et al documented an initial screening echocardiography false-positive rate of almost 50%. The additional benefit of a 2-stage approach for school-based echocardiographic screening is that it gives parents and caregivers an opportunity to interface with the clinician at the follow-up visit. At this visit, families learn about RHD, secondary prophylaxis, and the importance of continued follow-up. The specific protocols for these follow-up visits represent 2 aspects of an overall screening program that can and should be emphasized and refined over time.

The WHO/NIH criteria were developed with the goal of standardizing RHD detection by echocardiography in a high-risk population. They were intended for use in otherwise healthy subjects with no history of acute rheumatic fever. In an attempt to balance sensitivity (high disease catchments) and specificity (avoiding overdiagnosis), they included both clinical examination and echocardiographic data. They acknowledged the ambiguity of subclinical disease and attempted to account for it by offering 3 categories of disease: definite, probable, and possible.

After applying these guidelines, we believe that clinical examination is not a necessary component of echocardiographic screening protocols and may actually weaken them when used to classify disease. Clinical examination did not add any information that was not readily evident by echocardiography in any of the children in our cohort. Auscultation is, by nature, subjective. When scaling up screening protocols for country-wide RHD detection, it adds inevitable variability and inconsistency. One of the weaknesses of the 2006 WHO/NIH guidelines is that 2 patients who appear identical on echocardiograms can receive different diagnostic categories based solely on the presence (probable or definite) or absence (possible) of a murmur consistent with mitral or aortic regurgitation.

In addition, although the WHO/NIH joint guidelines proved helpful in the overall disease classification and epidemiology of a population, we found some difficulty in consistently applying them clinically for the diagnosis and treatment of the individual patient. Prescription of secondary prophylaxis for patients who are found to have definite and probable RHD is obvious. These children have traditional, clinically detectable RHD, and studies have shown the protective effect of penicillin in preventing advanced valvular disease. So how do we treat patients who fall into the “possible RHD” category? The guidelines leave this decision to the discretion of the treating physician. Under the WHO/NIH approach, a patient with echocardiographic findings of RHD in the absence of clinical examination findings can reach only the category of possible RHD. This is true even if a patient has both morphological valve changes and significant valvular regurgitation. Our cohort included 4 such patients. They were prescribed secondary prophylaxis. Children with isolated significant mitral regurgitation without morphological valve abnormalities were not given secondary prophylaxis. Thus, the WHO/NIH “possible” designation is imprecise, failing to capture different treatment courses within that diagnostic group.

This difficulty stems from the continued uncertainty of the significance of subclinical carditis. Certainly, echocardiographic detection of morphologically abnormal valves or
significant valvular regurgitation does not guarantee later progression to advanced valvular disease, nor has the clinical effectiveness or cost-effectiveness of secondary prophylaxis in this population been studied. Absent evidence-based treatment protocols for subclinical disease, however, the correct treatment course for these children remains unclear. Risks on both sides force clinicians to exercise caution when labeling children with RHD. Overdiagnosis carries the cost of potential lifelong antibiotic prophylaxis, the discomfort of injections, and the social stigma of chronic disease. Underdiagnosis, or even delayed diagnosis, diminishes the ability to detect clinically silent disease, to provide secondary prophylaxis, and to prevent more advanced disease. This ultimately decreases the value of RHD screening.

Studying the natural history of children diagnosed with subclinical RHD holds the most promise. These children presumably have the most to gain from early detection and secondary prophylaxis, but there are currently few data to support this assumption. In a very small Chilean study, 10 children with known acute rheumatic fever and the absence of auscultatory findings were found by echocardiography to have subclinical valvular changes. Six of these children were followed up prospectively for 5 years, and 3 continued to have valvular changes.22 More recently, follow-up data from a cohort of 100 echocardiographically diagnosed Indian schoolchildren with subclinical disease showed that at an average of 15 months from the time of diagnosis, 68% showed no progression of disease, 4% showed worsening of disease, and 28% showed regression of disease.15 No data on the effectiveness of secondary prophylaxis in this population have been reported. While more data are being collected, we emphasize that every child with suspicious findings should continue to have both clinical and imaging follow-up to monitor for disease progression.

In February 2012, the World Heart Federation published the first evidence-based criteria for echocardiographic detection of RHD. These guidelines resolve many of our concerns. They remove clinical examination from the diagnosis. They divide disease into definite and borderline and provide subcategories within each for different combinations of disease (isolated valvular regurgitation, isolated morphological change, etc.). Large-scale screening and follow-up studies using these new guidelines in the developing world will be very important to develop more precise screening protocols and treatment recommendations.

Currently, secondary prophylaxis is the best available weapon in the fight against RHD. Despite the limitations of the WHO 2006 guidelines, they are the most comprehensive that add echocardiography to clinical assessment. The inclusion of echocardiography without the exclusion of physician examination is an expected step in the evolution of RHD screening guidelines, especially in the developing world where the cost of echocardiography remains a potential obstacle to widespread screening. The advent of portable echocardiography makes it feasible to conduct screening outreach programs that identify disease at an early stage. Ongoing trends in miniaturization and portability may provide cost savings, but comparable screening accuracy is not guaranteed. More formal longitudinal comparative economic analyses are needed that would include the costs of a large-scale screening program, follow-up evaluations, increased use of penicillin, and savings from decreased burden of RHD. We anticipate, even with these added variables, that echocardiographic screening will prove to be a valuable investment in public health, even in the most resource-constrained communities.

Our data add to the growing body of support for widespread echocardiographic screening in the developing world. They show that prevalence rates of subclinical disease in sub-Saharan Africa are high, on par with those in other developing nations.15 Most important, our data inform choices about diagnosis, age, and socioeconomic status that should influence the design of future screening programs. As echocardiographic screening protocols continue to develop, we stress the need for validated definitions of echocardiography-diagnosed subclinical RHD. This will take time and can be accomplished only by well-constructed longitudinal follow-up studies. The next phase of this project includes a longitudinal component and should produce publishable results.

Conclusions
The 2006 WHO/NIH joint criteria showed RHD prevalence in Kampala, Uganda, that was comparable to the rate recently found in India (2%).15 Targeting screening efforts at 10-year-old children in lower socioeconomic cohorts may maximize subclinical detection. In light of the high prevalence of subclinical RHD in the developing world, including sub-Saharan Africa, international efforts should make long-term follow-up of subclinical rheumatic carditis a top priority in the fight against noncommunicable disease and medical equity in these regions.

Disclosures
None.

References


**CLINICAL PERSPECTIVE**

The World Health Organization has made the fight against noncommunicable disease, including acquired cardiovascular disease, a top priority for the next decade. The World Heart Federation has made “eliminating rheumatic fever and minimizing the burden of rheumatic heart disease” 1 of its 6 priorities for the coming 5 years. Rheumatic heart disease affects nearly 20 million people worldwide. It disproportionately affects the developing world, causing death and disability in the prime of life. Widespread screening for rheumatic heart disease based on standardized published echocardiography-based guidelines in the most endemic regions of the developing world will be a critical component of the World Heart Federation effort. Echocardiography allows earlier detection, when penicillin remains an effective and affordable prophylaxis against progressive valvular disease. Our article provides the largest study on prevalence data for echocardiography-based screening for rheumatic heart disease in sub-Saharan Africa and is the first to use published echocardiography-based guidelines in this region. Our results also help to define choices about age, socioeconomic status, and diagnostic protocol that will influence the development and implementation of future screening programs. Furthermore, we emphasize the need for longitudinal follow-up to validate current definitions of subclinical rheumatic heart disease. As echocardiography-based screening protocols increase in prominence and are redefined, these data call for increased awareness and focus on the world’s most prevalent heart disease.