Rheumatic Heart Disease Screening by Echocardiography
The Inadequacy of World Health Organization Criteria for Optimizing the Diagnosis of Subclinical Disease

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Background—Early case detection is vital in rheumatic heart disease (RHD) in children to minimize the risk of advanced valvular heart disease by preventive measures. The currently utilized World Health Organization (WHO) criteria for echocardiographic diagnosis of subclinical RHD emphasize the presence of pathological valve regurgitation but do not include valves with morphological features of RHD without pathological regurgitation. We hypothesized that adding morphological features to diagnostic criteria might have significant consequences in terms of case detection rates.

Methods and Results—We screened 2170 randomly selected school children aged 6 to 17 years in Maputo, Mozambique, clinically and by a portable ultrasound system. Two different echocardiographic sets of criteria for RHD were assessed: “WHO” (exclusively Doppler-based) and “combined” (Doppler and morphology-based) criteria. Independent investigators reviewed all suspected RHD cases using a higher-resolution, nonportable ultrasound system. On-site echocardiography identified 18 and 124 children with suspected RHD according to WHO and combined criteria, respectively. After consensus review, 17 were finally considered to have definite RHD according to WHO criteria, and 66 had definite RHD according to combined criteria, giving prevalence rates of 7.8 (95% confidence interval, 4.6 to 12.5) and 30.4 (95% confidence interval, 23.6 to 38.5) per 1000 children, respectively (P<0.0001, exact McNemar test).

Conclusions—Important consideration should be given to echocardiographic criteria for detecting subclinical RHD because the number of cases detected may differ importantly according to the diagnostic criteria utilized. Currently recommended WHO criteria risk missing up to three quarters of cases of subclinically affected and therefore potentially treatable children with RHD. (Circulation. 2009;120:663-668.)

Key Words: echocardiography ■ rheumatic heart disease ■ prevention ■ ultrasound

A
cute rheumatic fever and consequent rheumatic heart disease (RHD) remain extremely common in low- and middle-income countries, with social and economic as well as medical consequences.1–3 Secondary prophylaxis based on monthly penicillin injections in children identified to have evidence of RHD has been shown to be the most efficient and cost-effective strategy to reduce RHD burden.1,4–6 Early detection is thus highly desirable, and therefore maximizing case detection of subclinical RHD is of major public health importance in developing countries.4,5

Clinical Perspective on p 668

We and others have recently documented that the traditional means of screening for early RHD by auscultation is both insensitive and nonspecific and that on-site portable echocardiography is feasible and results in a case detection rate of up to 10 times greater than case detection by clinical examination alone.7,8 Given that echocardiography now provides the opportunity for enhancing early detection of subclinical RHD and thus potentially prevention of advanced disease, the establishment of optimal criteria for echocardiography-based diagnosis is essential.

RHD remains the main origin of heart valve disease in developing world. In these areas, it is recommended that significant subclinical valve lesions be labeled as probable RHD until proven otherwise and that affected children have long-term follow-up studies and be placed on secondary rheumatic fever prophylaxis.9 In 2001, a World Health Organization (WHO) Expert Committee established a consensus for the echocardiographic diagnosis of subclinical
RHD based on the detection of valvular regurgitation by Doppler interrogation of the cardiac valves. Specific criteria for grading the severity of such regurgitation were included to allow the distinction between pathological versus physiological regurgitation and thus the diagnosis of subclinical RHD. However, the boundary between physiological valve regurgitation and authentic but minimal rheumatic lesions remains difficult to discern in some cases. Pathophysiologically, repeated rheumatic carditis can result in subvalvular or valvular thickening before the development of leaflet retraction and thereby regurgitation. Thus, we have previously proposed that morphological changes of valves affected by the rheumatic inflammatory process, even before the development of pathological regurgitation, likely indicate subclinical RHD, which might benefit from identification and thence secondary prevention.

In the present study, therefore, we sought to assess the performance of Doppler-based versus Doppler- and morphology-based echocardiographic screening in a large population of school children in an area of Sub-Saharan Africa where rheumatic fever remains endemic. We hypothesized that adding morphological features to criteria definition might have significant consequences in terms of case detection rates and thus for eventual health outcomes for large numbers of children.

Methods

Design of the Study

A cross-sectional survey was conducted in Mozambique in Sub-Saharan Africa, representing a region of the developing world where previous surveys have documented an apparently high prevalence of RHD in school-aged children (no previous study is available regarding the incidence of rheumatic fever in Africa) and where local investigators and authorities were willing and able to participate. The survey was performed from May to October 2005 after approval by the Ethics Committee of the Ministry of Health and Ministry of Education after prospective planning, including predefined clinical and echocardiographic criteria for RHD diagnosis.

The subject population, sample size calculation, design, and randomization process have been described in detail previously. Briefly, among the 140,000 children aged 6 to 17 years living in Maputo city, 2,370 children were randomly selected (Epi Info software, version 3.3.2). All children of the 42 randomized classes (mean number of children per class, 51.6±14.2, from 39 to 86) from 6 public schools of Maputo city and suburbs were included in the study when parental written informed consent could be obtained. We sought to survey all students attending each selected class.

Rigorous cardiac auscultation and a detailed echocardiographic examination were both performed at school with the use of portable ultrasound equipment (SonoSite 4.2-MHz transducer), and cases of suspect valve lesions during the on-site ultrasound assessment were then reviewed at the Maputo Heart Institute with the use of a nonportable ultrasound system (Philips Sonos 4500 4.7-MHz transducer). These images were all recorded on super-VHS videotape to be approved by an independent review committee, comprising 3 physicians experienced in diagnosing RHD, blinded to any clinical data. We collected the results of the 3 reviewers to finally assess the degree of concordance. For each of the different sets of echocardiographic criteria (see below), children who also had a discordant diagnosis for RHD after the 3 independent reviews of their echocardiograms were considered to have physiological rather than pathological valvular regurgitation. Indeed, we had prospectively established in the research protocol that only concordant positive results for RHD would be effectively considered RHD.

### Table 1. Criteria Used to Define Subclinical RHD Using Echocardiography

<table>
<thead>
<tr>
<th>WHO criteria</th>
<th>Combined criteria</th>
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<tr>
<td>Doppler criteria</td>
<td>Doppler criteria</td>
</tr>
<tr>
<td>A regurgitant jet &gt;1 cm in length</td>
<td>Any degree of valvular regurgitation seen in at least 2 planes</td>
</tr>
<tr>
<td>A regurgitant jet in at least 2 planes</td>
<td>Associated with at least 2 morphological signs</td>
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<tr>
<td>A mosaic color jet with a peak velocity &gt;2.5 m/s</td>
<td>Leaft restriction</td>
</tr>
<tr>
<td>The jet persists throughout systole or diastole</td>
<td>Subvalvular thickening</td>
</tr>
<tr>
<td>No morphological criteria</td>
<td>Valvular thickening</td>
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Blood analyses for erythrocyte sedimentation rate, C-reactive protein concentrations, and streptococcal antibody titers were performed in children with clinical signs of RHD. Children were treated with salicylates and antibiotics whenever a diagnosis of acute rheumatic fever was made with the use of the revised Jones criteria. As prospectively planned in our study protocol, each child in whom RHD valve lesions were discovered by echocardiography now has medical surveillance every 6 months, including clinical and echocardiographic review, initiation of antibiotic prophylaxis in the presence of “WHO” criteria, and surgical treatment when clinically indicated. Because of the absence of guidelines for initiating antibiotic prophylaxis for subclinical RHD in the presence of “combined” criteria, we have included all of these children in a specific follow-up clinical research program.

### Different Sets of Echocardiographic Criteria

Cardiac murmurs were classified as nonpathological (functional) or pathological, by experienced cardiologists, according to traditional criteria. Murmurs were considered pathological when associated with tachycardia or tachypnea, abnormal pulses, precordial bulge, displaced apex beat, presence of thrill, abnormally loud or fixed second heart sound, diastolic murmur, loud or harsh murmur, or long murmur (eg, pansystolic). The diagnosis of “subclinical” RHD was considered in the presence of silent rheumatic valve features (according to at least 1 of the 2 sets of echocardiographic criteria), acute and/or chronic, even in the absence of a history of acute rheumatic fever.

To assess the echocardiographic RHD prevalence (including clinical as well as subclinical cases), we tested 2 sets of criteria (Table 1). The first criteria (WHO criteria) refer to a set of consensus recommendations by a WHO expert panel, widely used by practitioners for the diagnosis of subclinical RHD, and are based only on Doppler characteristics of the valvular regurgitation, defined by the association of a regurgitant jet >1 cm in length, seen in at least 2 planes, a mosaic color jet with a peak velocity >2.5 m/s, persisting throughout systole or diastole. On the other hand, the second criteria (combined criteria) consider subclinical RHD as the presence of at least 2 morphological rheumatic valvular features associated with any Doppler-detected valvular regurgitation (diagnosed when color Doppler flow mapping demonstrated reversed flow away from the valve when the valve was closed), seen in at least 2 planes. Morphological criteria were based on the study of (1) leaflet morphology (typical marked thickening of the margins); (2) leaflet mobility (abnormal motion due to the posterior leaflet tip restriction); and (3) subvalvular apparatus morphology (prominent thickening, most often just below the valve, and shortening of chordal structures). Only the aortic and mitral valves were considered in this
setting because mild pulmonary or tricuspid regurgitation is frequent and seldom rheumatic in origin. In addition, no valve stenosis was found in this group of relatively young children.

Statistical Analyses
All patients’ characteristics were described as mean±SD or proportions, as appropriate. RHD prevalences with exact 95% confidence intervals (CIs) were computed for the whole sample. The McNemar test for paired data was used for comparison of prevalence rates between the 2 criteria. Regarding the degree of consistency of echocardiographic interpretation of rheumatic valve changes between the 3 echocardiographic experts, we used the pairwise κ coefficient to determine the interobserver variability as well as percentage of concordant cases. Prevalence rates of RHD (according to combined and WHO criteria) between categories of age and between sexes were compared with the use of exact χ² test. Odds ratios with exact CIs for positive diagnosis were calculated. A 2-sided P value <0.05 was considered statistically significant. All data were analyzed in Paris Cardiovascular Research Center, INSERM 970, Paris, France, with the use of Statistical Analysis System software (version 9.1). This report was prepared in compliance with the STROBE checklist. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results
Among the 2370 randomly selected children, 200 were not included in the study because no written parental or guardian consent was obtained (8.5%). The study population thus comprised 2170 children, aged 6 to 17 years (mean age, 10.6 [2.5] years; 47.5% male). The majority of children in each class were examined at the first screening visit at school (94.3%); the remaining 5.7% required a mean of 3.2 follow-up visits to allow screening of the entire prespecified group.

Clinical evidence of RHD confirmed by echocardiography was found in 5 children, a prevalence of 2.3 per 1000 (95% CI, 0.7 to 5.4). Of these, 2 had clinical and biological Jones criteria for acute rheumatic fever; anti-inflammatory and antibiotic treatment was initiated in each case.

In regard to the subclinical evidence of RHD, the results of the systematic echocardiographic screening according to WHO or combined criteria are reported in Figure 1 and Table 2. Among the 208 children (9.6%) with echocardiographic features of at least minimal valve regurgitation, on-site examination identified 18 and 124 children suspected to have RHD according to WHO and combined criteria, respectively (P<0.0001, exact McNemar test). All of the suspected cases were reviewed with the use of the nonportable ultrasound system. After review by the 3 experts, 17 of the 18 were confirmed to have definite RHD according to WHO criteria (94%) (echocardiographic features shown in Figure 2), whereas 66 of the 124 cases were considered to have definite RHD by the use of combined criteria (53%) (echocardiographic features shown in Figure 3). The definite echocardiographic RHD prevalences were thus 7.8 per 1000 (95% CI, 4.6 to 12.5) and 30.4 per 1000 (95% CI, 23.6 to 38.5) for WHO and combined criteria, respectively (P<0.0001, exact McNemar test) (Figure 4). Positive predictive values were

| Table 2. Baseline Characteristics and Prevalence Rates of Echocardiographic Screening for WHO and Combined Criteria for RHD |
|-----------------|---------------------|---------------------|
|                 | WHO Criteria (n=17)  | Combined Criteria (n=66)  |
| Baseline characteristics |                  |                      |
| Age, mean (SD), y | 11.4 (2.0)         | 11.0 (2.5)           |
| Males, n (%)      | 9 (52.9)           | 23 (34.8)           |
| History of acute rheumatic fever, n (%) | 2 (11.8) | 4 (6.1) |
| Prevalence of RHD, per 1000 (exact 95% CI) |           |                      |
| Girls             | 7.0 (3.0–13.8)     | 37.8 (27.5–50.5)    |
| Boys              | 8.7 (4.0–16.5)     | 22.3 (14.2–33.3)    |
| Prevalence by age tertiles |       |                      |
| 6-9 y             | 2.7 (0.3–9.7)      | 25.7 (15.5–39.9)    |
| 10-11 y           | 8.8 (3.2–19.1)     | 25.0 (14.6–39.7)    |
| 12-17 y           | 12.0 (5.5–22.7)    | 40.0 (27.1–56.6)    |
| Estimated cases in Maputo City,* n (95% CI) | 8 892 (5244–14 250) | 34 656 (26 904–43 890) |

*Number of cases was estimated by applying the observed prevalence in our sample (n=2170) to the whole population of children aged 6 to 17 y in Maputo (n=1 140 000).

RHD according to WHO and combined criteria, respectively (P<0.0001, exact McNemar test). All of the suspected cases were reviewed with the use of the nonportable ultrasound system. After review by the 3 experts, 17 of the 18 were confirmed to have definite RHD according to WHO criteria (94%) (echocardiographic features shown in Figure 2), whereas 66 of the 124 cases were considered to have definite RHD by the use of combined criteria (53%) (echocardiographic features shown in Figure 3). The definite echocardiographic RHD prevalences were thus 7.8 per 1000 (95% CI, 4.6 to 12.5) and 30.4 per 1000 (95% CI, 23.6 to 38.5) for WHO and combined criteria, respectively (P<0.0001, exact McNemar test) (Figure 4). Positive predictive values were
calculated at 66 of 124 (53%) and 17 of 18 (94%) for combined and WHO criteria, respectively. On the other hand, and assuming that the use of portable echocardiography in this setting allowed the detection of all RHD cases in the field, maximum sensitivity was calculated at 17 of 68 (25%) and 66 of 68 (97%) for WHO and combined criteria, respectively. Of the 17 children with a definitive diagnosis of RHD by WHO criteria, all were found to have exclusively mitral valve disease. Of the 66 children identified by the combined criteria, 63 (95.5%) had mitral valve disease only, 2 had both aortic and mitral valve disease, and 1 had only aortic valve disease. No cases of mitral or aortic stenosis were seen. None of the children studied had evidence of severe mitral regurgitation with annular dilatation. We found no cases of mitral diastolic flow acceleration in association with limitation of leaflet mobility.

The interobserver variability for diagnosing a subclinical RHD valve abnormality showed excellent agreement for both WHO criteria (noncalculable $\kappa$ value; mean concordant pairs, 96.3%) and combined criteria ($\kappa$ value of 0.92 [95% CI, 0.85 to 0.99]; 0.92 [95% CI, 0.85 to 0.99]; and 0.90 [95% CI, 0.83 to 0.98], respectively, for the 3 pairs of independent reviewers; mean concordant pairs, 95.7%). In regard to WHO criteria, of the 18 suspected RHD cases diagnosed at school, 17 were concordantly considered RHD, and 1 presented a discordant diagnosis for RHD. In regard to combined criteria, among the 124 suspected RHD cases diagnosed at school, 66 were concordantly considered RHD, 50 were concordantly considered non-RHD, and 8 showed discordant interpretation from the 3 reviewers.

The majority of children with WHO criteria for RHD also had combined criteria for RHD (88%). However, of these 17 children with definite lesions according to WHO criteria, 2 children showed isolated mitral regurgitation without any morphological signs to suggest a rheumatic origin (Table 3).

The echocardiographic prevalence of RHD rose with increasing age, peaking at 12.0 per 1000 (95% CI, 5.5 to 22.7) for WHO criteria ($P=NS$) and at 40.0 per 1000 (95% CI, 27.1 to 56.6) in those aged 12 to 17 years for combined criteria ($P=NS$). Although the prevalence of echocardiographic RHD showed no female predominance regarding children according to WHO criteria (odds ratio, 0.80; 95% CI, 0.27 to 2.35; $P=0.8$, exact $\chi^2$ test), RHD prevalence was significantly higher in girls than in boys (odds ratio, 1.72; 95% CI, 1.00 to 3.01; $P=0.04$, exact $\chi^2$ test) according to combined criteria.

Discussion
Recent work has strongly supported the use of portable echocardiography for screening for subclinical RHD in developing nations. Optimizing case detection in this way maximizes the chances of appropriate prevention of advanced RHD. Our results demonstrate, however, that the currently recommended WHO criteria for preclinical RHD may risk missing up to three quarters of cases of subclinically affected and thus potentially treatable children with early RHD, possibly tens of thousands of children worldwide. In adding the diagnostic criterion of morphological valve changes, otherwise well defined in more advanced rheumatic valve lesions, we have detected many children with subclinical RHD but without significant valve regurgitation who would not be eligible for secondary RHD prophylaxis under current international guidelines.

Mitral valve prolapse and degenerative valve disease are the most common causes of important left heart valve regurgitation in adults in developed countries. By contrast, mitral and aortic regurgitation are more likely due to RHD in

Table 3. Number of Detected Cases According to WHO and Combined Criteria

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<th>Combined +</th>
<th>Combined −</th>
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<tr>
<td>WHO +</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>WHO −</td>
<td>51</td>
<td>2102</td>
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<td>66</td>
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endemic areas. Repetitive attacks of rheumatic fever may lead to valve inflammation, with leaflet and subleaflet thickening. Because these changes precede leaflet retraction and regurgitation in rheumatic disease and given that there are almost no other causes of valve thickening in childhood, the identification of morphological valve changes in addition to the detection of regurgitation represents a logical means of enhancing case detection. By contrast, the situation is less clear for the diagnosis of acute rheumatic carditis with valve involvement by ultrasound because of the frequent absence of significant morphological changes and also a lower specificity. We note, however, that the 2007 Australian guidelines now consider subclinical valve regurgitation a major criterion for acute rheumatic fever with carditis in high-risk children (those living in communities with high rates of acute rheumatic fever).

In many populations, acute rheumatic fever and RHD are more common in females than males. Whether this trend is a result of innate susceptibility or increased exposure to group A streptococcus because of greater involvement of women in child rearing is unclear. However, there is now evidence of genetic susceptibility for RHD, including several alleles for major histocompatibility complex class II and tumor necrosis factor. Although we found the expected increase of RHD in females using combined criteria, we observed no female predominance using WHO criteria. Moreover, although the majority of children of the present study identified as having significant regurgitation (WHO criteria) also showed morphological changes (combined criteria), 2 boys demonstrated WHO criteria but had no morphological changes suggestive of RHD.

We have found that the morphological changes that we regarded as diagnostic of subclinical RHD could be detected with similar certainty compared with the traditional WHO criteria, as assessed by concordance between experienced observers for ultrasound-based diagnosis. In regard to feasibility in the field, the WHO criteria may be easier to use at school with a portable ultrasound system, as attested by the high positive predictive value. However, this set of criteria suffers from a substantially lower sensitivity; thus, the combined criteria are better suited for screening for subclinical RHD. The fact that some children are "overdetected" on-site does not necessarily represent a limitation but emphasizes the importance of eventually confirming suggestive findings with more sophisticated ultrasound equipment. More recent portable ultrasound systems with higher resolution might, in the future, be able to provide more accurate on-site detection rates. In this context of screening, sensitivity should be emphasized, and the combined criteria appear to be optimal in this regard. Finally, the feasibility of widespread screening for RHD by local teams using portable echocardiographic systems must be evaluated in practice in developing countries. Echocardiographic screening may present some difficulties because such a program may have significant costs, and practitioners would require education about this technology. Charitable organizations might bear some of these relatively modest costs. Moreover, after appropriate training, the use of echocardiography for assessing valves is relatively straightforward and accessible not only for cardiologists but also for many doctors and/or allied health professionals.

The main issue after case identification remains the continued surveillance of children with subclinical RHD; further study is under way, therefore, to understand the natural history of such valve lesions and to evaluate the risk/benefit ratio of secondary prophylaxis for children whose subclinical RHD is detected in this way. Echocardiographic detection of morphologically abnormal valves does not necessarily imply an inevitable progression to advanced valvular disease, nor is the benefit of antibiotic prophylaxis proven, in such cases. Thus, prospective studies on the impact of secondary prevention and cost-effectiveness of such a strategy require further rigorous evaluation. Indeed, it is as yet unproven that penicillin prophylaxis for all children detected echocardiographically have subclinical rheumatic valve lesions will prevent later advanced valve disease, although this seems likely from first principles. Nevertheless, one must consider issues of cost and rare but possible adverse events of such treatment. Moreover, further studies are needed to attest to the cost-effectiveness of such strategies. The cost of a basic portable echocardiographic device is moderate compared with the number of children potentially detected and might be obtainable from charitable organizations; the education of assistants to use echocardiography in diagnosing clinical and subclinical RHD should also be feasible in a short time.

Although the transfer to VHS recording may result in some loss of resolution, the 3 reviewers did not report any difficulties for final diagnosis, and their readings demonstrated high concordance rates. On the other hand, we acknowledge that nonquantitative measures for assessing the rheumatic origin of valve abnormalities may present a limitation for wider use by less experienced observers. In addition, we cannot exclude the possibility that some of subclinical lesions detected during the survey were not related, at least in part, to an acute inflammatory process. However, because the distinction between "acute" and "chronic" RHD remains challenging in the field, and because the medical strategy is the same for both, we have chosen a pragmatic approach in considering acute and chronic RHD forms together. We acknowledge that WHO criteria may appear more likely to be related to acute RHD, whereas morphological changes as defined in the combined criteria may be more likely to suggest chronic RHD lesions. Unfortunately, at this time, there are no biological or other imaging markers able to confirm or eliminate early, subclinical RHD with diagnostic certainty. This lack of "gold standard" limits the calculation of sensitivity and specificity for each set of echocardiographic criteria.

In conclusion, on-site echocardiography should be very useful for improving the detection rates of subclinical RHD in children in the developing world. Our data indicate that inclusion of morphological valve changes in addition to regurgitation has the potential to increase case detection rates by up to 3-fold, with major potential public health benefits.

Acknowledgments

We gratefully acknowledge the head directors of the 6 primary selected schools and the nursing staff of the Maputo Heart Institute for their help in the study.
Sources of Funding
The primary mission of La Chaîne de l’Espoir, Paris, France, and Cadeia da Esperança, Coimbra, Portugal, nongovernmental development organizations, is to aid children whose lives are endangered or hampered by lack of skills and resources, when a single and ordinary surgical act could offer them a chance for a normal life. These organizations sponsored the echocardiographic equipment for this study. The sponsors did not participate in the design and conduct of the study, in the collection, analysis, or interpretation of the data, or in the preparation, review, or approval of the manuscript.

Disclosures
None.

References

CLINICAL PERSPECTIVE
It has recently been estimated that >200 000 patients die from rheumatic heart disease (RHD) every year worldwide, with most of these cases occurring in developing nations. RHD usually results from the cumulative cardiac damage from recurrent episodes of acute rheumatic fever. After a first attack, penicillin therapy has been shown to be effective in reducing the risk of evolution for more severe lesions. Accordingly, identifying children with early signs of RHD is a crucial issue. In this setting, echocardiography has been shown to be an efficient tool to detect subclinical rheumatic valve features in school-aged children. In the present article, we have found that focusing on morphological criteria of valve changes, rather than echo-Doppler criteria, has a major impact on the number of detected cases and that the diagnostic criteria proposed by the World Health Organization Expert Committee in 2001 may be relatively insensitive for early RHD case detection. Because the boundary between physiological valve regurgitation and authentic but minimal rheumatic lesions remains difficult to discern in some cases and because no gold standard exists for RHD, the challenge now is to define/recommend optimal criteria that may be easily used worldwide and allow accurate detection of the largest number of children who might benefit from early preventive efforts.
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Circulation. 2009;120:663-668; originally published online August 10, 2009;
doi: 10.1161/CIRCULATIONAHA.109.849190
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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