ORIGINAL ARTICLE

Prevalence of Rheumatic Heart Disease Detected by Echocardiographic Screening

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ABSTRACT

BACKGROUND

Epidemiologic studies of the prevalence of rheumatic heart disease have used clinical screening with echocardiographic confirmation of suspected cases. We hypothesized that echocardiographic screening of all surveyed children would show a significantly higher prevalence of rheumatic heart disease.

METHODS

Randomly selected schoolchildren from 6 through 17 years of age in Cambodia and Mozambique were screened for rheumatic heart disease according to standard clinical and echocardiographic criteria.

RESULTS

Clinical examination detected rheumatic heart disease that was confirmed by echocardiography in 8 of 3677 children in Cambodia and 5 of 2170 children in Mozambique; the corresponding prevalence rates and 95% confidence intervals (CIs) were 2.2 cases per 1000 (95% CI, 0.7 to 3.7) for Cambodia and 2.3 cases per 1000 (95% CI, 0.3 to 4.3) for Mozambique. In contrast, echocardiographic screening detected 79 cases of rheumatic heart disease in Cambodia and 66 cases in Mozambique, corresponding to prevalence rates of 21.5 cases per 1000 (95% CI, 16.8 to 26.2) and 30.4 cases per 1000 (95% CI, 23.2 to 37.6), respectively. The mitral valve was involved in the great majority of cases (87.3% in Cambodia and 98.4% in Mozambique).

CONCLUSIONS

Systematic screening with echocardiography, as compared with clinical screening, reveals a much higher prevalence of rheumatic heart disease (approximately 10 times as great). Since rheumatic heart disease frequently has devastating clinical consequences and secondary prevention may be effective after accurate identification of early cases, these results have important public health implications.

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In poor and developing nations, rheumatic heart disease remains a major cause of morbidity and premature death and imposes a substantial burden on health care systems with limited budgets.[1,2] Nevertheless, primary and secondary prevention efforts may be highly effective.[1,3] Secondary prevention relies on accurate case detection for the appropriate use of prophylactic antibiotics and regular medical surveillance. Exact prevalence data are also highly desirable to facilitate health care planning.

Almost all population-based epidemiologic surveys have relied on careful clinical examination of school-age children, with confirmation of clinically suspected cases by echocardiography. Such surveys show current prevalence rates of rheumatic heart disease of approximately 1 to 5 cases per 1000 among school-age children in developing countries, with the highest rates in sub-Saharan Africa.[2]

Cardiac ultrasonography is known to be more sensitive than auscultation for the detection of pathologic valve disease,[4] and the recent availability of high-quality portable ultrasound equipment makes it possible to screen large numbers of children at schools in developing nations. Furthermore, the 2004 World Health Organization Expert Consultation Report states that echocardiographically diagnosed, clinically silent rheumatic valve involvement should be managed as rheumatic heart disease until proved otherwise.[3] We therefore hypothesized that comprehensive screening, including echocardiography in all children, might reveal a higher prevalence of cases than clinical examination with echocardiographic confirmation of clinically suspected cases only.

We performed two large, population-based studies of school-age children, one in Southeast Asia (Cambodia) and one in sub-Saharan Africa (Mozambique), to assess the feasibility of echocardiographic screening and to ascertain whether this method would yield a more realistic estimate of the prevalence of rheumatic heart disease than that obtained by screening with the use of predominantly clinical criteria.

METHODS

SETTING AND SURVEY METHODS

Our study was conducted in Cambodia and Mozambique, because these countries are representative of two regions of the developing world where previous surveys have documented an apparently high prevalence of rheumatic heart disease in school-age children[2] and because local investigators and authorities were willing and able to participate in the studies. The two studies were carried out after prospective planning by a central group of investigators, which included establishing protocols for prospectively defined clinical and echocardiographic criteria for the diagnosis of rheumatic valvular abnormalities.

The first study was carried out in Cambodia in 2001 and 2002 after approval by the Ministry of Health. The investigators approached the directors of randomly selected schools in the capital of Phnom Penh, and all agreed to participate. All children in each school were invited to participate; those children whose parents or guardians gave oral informed consent were brought to the Phnom Penh Heart Center, where they underwent comprehensive clinical and echocardiographic examination (with a Philips Sonos 4500 4–7 MHz transducer) for signs of rheumatic heart disease. Images were recorded on super-VHS videotape for later review by an independent physician who was experienced in diagnosing rheumatic heart disease and was not aware of the clinical findings. The results of this study appeared to confirm our hypothesis that a much higher prevalence of rheumatic heart disease would be found with echocardiographic screening. We then decided to repeat the study with more rigorous randomization procedures for subject selection and with confirmation of echocardiographic findings by multiple independent observers.

We conducted a survey in Mozambique from May through October 2005 after approval of the survey by the ethics committee of the Ministry of Health and the Education Ministry. A total of 2170 pupils from six public primary schools were randomly selected from among the 1,140,000 children 6 through 17 years of age living in the capital city of Maputo. The overall sample was equally distributed among seven class levels, with 310 subjects per class level, in order to ensure an even age distribution. Two thirds of the children (1440) were from suburban schools and one third (730) were from urban schools. For each class level, classrooms were selected by means of a systematic randomization procedure with Epi Info software (version 3.3.2). In each selected classroom, all chil-

dren for whom written informed consent could be obtained from a parent or guardian (91.6% of children) were included in the study.

For each child, any history of acute rheumatic fever was noted. The participating children then underwent a detailed clinical and echocardiographic examination (with a SonoSite 4.2 MHz transducer) at the school. Absentees were noted and revisits were made to examine all of them. All children in whom cardiac abnormalities were noted with the portable ultrasound system underwent repeated scanning at the Maputo Heart Institute (with a Philips Sonos 4500 4–7 MHz transducer). These images were recorded on super-VHS videotape for later analysis by three independent physicians experienced in diagnosing rheumatic heart disease.

In both studies, children with a diagnosis of acute rheumatic fever according to the revised Jones criteria were treated with salicylates and antibiotic agents.[5] Each child in whom rheumatic valve lesions were detected by echocardiography was followed up with medical surveillance every 6 months, including clinical and echocardiographic review, initiation of antibiotic prophylaxis in cases of lesions considered to be significant according to World Health Organization criteria, and surgical treatment where clinically indicated.

CLINICAL AND ECHOCARDIOGRAPHIC DEFINITIONS

Clinical examination was performed by physicians experienced in the diagnosis of rheumatic heart disease. Careful cardiac auscultation was performed with the patient in the supine and left lateral decubitus positions. Children in whom an organic murmur was detected clinically and the presence of rheumatic heart disease was confirmed echocardiographically were classified as having clinically detected rheumatic heart disease.

The echocardiographic criteria were agreed on by all observers in both the Cambodian and the Mozambique studies before the ultrasound scans were read by echocardiographers who were unaware of the clinical findings. Only left-sided valves were examined for features of rheumatic heart disease; mild tricuspid regurgitation and pulmonary regurgitation were frequently noted but were not regarded as indicating rheumatic heart disease. Rheumatic heart disease was defined by the presence of any definite evidence of mitral- or aortic-valve regurgitation seen in two planes by Doppler echocardiography, accompanied by at least two of the following three morphologic abnormalities of the regurgitant valve: restricted leaflet mobility, focal or generalized valvular thickening, and abnormal subvalvular thickening. For a definite diagnosis of rheumatic heart disease, these features had to be identified concordantly by each of the echocardiographers, all of whom were experienced in the diagnosis and treatment of rheumatic heart disease.

STATISTICAL ANALYSIS

Each study enrolled more than 2000 children and had more than 90% power at the 0.01 significance level to test the hypothesis that echocardiographic screening would reveal twice as many cases of rheumatic heart disease as would be expected on the basis of published prevalence data from clinical screening studies (5 cases per 1000 children).[2] Our sample-size calculation was based on the results of previous studies of the clinical prevalence of rheumatic heart disease; since the prevalence observed in our studies was higher than expected, our sample sizes clearly were overestimated.

All data were analyzed at INSERM, Unit 780 Avenir, Cardiovascular Epidemiology, Villejuif, France, with SAS software (version 8.2). Descriptive data are presented as means ±SD; sample means were compared with an independent-samples Student's t-test. A two-sided P value of less than 0.05 was considered to indicate statistical significance. We calculated the fraction of children whose findings were normal by clinical criteria and abnormal by echocardiographic criteria. In addition, the rate of detection by echocardiographic screening was calculated by means of the total probability formula as follows: rate of detection = $p1 + (1 - p1) \times p2$, where p1 is the probability of an abnormal result by clinical screening and p2 is the probability of an abnormal result by echocardiographic screening after a normal result by clinical screening.

RESULTS

CAMBODIA

Of the 3677 children examined in Cambodia, 52.0% were male, and the mean age was 11.7±2.5 years (Table 1). Clinical evidence of rheumatic heart disease confirmed by echocardiography was found in 8 children, corresponding to a prevalence of 2.2 cases per 1000 children (95% confidence interval [CI], 0.7 to 3.7). Five of these eight children ful-

filled the revised Jones criteria for acute rheumatic fever and were treated.

Echocardiographic screening showed that 79 children had Doppler evidence of left-heart valve regurgitation and morphologic features of rheumatic heart disease, corresponding to a prevalence of 21.5 cases per 1000 children (95% CI, 16.8 to 26.2) (Fig. 1). Thus, 71 children were found by echocardiography to have clinically silent rheumatic heart disease. Of the 79 children with a diagnosis of rheumatic heart disease, 61 (77.2%) had only mitral-valve disease, 8 had both aortic- and mitral-valve disease, and 10 had only aortic-valve disease. No cases of valvular stenosis were detected.

MOZAMBIQUE

Of the 2170 children examined in Mozambique, 47.5% were male, and the mean age was 10.6±2.5 years. Three children had a history of acute rheumatic fever but had no cardiac murmur on examination, one child had known rheumatic heart disease, and one had known congenital heart disease. Clinical evidence of rheumatic heart disease confirmed by echocardiography was found in 5 children, corresponding to a prevalence of 2.3 cases per 1000 (95% CI, 0.3 to 4.3). Two of these five children fulfilled the revised Jones criteria for acute rheumatic fever and were treated.

Echocardiographic screening showed that 124 children (5.7%) had Doppler evidence of left-heart valve regurgitation. Sixty-six of these children were concordantly confirmed by the three independent experts to have valvular rheumatic damage, corresponding to a prevalence of 30.4 cases per 1000 (95% CI, 23.2 to 37.6) (Fig. 1). Of these 66 children, 63 (95.5%) had only mitral-valve disease, 2 had both aortic- and mitral-valve disease, and 1 had only aortic-valve disease (Fig. 2). No cases of valvular stenosis were detected. A pairwise kappa test showed excellent agreement among the three observers.

Of the 456 children with a detected cardiac murmur, 91 were suspected to have organic lesions at auscultation, but only 10 of them had cardiac lesions confirmed by echocardiography (5 had valvular lesions associated with rheumatic heart disease, and 5 had congenital heart lesions). The prevalence of echocardiographically diagnosed rheumatic heart disease was higher in girls than in boys (odds ratio, 1.7; 95% CI, 1.0 to 2.8; P=0.04) and in suburban than in urban children (P=0.04).

Table 1. Characteristics of the Patients.*

Characteristic	Children in Cambodia (N=3677)	Children in Mozambique (N=2170)
Age — yr		
Mean	11.7±2.5	10.6±2.5
Range	6–17	6–17
Median	12	11
Male sex — no. (%)	1912 (52.0)	1031 (47.5)
Cases of rheumatic heart disease — no.		
Clinical detection	8	5
Echocardiographic detection	79	66
Echocardiographic but not clinical detection	71	61
Prevalence of rheumatic heart disease		
Clinical detection — no. of cases/1000 children (95% CI)	2.2 (0.7–3.7)	2.3 (0.3–4.3)
Echocardiographic detection — no. of cases/1000 children (95% CI)	21.5 (16.8–26.2)	30.4 (23.2–37.6)
Echocardiographic but not clinical detection — no. of cases/1000 children	19.3	28.1
Ratio of echocardiographic to clinical detection	9.8	13.2
Echocardiographic detection in girls vs. boys — odds ratio (95% CI)	1.3 (0.9–2.1)†	1.7 (1.0–2.8)‡
Involvement of mitral valve — % of cases (95% CI)	87.3 (78.2–93.0)	98.4 (91.9–99.7)

* Plus–minus values are means ±SD.
† P=0.07.
‡ P=0.04.

The prevalence of subclinical rheumatic heart disease increased with age from 2.4% in the lowest tercile (9 years or less) to 4.1% in the highest tercile (12 years or more) (P=0.04).

By applying the observed prevalence in our sample of 2170 children to the whole population of children 6 through 17 years of age in Maputo (1,140,000), we estimate that 2622 cases of rheumatic heart disease would be detected by clinical screening as compared with 34,656 cases that would be detected by echocardiographic screening.

DISCUSSION

Although there is little doubt that rheumatic heart disease remains a major cause of morbidity and mortality in developing nations, recent reports of approximately 15 million cases in the developing

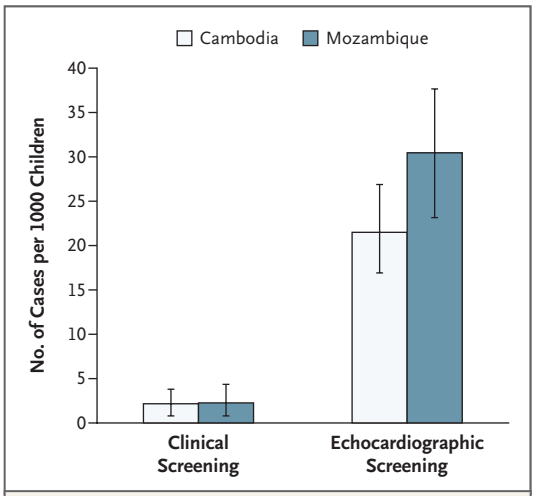

Figure 1. Prevalence of Rheumatic Valvular Abnormalities among Schoolchildren in Cambodia and Mozambique as Detected by Clinical Screening with Echocardiographic Confirmation and by Echocardiographic Screening.
The I bars indicate 95% confidence intervals.

world[1,2] may underestimate the actual burden of this disease, because these estimates are based on prevalence data obtained by comprehensive clinical screening rather than echocardiographic screening. Our findings suggest that echocardiographic screening might detect approximately 10 times as many cases as clinical screening in school-age children in Southeast Asia and sub-Saharan Africa.

Even echocardiographic screening of schoolchildren may underestimate the true prevalence of rheumatic heart disease, since the major risk factors for rheumatic fever include poverty, overcrowding, and poor access to medical services, all of which are probably associated with a reduced likelihood of attending school. Furthermore, the high prevalence rates we observed were for two populations of children with an average age of only 10 to 12 years, and community data from Australian aborigines suggest that the prevalence of rheumatic heart disease is much higher in children over 15 years of age.[1,6]

There are at least two pressing reasons to obtain accurate prevalence data on rheumatic valvular abnormalities in children: to guide regional health service planning and to accurately identify affected children to be targeted for secondary prevention. Although many cases of rheumatic valvular abnormalities in children may resolve spontaneously,[7] many will progress to clinically manifested disease in young adulthood.[1] Prophylactic antibiotic therapy and regular medical surveillance, if adequately administered, may be highly effective in preventing disease progression, even in children with subclinical disease.[3]

The field surveys reported here were planned and coordinated centrally from our institutions located in Paris, and the choice of countries for this project was based in part on our contacts in and knowledge of government and medical services in Cambodia and Mozambique. The initially surprising findings in Cambodia prompted us to undertake a similar study in Mozambique, with more rigorous protocols for randomized selection of schools and children, as well as protocols for follow-up of subjects, to assess the generalizability of our findings. Although environmental factors, genetic predisposition, specific virulence factors of group A streptococcus serotypes, management of antibiotic prophylaxis, and access to preventive care may all affect prevalence rates in specific areas, there is no reason to believe that our findings, which were remarkably similar in these two locations, would be valid only in the countries studied. We believe that this pattern is likely to be replicated elsewhere, while acknowledging that this question may require considerably more investigation.

Among more than 100 cross-sectional school surveys of rheumatic heart disease reported to date, we are aware of only one that included echocardiography of all surveyed children.[8] In this study, which was conducted in Kenya, the prevalence of echocardiographically detected trivial mitral-valve regurgitation was 62 cases per 1000 and the prevalence of clinically detected rheumatic heart disease was 2.2 cases per 1000. Because these investigators did not present any data on valve morphology or the characteristics of the regurgitant jet, it was not clear whether the regurgitation was physiologic or was due to rheumatic or congenital disease. Indeed, many authors have emphasized the need to avoid overestimating the prevalence of rheumatic heart disease, which can result from inclusion of all cases of minor valve regurgitation, and to examine potentially affected valves for other structural or functional evidence of a rheumatic cause.[4,9]

There has been some debate concerning the echocardiographic signs of early rheumatic heart disease.[4,9-11] Some groups have preferred an echocardiographic definition of rheumatic heart dis-

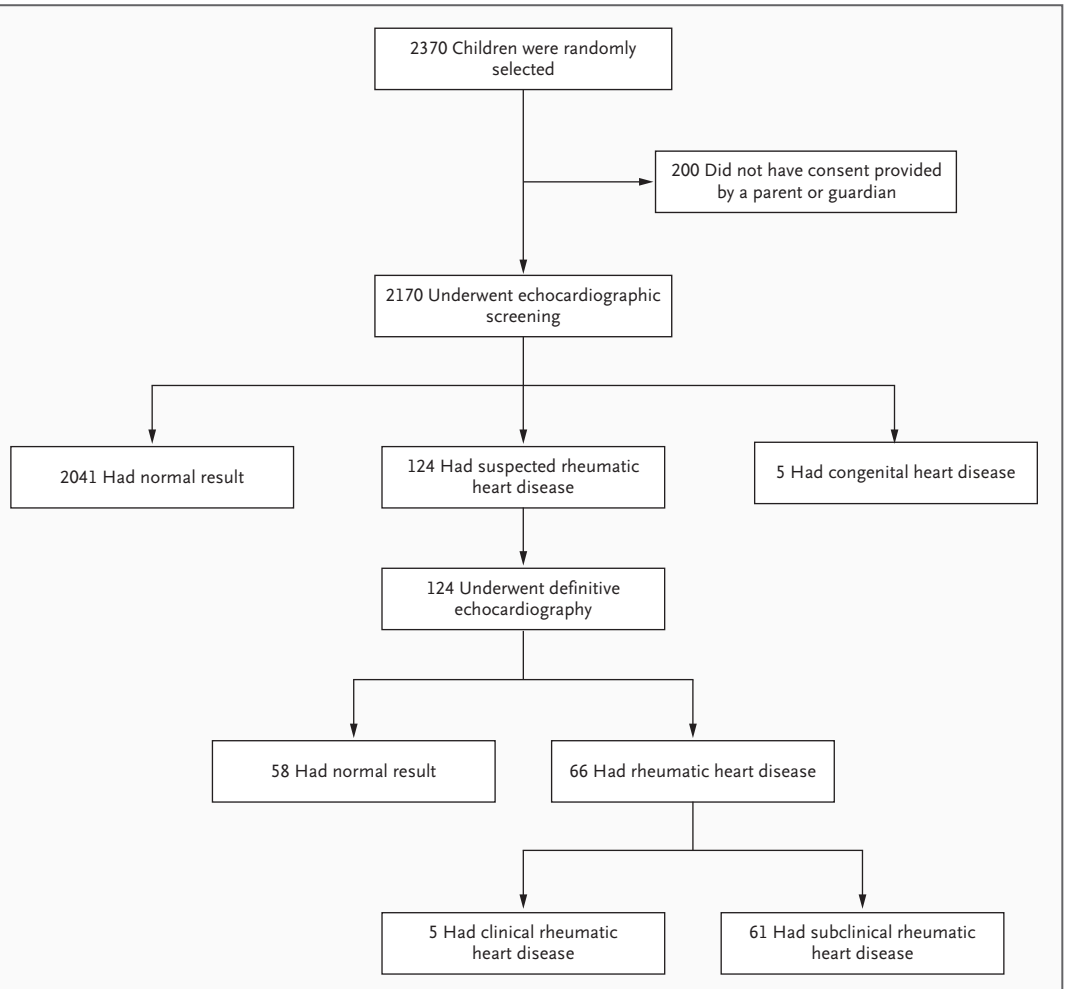

Figure 2. Outcome of Echocardiographic Screening for Rheumatic Heart Disease in Mozambique.
Definitive echocardiography was performed to identify rheumatic heart disease, defined by the presence of any definite evidence of mitral- or aortic-valve regurgitation seen in two planes on Doppler echocardiography, accompanied by at least two of the following three morphologic abnormalities of the regurgitant valve: restricted leaflet mobility, focal or generalized valvular thickening, and abnormal subvalvular thickening.

ease based on the length, velocity, and persistence of the regurgitant jet.[3,12,13] However, these features may depend on the gain settings on the ultrasound equipment; thus, diagnosing subclinical rheumatic heart disease when Doppler criteria for abnormalities are also associated with morphologic valve changes would be expected to improve the specific diagnosis of rheumatic heart disease. In addition, the use of morphologic criteria combined with Doppler criteria for diagnosing rheumatic valve involvement may result in underdiagnosis of subclinical rheumatic heart disease, particularly in children who are screened soon after a first episode of acute rheumatic fever. Although portable ultrasound technology now makes it possible to perform most cardiac diagnostic assessments in schools, our findings support the need for a definitive cardiac ultrasound examination in suspected cases to avoid overdiagnosis.

Two recent reports have also advanced arguments in favor of echocardiographic screening in rheumatic heart disease prevalence studies. Meira and colleagues[7] reported that in 34% of their patients with carditis, clinical examination after the acute phase showed normal findings, although progression to chronic subclinical valvular disease was confirmed by echocardiography in 82% of

such cases. Furthermore, the latest report on rheumatic heart disease from the World Health Organization states that in areas where rheumatic heart disease is endemic, echocardiography may be used to diagnose "silent but significant rheumatic carditis of insidious onset" and recommends that such cases be managed as rheumatic heart disease until proved otherwise.[3] Although echocardiographic criteria are still not included in the Jones criteria, this recommendation may represent a new step toward acknowledgment of subclinical lesions.

Even though portable echocardiographic equipment is now highly developed and accurate, echocardiographic screening may not be a practicable local solution for case identification under the current financial constraints on provision of diagnostic services in developing nations. Nevertheless, the observation that approximately 90% of cases of rheumatic heart disease in our study were clinically silent, occurring in asymptomatic children without audible murmurs, suggests that echocardiographic screening would be a desirable goal to optimize case identification and targeted (secondary) prevention measures. Funds for the purchase of the ultrasound equipment — the major expense of an ultrasound-based screening program for rheumatic heart disease — might be obtainable from charitable organizations. Our results might encourage a strategy of echocardiography-based screening programs for rheumatic heart disease, involving education and both primary and secondary prophylaxis, and based on accurate assessment of the prevalence of rheumatic heart disease.[14]

In summary, we have documented a much higher prevalence of rheumatic valvular abnormalities in school-age children than was previously suspected in both Southeast Asia and sub-Saharan Africa. Comprehensive echocardiographic screening identified approximately 10 times as many children with rheumatic heart disease as were identified by the traditional strategy of clinical screening with echocardiographic confirmation. Because rheumatic heart disease remains a major cause of morbidity and mortality in developing nations, these data have potentially important implications for case finding, delivery of effective primary and secondary prevention, and adequate planning of health services.

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APPENDIX

The principal investigators in this study were P. Ou in Cambodia and E. Marijon and B. Ferreira in Mozambique.

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