Title page

Prevalence of rheumatic heart disease in North-Central Nigeria: a school-based cross-sectional pilot study

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Abstract

Objectives: Rheumatic Heart Disease (RHD) is the most common acquired heart disease in children and young adults in low-and-middle-income countries. There is paucity of data on echocardiography screening of school children for RHD in Nigeria.

Methods: In this pilot study, we conducted clinical and echocardiography screening on a cross-section of randomly selected secondary school children in Jos, North-Central Nigeria from March to September 2016. For outcome classification into borderline or definite RHD, we performed a confirmatory echocardiography using the World Heart Federation criteria for those suspected to have RHD from the screening.

Results: A total of 417 secondary school children were screened, of which 247 (59.2%) were female. The median age was 14 years (IQR: 13-15). Clinical screening detected 8/417 children while screening echocardiography detected 42/417 suspected cases of RHD. Definitive echocardiography confirmed 9/417 with RHD corresponding to a prevalence of 21.6 per 1000 (95% CI, 6.7-36.5). All but one of the confirmed RHD cases (8/9) were borderline RHD corresponding to a prevalence of 19.2 per 1000 (95% CI, 8.3-37.5) for borderline RHD and 2.4 per 1000 (95% CI, 0.1-13.3) for definite RHD. RHD was more common in boys and cardiac auscultation missed over 50% of the cases.

Conclusions: This study showed a high prevalence of RHD among secondary school children in North-Central Nigeria with a vast predominance of asymptomatic borderline lesions. Larger school-based echocardiography screening using portable or handheld echocardiography aimed at early detection of subclinical RHD should be adopted.

Keywords: rheumatic heart disease; prevalence; school children; echocardiography screening; Nigeria

Introduction

Rheumatic heart disease (RHD) is a chronic sequela of acute rheumatic fever (ARF), which is an abnormal autoimmune response to Group A Streptococcal (GAS) infection, usually of the throat, in susceptible individuals (1, 2). It is the most common acquired heart disease in children in low-income and middle-income countries with an estimated global burden of 33.4 million cases, and 319,400 annual deaths as of 2015 (3, 4).

RHD is a disease of poverty, social inequality, overcrowding, and limited access to healthcare (3). RHD and ARF have remained vastly neglected despite the heavy morbidity and socio-economic burden they impose on populations in endemic countries (5). Recurrent episodes of ARF can insidiously lead to sub-clinical RHD which may ultimately progress to severe valvular damage and heart failure (1). Secondary antibiotic prophylaxis, using monthly benzathine penicillin G (BPG) injections, still remains the most effective therapeutic intervention for prevention of disease progression in low-and-middle-income countries (1, 2). Therefore, screening of high-risk populations for early identification of sub-clinical disease, and the use of penicillin prophylaxis to prevent disease progression, are essential steps for reducing the burden of disease in these countries where ARF and RHD still remain of public health importance (2, 6, 7).

With the World Health Organisation (WHO) and World Heart Federation (WHF) targeting a 25% reduction in mortality due to ARF and RHD among individuals aged <25years by the year 2025 (8, 9), there is an increasing interest in echocardiography-based screening for RHD in endemic regions. Indeed, echocardiographic screening of school-aged children has revealed a substantial burden of silent RHD that has not previously come to clinical attention, and has contributed to a better understanding of RHD prevalence (10-13).

In 2012, the WHF developed a standardised evidence-based guideline for the diagnosis of subclinical RHD to improve the reliability, comparability and reproducibility of echocardiographic screening studies (14). Currently, there are very few published data from Nigeria, and none from northern Nigeria, on the population prevalence of RHD. A recent echocardiography-based study from Lagos, South-Western Nigeria, reported a prevalence of 2.7/1000 in urban primary school children, using the WHF criteria (13). Prior to the echocardiography era, auscultation-based screening studies among school children reported a low RHD prevalence of 0.8 per 1000 in Lagos, South-Western Nigeria in 1972 (15), and 0.57 per 1000 in Mid-Western Nigeria in 2013 (16).

In the present study, we have piloted portable echocardiography screening in a cross-section of secondary school children in North-Central Nigeria and compared results with clinical screening. Our study provides an opportunity to estimate the prevalence of subclinical RHD in a rural and peri-

urban region of northern Nigeria and gives preliminary data for consideration towards the establishment of a national prevention programme.

Methods

Study design and setting

We performed a cross-sectional pilot screening of secondary school children in Jos-South Local Government Area (LGA) of Plateau State, North-Central Nigeria between March 2016 and September 2016. Plateau State has a higher percentage of the total population living below the national poverty lines of 54% compared to Nigeria's national average of 46% (17). Jos-South is the second most populous LGA in Plateau State, with an estimated population of 306,716 (18). Jos South LGA is predominantly sub-urban, where the three main occupations are subsistence farming, civil service and petty trading (18). At the time of conducting the study, there were 83 secondary schools in the LGA of which 20 were government-run and 63 were private schools. The average school attendance in Plateau State was 81.8% of the secondary school age population (19). About a quarter of the residents live in high-density neighbourhoods with over-crowding and poor sanitary conditions (20).

Ethics statement

This study was approved by the Institutional Health Research Ethical Committee of the Jos University Teaching Hospital (REF: JUTH/DCS/ADM/127/XIX/6071). Local authorisations were granted by the Regional Administration of the Secondary School Education Board of the Plateau State Ministry of Education, and the administrative heads of each school. Written informed consent was obtained from parents/guardians, and assent from all the participating students.

Sample size considerations and sampling strategy

Based on international literature, our sample size calculations were based on an assumed population prevalence of 1.5% in school children. We calculated a minimum sample size of 395 to estimate a prevalence of 1.5% with a precision of 1.2% with a confidence level of 95%. Assuming a non-completion or dropout rate of 10%, we aimed to enrol 439 students.

We used a multistage sampling strategy. For the first stage, using a list of random numbers, we did a simple random selection of two government-run and three private schools making a total of five secondary schools included in the study. For the second stage, we determined the number of students to be recruited from each school using the proportion each school contributed to the total population of the five selected schools. At each school, the allocated sample size was divided

proportional to the population of children in each class. Systematic random sampling was then used to select children from each class using the attendance registers. We enrolled children in junior secondary one through senior secondary six (equivalent to grades seven through twelve) attending the selected schools. All children from a selected school were eligible for potential inclusion. We excluded children who did not return their signed consent forms or who refused assent.

Study procedures

The administrative heads of all selected schools were contacted and visited by the research team to obtain their consent to participate in the study. During a subsequent visit to the selected schools, the staff and students were given awareness messages on the objectives and procedures of the study. Information sheets and consent forms were sent home to the parents or guardians of the selected students, and the signed forms were collected by their respective class teachers on the following day.

On the day of screening, the study team (consisting of a paediatrician skilled in performance and interpretation of echocardiography, 1 field coordinator, 1 research assistant and 1 data entry staff), organized a private screening area and ensured that a member of the school staff would be present during interactions between study staff and participants. Each child was briefly interviewed using a standardized questionnaire including socio-demographic information and a focused medical history on prior sore throat. Socio-economic status was assessed using a method combining occupation and educational attainment of parents/guardians which is described elsewhere (21). For each child, the household density was calculated as number of family members divided by number of sleeping rooms and overcrowding was defined as ≥2.5 persons/room (22).

Cardiac auscultation followed by echocardiography screening were performed by the study paediatrician in a separate room. A rapid, 2-dimensional and colour-Doppler study using a portable echocardiography machine (Sonosite Plus® ultrasound machine) with a 2MHz transducer probe was performed for all enrolled students. Any child with mitral or aortic valve thickening and/or valvular regurgitation was considered to have an abnormal echocardiogram. The overall echocardiographic screening procedure lasted about 5 min per participant. Children with a cardiac murmur and/or abnormal screening echocardiogram were referred to the hospital for a standard confirmatory echocardiogram performed using an Aloka Prosound SSD 4000 plus® ultrasound machine with a transducer frequency range of 2.5–5MHz by a cardiologist.

Based on the WHF Criteria for echocardiographic diagnosis of RHD in individuals 20 years or younger, children were categorised as either having definite RHD, borderline RHD or normal echocardiographic findings (14). In summary, definite RHD is defined by a combination of at least 2

morphologic criteria with pathologic mitral or aortic regurgitation, or mitral stenosis, or borderline disease of both aortic and mitral valves. Borderline RHD is defined by at least 2 morphologic features or the presence of pathologic mitral or aortic regurgitation. Children with definite RHD were advised to start secondary prophylaxis and referred to a tertiary hospital while those with borderline RHD were referred for follow-up echocardiogram in one year.

Statistical analysis

We analysed the data using Stata version 12.1 (StataCorp, USA) and Excel 2016. Baseline characteristics and clinical findings are presented as frequencies and percentages for categorical variables, or medians and interquartile ranges (IQRs) for continuous variables. We compared characteristics of children with RHD and children without RHD using the Wilcoxon rank-sum test for non-parametric variables, and Student t-test or Fisher's exact test for continuous and categorical variables respectively. All statistical analysis took into account the multistage sampling technique using the Stata *svy* command. Comparisons were two-sided and *P* values < 0.05 were considered significant.

Results

From March 2016 to September 2016, a total of 469 eligible children from 5 randomly selected secondary schools were invited to undergo screening for RHD. After exclusion of 52 children because of failure to return informed consent forms (n=50) or refusal of assent (n=2), 417 children were enrolled for screening (Figure 1).

Demographic and socioeconomic characteristics are summarized in Table 1. Briefly, the median age was 14 years (IQR: 13-15), ranging from 10 to 19 years, with a majority (n=247, 59.2%) of female and from the *Berom* tribe (n=175, 42%). More than half of the children (n=223, 53.5%) lived in homes with three or fewer bedrooms and about a quarter of them (n=116, 27.8%) were living in overcrowded households. The children were evenly distributed across the social class groups. About 70% of the children reported a previous history of painful sore throat.

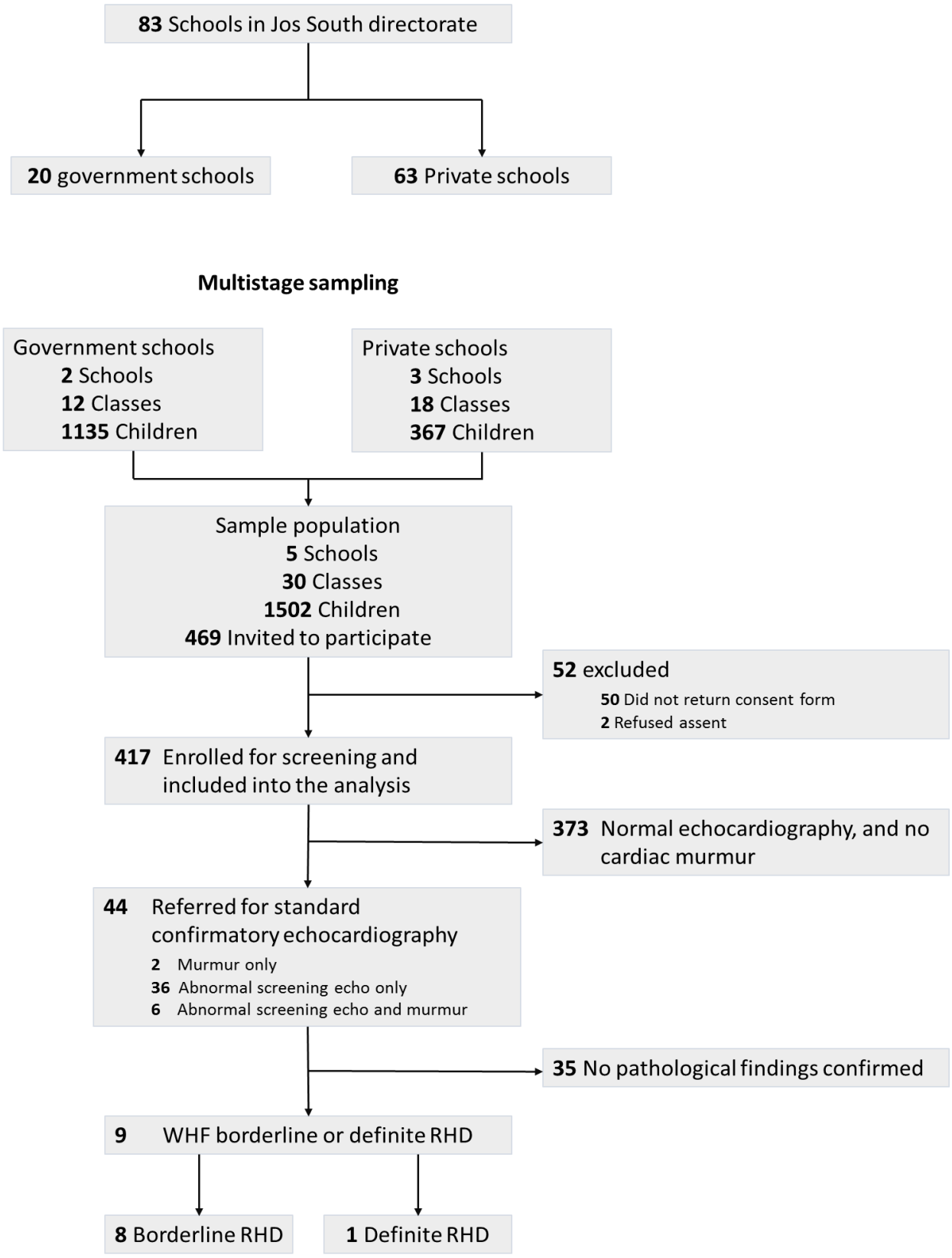

Figure 1. Study Flowchart According to STROBE guidelines (23)

Table 1. Sociodemographic Characteristics of study participants*

Characteristic	Overall (N = 417)	Healthy (n = 408)	Borderline or definite RHD (n = 9)	*P* value
Individual Characteristics				
Age, median (IQR), years	14 (13-15)	14 (13-15)	15 (13-15)	0.54
Age group (years)				
10-12	87 (20.9)	86 (21.1)	1 (11.1)	0.66
13-15	249 (59.7)	241 (59.1)	8 (8.9)	
≥ 16	81 (19.4)	81 (19.8)	0 (0.0)	
Sex				
Female	247 (59.2)	245 (60.0)	2 (22.2)	0.22
Male	170 (40.8)	163 (40.0)	7 (77.8)	
Ethnicity				
Berom	175 (42.0)	170 (41.7)	5 (55.6)	0.74
Ngas	24 (5.7)	24 (5.9)	0 (0.0)	
Ibo	20 (4.8)	19 (4.7)	1 (11.1)	
Yoruba	20 (4.8)	20 (4.9)	0 (0.0)	
Mwaghavul	19 (4.6)	19 (4.7)	0 (0.0)	
Others	159 (38.1)	156 (38.1)	3 (33.3)	
History of painful sore throat	291 (69.8)	284 (69.6)	7 (77.8)	0.38
Characteristic of school				
Government	313 (75.1)	306 (75.0)	7 (77.8)	>0.99
Private	104 (24.9)	102 (25.0)	2 (22.2)	
Family characteristics				
No. of rooms				
≤ 3	223 (53.5)	219 (53.7)	4 (44.4)	0.39
4-6	148 (35.5)	144 (35.3)	4 (44.4)	
≥ 7	46 (11.0)	45 (11.0)	1 (11.1)	
No. of family members, median (IQR)	6 (5-7)	6 (5-7)	6 (6-7)	0.91
Overcrowding	116 (27.8)	113 (27.7)	3 (33.3)	0.62
Socio-economic status				
Lower	138 (33.1)	136 (33.3)	2 (22.2)	0.09
Middle	127 (30.5)	122 (29.9)	5 (55.6)	
Upper	152 (36.5)	150 (36.8)	2 (22.2)	

Abbreviations: IQR, interquartile range; RHD, rheumatic heart disease. *Data are presented as number (percentage) of children unless otherwise indicated.

Cardiac auscultation detected a heart murmur in 8/417 children (1.9%), while screening echocardiography detected an abnormal echocardiogram in 42 children (10.1%). A total of 9 children had a confirmed RHD diagnosis by standard echocardiography, resulting in an overall prevalence of 21.6 per 1,000 children, 95% CI, 6.7-36.5 (Table 2). Only one child had definite RHD with the rest being all borderline RHD. Children with RHD had similar socio-demographic characteristics compared

to non-RHD children except for the sex ratio, as 7/9 RHD cases were boys (77.8% *versus* 40% in non RHD children). All 9/9 (100%) RHD cases had abnormal screening echocardiograms, while the majority had no audible murmur (n = 5, 55.6%).

Table 2. Prevalence of definite and borderline rheumatic heart disease

Variable	Frequency (n=417)	Per thousand
Definite RHD	**1**	**2.4**
Pathologic MR with at least two morphological features of RHD of the MV	1	2.4
MS mean gradient >4mmHg	0	0
Pathologic AR with at least two morphological features of RHD of the AV	1	2.4
Borderline disease of both MV and AV	0	0
Borderline RHD	**8**	**19.2**
At least two morphological features of RHD of the MV without pathologic MR or MS	8	19.2
Pathologic MR	0	0
Pathologic AR	0	0
Total	**9**	**21.6**

Abbreviations: RHD, rheumatic heart disease; MV, mitral valve; MR, mitral regurgitation; MS, mitral stenosis; AV, aortic valve; AR, aortic regurgitation.

The one case of definite RHD was an 11-year-old male who had mixed lesions of both mitral and aortic valves (Table 3). More specifically, the anterior mitral valve leaflet (AMVL) was thickened (0.6 cm) as well as the chordae, and there was a pathologic mitral regurgitation (MR) with MR jet length of 4.3 cm, and MR jet velocity of 4.26 m/s. The aortic valves showed irregular thickening with coaptation defect, and there was a pathologic aortic regurgitation (AR) with AR jet length of 3.7 cm, and AR jet velocity of 3.60 m/s.

The eight borderline RHD cases included two females and six males with ages ranging from 13 to 15 years. All of them had at least two morphologic features of the MV, including thickening of the AMVL ranging from 0.3cm to 0.6cm. In addition to AMVL thickening, 6/8 (75%) also had chordal thickening, while 2/8 (25%) had excessive leaflet tip motion. The aortic valve was not affected in any of the borderline RHD cases.

Table 3. Socio-demographic, clinical and valvular characteristics of children with RHD

Variable	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
Age (years)	11	13	13	15	15	15	15	15	15
Sex	M	M	F	M	M	M	M	M	F
Type of school	Gov	Gov	Gov	Gov	Gov	Gov	Gov	Private	Private
Cardiac murmur	+	+	+	-	-	-	-	+	-
Screening echo	Abn	Abn	Abn	Abn	Abn	Abn	Abn	Abn	Abn
Mitral valve									
Pathologic MR	+	-	-	-	-	-	-	-	-
MS	-	-	-	-	-	-	-	-	-
≥ 2 morphologic features	+	+	+	+	+	+	+	+	+
Aortic valve									
Pathologic AR	+	-	-	-	-	-	-	-	-
≥ 2 morphologic features	+	-	-	-	-	-	-	-	-
RHD diagnosis	Definite	Bord	Bord	Bord	Bord	Bord	Bord	Bord	Bord

Abbreviations: M, male; F, female; Gov, government; Echo, echocardiography; Abn, abnormal; RHD, rheumatic heart disease; MV, mitral valve; MR, mitral regurgitation; MS, mitral stenosis; AV, aortic valve; AR, aortic regurgitation; Bord, borderline; +, present; -, absent.

Discussion

This cross-sectional pilot study estimated the prevalence of echocardiographic RHD among asymptomatic school children in North-Central Nigeria using the WHF criteria to be 21.6 per 1,000, all but one being borderline RHD. The disease was more common in boys compared with girls, and cardiac auscultation missed over 50% of the cases of RHD.

Our findings differ significantly from a previous screening of 418 school children for heart disease in Jos in 2010, where no case of RHD was recorded (24). Unlike our present study, the authors performed an initial clinical screening alone, with echocardiograms done only for children with murmurs. Auscultation has been shown to be less sensitive than echocardiography, sometimes missing up to 50% of cases, as demonstrated in our study (25).

The observed prevalence in our study was 10-times higher than reported in a cross-sectional survey of school children (4,107 students aged 5 to 16 years) in Lagos, South-Western Nigeria which documented a prevalence of 2.1 per 1,000 population in 2017 (13). Similar variations in prevalence within the same country have been reported (26), and indicate the multifactorial nature of the risk factors involved in the pathogenesis of RHD, with differing risk factors between the study

populations such as age, living conditions or social class. For example, the cited study was conducted in Lagos, a more cosmopolitan and culturally diverse city than Jos, with fewer people living below the national poverty lines (17). In addition, unlike our study, they included younger children below 10 years. RHD has been shown to be more common in older children (27, 28), and this may further explain the much higher prevalence that we report.

The prevalence in our study compares to reports from Senegal (16.3 per 1,000) (29), Ethiopia (19 per 1,000) (28), and South Africa (20.2 per 1,000) (26). However, it differed considerably when compared with other African countries which documented prevalence of 11.8 (Zambia)(30), 31 (Ethiopia)(26), 34 (Malawi)(31), and 40.2 (Uganda)(11) per 1000 school children, respectively. Several reasons may account for the heterogeneity across reports within the same country and between countries. RHD prevalence varies as a function of socioeconomic context, sampling strategy, and diagnostic criteria applied. These variations further underscore the need for prevalence estimation from different countries, and from different regions within countries using uniform and comparable designs.

We found more cases of borderline RHD compared to definite RHD, which is consistent with other reports (11, 13, 26, 28-31). Although children with borderline disease are at substantial risk of progression to definite RHD, the natural history of the disease is still unclear, with limited data on the long-term outcome (32, 33). All children with borderline disease in our study were referred for a follow-up review and echocardiography after one year.

In our study, there were more boys than girls diagnosed with RHD, even though girls made up a larger proportion of our study participants. Even though there have been varying reports on the sex distribution of RHD, most studies have documented that the disease is more common in girls (22, 28, 30). The reasons for the female predilection are not clear, although it has been proposed in literature that social factors such as poorer access to health care, repeated exposure to GAS, and genetically-mediated immunological factors might predispose girls to autoimmune diseases (34). While some studies have reported no sex predilection for RHD (3), the small sample size and hence small number of children detected with RHD in this pilot study makes it difficult to extrapolate or draw conclusions on our prevalence estimates according to sex, age and other parameters.

A limitation of our study is that the screening echocardiography and cardiac auscultation were performed by the same person, with the possibility of some observer bias. Also, as the study was limited to school-going children, we are unable to extrapolate the population-based prevalence, as this could either underestimate or overestimate the true disease burden. However, our findings suggest that there may be a potentially large pool of asymptomatic RHD cases among school

children and highlights the need to consider a routine school-based screening programme for RHD. Larger echocardiography-based school screening studies from different parts of Nigeria, including Plateau State are necessary to define the true burden of the disease.

Conclusions

This pilot school survey identified a large and clinically silent burden of RHD in school children (21 per 1,000 children) in North-Central Nigeria. This study also confirmed the low sensitivity of cardiac auscultation for RHD screening. We recommend larger, echocardiography-based school screening studies using portable or handheld devices to further define the burden of silent RHD in different parts of Nigeria. We also propose longitudinal studies to evaluate the importance of early detection of borderline RHD, to monitor the extent of disease progression over time, and to assess the need for secondary prophylaxis.

List of abbreviations

AMVL:	Anterior mitral valve leaflet
AR:	Aortic regurgitation
ARF:	Acute rheumatic fever
AV:	Aortic valve
BPG:	Benzathine penicillin G
GAS:	Group A streptococcus
IQR:	Inter-quartile range
LGA:	Local Government Area
MR:	Mitral Regurgitation
MS:	Mitral Stenosis
MV:	Mitral Valve
RHD:	Rheumatic Heart Disease
WHF:	World Heart Federation
WHO:	World Health Organisation

Acknowledgements

The authors are grateful to the State Secondary Educational Board, Jos, Plateau State, and the administrative heads of each school for their support.

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