International Journal of Cardiology 219 (2016) 439–445

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Echocardiographic prevalence of rheumatic heart disease in Brazilian schoolchildren: Data from the PROVAR study

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ARTICLE INFO

Article history:
Received 10 April 2016
Received in revised form 18 May 2016
Accepted 21 June 2016
Available online 23 June 2016

Keywords:
Rheumatic heart disease
Echocardiography
Screening
Telemedicine

ABSTRACT

Background: Accurate estimates of Rheumatic Heart Disease (RHD) burden are needed to justify improved integration of RHD prevention and screening into the public health systems, but data from Latin America are still sparse.
Objective: To determine the prevalence of RHD among socioeconomically disadvantaged youth (5–18 years) in Brazil and examine risk factors for the disease.
Methods: The PROVAR program utilizes non-expert screeners, telemedicine, and handheld and standard portable echocardiography to conduct echocardiographic screening in socioeconomically disadvantaged schools in Minas Gerais, Brazil. Cardiologists in the US and Brazil provide expert interpretation according to the 2012 World Heart Federation Guidelines. Here we report prevalence data from the first 14 months of screening, and examine risk factors for RHD.
Results: 5996 students were screened across 21 schools. Median age was 11.9 [9.0/15.0] years, 59% females. RHD prevalence was 42/1000 (n = 251): 37/1000 borderline (n = 221) and 5/1000 definite (n = 30). Pathologic mitral regurgitation was observed in 203 (80.9%), pathologic aortic regurgitation in 38 (15.1%), and mixed mitral/aortic valve disease in 10 (4.0%) children. Older children had higher prevalence (50/1000 vs. 28/1000, $p < 0.001$), but no difference was observed between northern (lower resourced) and central areas (34/1000 vs. 44/1000, $p = 0.31$). Females had higher prevalence (48/1000 vs. 35/1000, $p = 0.016$). Age (OR = 1.15, 95% CI:1.10–1.21, $p < 0.001$) was the only variable independently associated with RHD findings.
Conclusions: RHD continues to be an important and under recognized condition among socioeconomically disadvantaged Brazilian schoolchildren. Our data adds to the compelling case for renewed investment in RHD prevention and early detection in Latin America.

1. Introduction

Rheumatic Heart Disease (RHD) is the most common acquired heart disease in children and young adults [1]. The burden is especially high in low and mid-income countries, home to three-quarters of the world's children [2]. RHD also remains prevalent among socially and economically disadvantaged populations in some high-income countries, such as Australia and New Caledonia [3,4]. Conservative estimates predict that thirty-two million people currently have RHD, leading to as many as 345,000 annual deaths [2]. However, global RHD estimates continue to rely heavily on prediction and modeling, as there is a lack of high-quality epidemiological data from the world's most affected regions.

Despite overall economic growth, Latin America and the Caribbean have some of the highest levels of income disparity, demonstrated by their Gini indices [5]. Brazil, an upper-middle income country, ranks 14th among the world's most economically unequal societies [6]. Socioeconomic conditions including poverty, poor sanitation, and

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http://dx.doi.org/10.1016/j.ijcard.2016.06.088
0167-5273/

overcrowding plague sectors of its populations, creating conditions favorable for the spread of infectious diseases, including Group A streptococcal infection, the predecessor to RHD [1,7].

RHD has been shown to exert a substantial burden on the health system of Brazil. A retrospective review showed that RHD was responsible for over 60% of adults undergoing heart valve surgery in Salvador, Brazil [8]. In 2013 the Brazilian Public Health System reported 5169 hospitalizations related to acute rheumatic fever (ARF), and 8841 related to chronic RHD, at a cost of 33 million USD, mostly related to cardiovascular surgeries [9]. As RHD is typically a cumulative process starting in childhood [10], it is likely that latent RHD, or RHD that has not come to clinical attention, is highly prevalent among children growing up in economically disadvantaged sectors of Brazil. Accurate estimates of RHD burden are needed to justify improved integration of RHD prevention and screening into the public health system, preventing advanced disease in adulthood.

Here, we present data from the first large-scale Brazilian echocardiographic screening program for RHD (the PROVAR study).

2. Objectives

Our primary objective was to determine the prevalence of latent RHD among economically disadvantaged schoolchildren, aged 5–18, in the state of Minas Gerais, and secondarily to identify risk factors for RHD within this population.

3. Methods

PROVAR (*Programa de Rastreamento da VAlvopatia Reumática*) is a collaboration between the Universidade Federal de Minas Gerais and the Telehealth Network of Minas Gerais [11], Belo Horizonte, Minas Gerais, Brazil, and Children's National Health System, Washington DC, USA.

The PROVAR team conducted a prospective cross-sectional study in Brazilian primary and secondary schoolchildren between October 2014 and December 2015. Approval was obtained from the institutional review boards of Children's National Health System and the Universidade Federal de Minas Gerais as well as the local Boards of Health and Education.

Schools in the low-income areas of metropolitan Belo Horizonte (capitol) and Montes Claros / Bocaiúva (northern poorer areas) (Fig. 1) were selected based on socioeconomic data (e.g.: Human Development Index (HDI) and local indicators of health vulnerability) under advisement of the local regulatory authorities. All asymptomatic students attending the selected schools were eligible for study participation, except for those with known past history of ARF, RHD or secondary prophylaxis. Permission for school participation was obtained from the schools' headmasters and informational letters, educational brochures and informed consents were sent home with all students. Children were required to return a signed parental consent and complete written informed assent, and those who were 18 were permitted to sign informed consent without parental permission. The school and research team actively contacted consented students absent on screening days in order to maximize participation.

Two nurse research coordinators, one biomedical technician, and one imaging technician conducted the school screening. Training for these healthcare workers consisted of a combination of an online RHD educational course [12] translated into Portuguese (WiRED International, http://www.wiredhealthresources.net/EchoProject/index.html) and a hands-on training supervised by a cardiologist (MN) in the University's Echocardiography Lab (12-weeks). Eight undergraduate medical students and three health agents gave support to the research teams.

School-wide RHD education was provided to all students, teachers, and staff prior to echocardiographic screening. Consented students provided information on basic demographic and socioeconomic variables and underwent a simplified echocardiographic protocol focusing on the left-sided cardiac valves (Vivid Q®, GE Healthcare (Milwaukee, WI, USA) or VSCAN®, GE Healthcare). After acquisition, DICOM images (VIVID Q) were uploaded to cloud computing solutions with image viewing, measurement, and reporting capabilities (LifeImage® (Newton, MA, USA) and ViTel Net®, (McLean, VA, USA). Images acquired on the handheld VSCAN device were uploaded to a secure Dropbox® account and subsequently downloaded for interpretation by dedicated VSCAN Gateway® software. Images were uploaded on a weekly basis and analyzed via telemedicine by cardiologists in Brazil and the United States. The presence of structural or functional valvular abnormalities was assessed and children were classified as “normal”, “borderline RHD”, “definite RHD”, or “other” according to the 2012 WHF criteria [13] (Table 1, Figs. 2 and 3). For handheld studies in which spectral Doppler is not available, modified WHF criteria based on the features of color regurgitant jet and morphologic signs of RHD was used, as has been previously described [14,15]. Two experts blindly interpreted 10% of all acquired studies including 100% of studies initially flagged as abnormal. When discrepancies occurred during this process, a third expert blindly reviewed the images and the consensus diagnosis was accepted.

Fig. 1. Map showing the state of Minas Gerais in the Brazilian territory and the cities involved in the PROVAR screening program.

Table 1
2012 World Heart Federation Echocardiographic Criteria for Diagnosis of Rheumatic Heart Disease [13].

Individuals aged ≤20 years
Definite RHD (either A, B, C, or D):
A) Pathological MR and at least two morphological features of RHD of the MV
B) MS mean gradient ≥4 mm Hg*
C) Pathological AR and at least two morphological features of RHD of the AV‡
D) Borderline disease of both the AV and MV§
Borderline RHD (either A, B, or C):
A) At least two morphological features of RHD of the MV without pathological MR or MS
B) Pathological MR
C) Pathological AR
Normal echocardiographic findings (all of A, B, C, and D):
A) MR that does not meet all four Doppler echocardiographic criteria (Physiological MR)
B) AR that does not meet all four Doppler echocardiographic criteria (Physiological AR)
C) An isolated morphological feature of RHD of the MV (for example, valvular thickening) without any associated pathological stenosis or regurgitation
D) Morphological feature of RHD of the AV (for example, valvular thickening) without any associated pathological stenosis or regurgitation

Abbreviations: AR: aortic regurgitation; AV: aortic valve; MS: mitral stenosis; MR: mitral regurgitation; MV: mitral valve; RHD: Rheumatic Heart Disease.

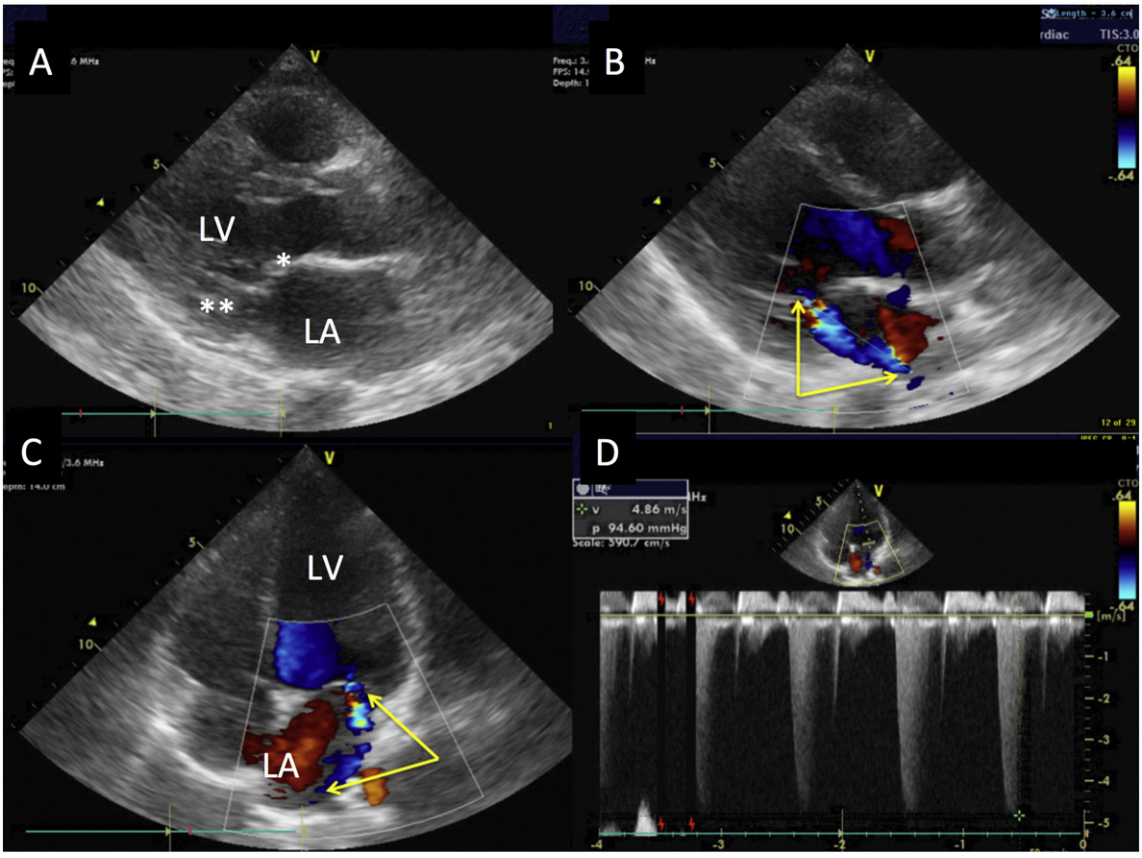

Fig. 2. Echocardiographic images from a 17-year-old girl with definite RHD (Category A: Pathological mitral regurgitation and at least two morphological features of RHD of the mitral valve). Panel A shows a parasternal long axis view in black and white with a thickened mitral valve (*) and chordae (**). There was also restriction to valve motion. Panel B shows a parasternal long axis color Doppler view in systole with a > 3 cm jet of mitral regurgitation (yellow arrows). Panel C shows an apical four chamber color Doppler view in systole with a >3 cm jet of mitral regurgitation (yellow arrows). Panel D shows a CW spectral Doppler image of mitral regurgitation with a pan systolic mitral regurgitation jet of 5 m/s. LA: Left Atrium, LV: Left Ventricle.

All positive (borderline, definite, and other) cases were referred to Hospital das Clínicas da UFMG for follow-up echocardiography, clinical evaluation and treatment recommendations. This evaluation will be repeated on a yearly basis (or more frequently as clinically indicated). Specific care of these patients was left to the discretion of the caring cardiologist with experience in RHD. Secondary prophylaxis, in general

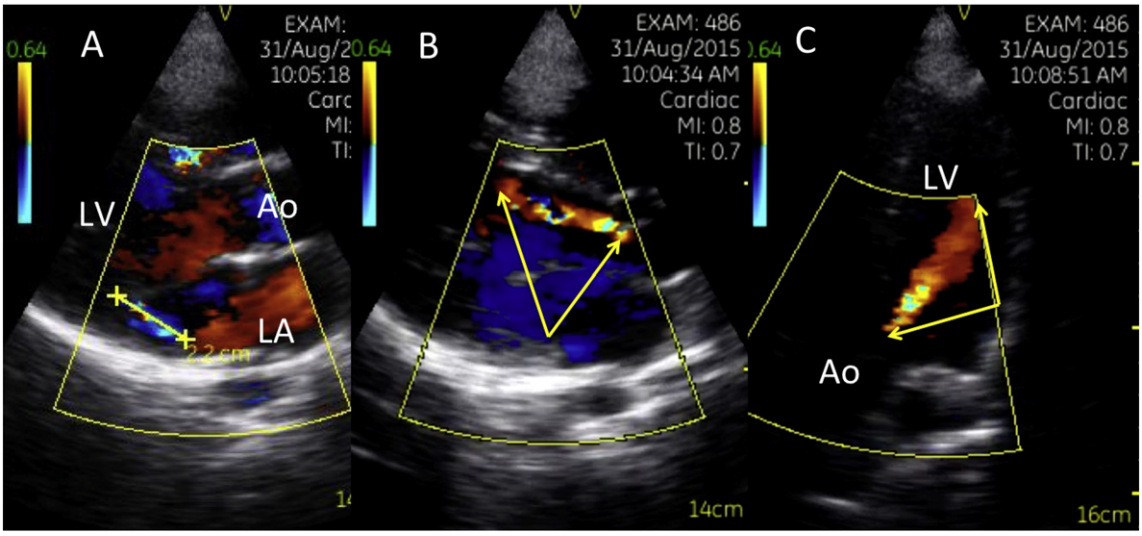

Fig. 3. Hand held echocardiographic images from an 18-year-old boy with definite RHD (Category D: Borderline disease of both mitral and aortic valves). Panel A shows a parasternal long axis color Doppler view in systole with a >2 cm jet of mitral regurgitation. Panel B shows the same view in diastole with a >2 cm jet of aortic insufficiency (yellow arrows). Panel C shows an apical 4 chamber view in diastole with a >2 cm jet of aortic insufficiency (yellow arrows). Ao: Aorta; LA: Left Atrium, LV: Left Ventricle.

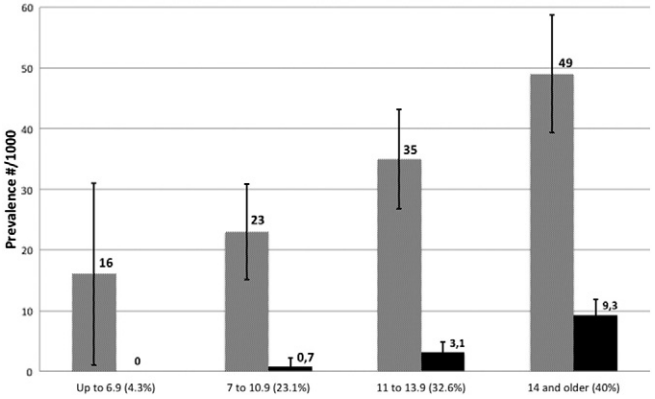

Fig. 4. Prevalence of positive RHD cases (borderline and definite) according to age group. Abbreviations: RHD: Rheumatic Heart Disease.

every 3-week penicillin injections were prescribed to definite cases, and children with borderline RHD were enrolled in biannual medical surveillance.

3.1. Statistical analysis

All data were systematically entered to the RedCap® online database [16]. Statistical analysis was performed using SPSS® software version 22.0 for Mac OSX (SPSS Inc., Chicago, Illinois). The distribution pattern of the variables was assessed with the Shapiro–Wilk test. Continuous variables were expressed as mean ± standard deviation (SD) or as median and interquartile range (IQR, [Q1/Q3]) when appropriate. Categorical variables were expressed as absolute values and percentages. The between-group comparison was performed using the Student t-test for continuous variables with normal distribution and by the Mann–Whitney test for those with non-normal distribution. The comparison of categorical variables was performed using Fisher's Exact Test. A multivariate logistic regression model was built to assess the predictors of overall positive screening echocardiograms (borderline + definite RHD) and definite cases separately. When necessary, transformations were done for analysis of variance. Kappa was used to assess interreviewer reliability and percentage of agreement between reviewers was also reported. A two-tailed significance level of 0.05 was considered statistically significant.

4. Results

Echocardiographic screening occurred in 21 public schools (18 in Belo Horizonte, 2 in Montes Claros and 1 in Bocaiúva) (Fig. 1), over 14 months. The educational RHD curriculum was delivered to more than 17,000 children. Even with multiple strategies to improve the families' health awareness, only 5996 children returned signed parental informed consent and underwent screening echocardiography. The median age was 11.9 [9.0/15.0] years, 59% were females, and 20.1% were from areas of the north of the state. The average screening pace was 75 exams/day/team. All studies were successfully uploaded via cloud server or Dropbox® for interpretation and none warranted exclusion secondary to missing or poor quality images.

The overall prevalence of RHD was 42/1000 (251/5996): 37/1000 borderline RHD (n = 221) and 5/1000 definite RHD (n = 30). The majority of patients with borderline RHD (181, 81.9%) had isolated pathological mitral regurgitation (MR) and most of the definite cases (17, 56.7%) had pathological MR and at least two morphological features of RHD of the mitral valve (MV); 33.3% had mixed valve disease (Table 3) Other structural abnormalities not related to RHD were observed in 7/1000 children (n = 39): the most frequent were mitral valve prolapse (n = 11), atrial septal defects (n = 6) and ventricular septal defects (n = 4).

RHD prevalence was significantly higher among children ≥12 years old: 43/1000 borderline, 7/1000 definite vs. 27/1000 borderline and 1/1000 definite in younger individuals ($p < 0.001$). A cumulative effect was observed, with a progressive increase in RHD prevalence with age (Fig. 4), reaching as high as 58/1000 in children ≥14 years old. Girls also had higher prevalence rates: 42/1000 borderline and 6/1000 definite vs. 31/1000 borderline and 4/1000 definite ($p = 0.016$). Prevalence was similar in Belo Horizonte, capitol of the state (44/1000), compared to the northern areas of Montes Claros (34/1000) and Bocaiúva (33/1000), ($p = 0.31$). The variables associated with RHD findings are depicted in Table 2. In the multivariate logistic regression model adjusted for demographic and socioeconomic variables, the only independent predictor of RHD was age (OR = 1.15, 95% CI: 1.10–1.21, $p < 0.001$). There was a non-significant trend for the association with female gender. The presence of definite RHD was also independently associated with age (OR = 1.55, 95% CI 1.26–1.90, $p < 0.001$).

3965 (66%) were conducted using the standard portable equipment and 2031 (34%) utilizing handheld echocardiography. RHD prevalence by type of machine used for image acquisition was similar for definite cases (5/1000 6/1000, $p = 0.56$), but slightly higher for borderline cases in handheld machines (33/1000 vs. 45/1000, $p = 0.02$).

Five cardiologists with expertise in RHD participated in image interpretation. The inter-reviewer reliability was very good, with an overall Kappa between the first and second echo reviews of 0.89 (95% CI 0.86–0.92), and an overall agreement between the first two reviewers of 92%. There was 97% agreement between the first and second reader for normal studies. Abnormal studies had a 99% agreement as abnormal (borderline RHD, definite RHD, and other), but the specific classification differed among reviewers in 7% (16/221) of borderline studies and 27% (8/30) of definite studies, requiring a third reader to reach consensus.

5. Discussion

Despite the epidemiological transition that has occurred in Brazil [9], data from the PROVAR Study show that Brazilian children from socially disadvantaged backgrounds continue to be burdened by RHD [17,18]. The overall RHD prevalence of 4.2% substantially exceeds previously predicted rates [19]. Even conservatively considering only cases of definite RHD, for which there is more clinical certainty, 1 out of every 200 children is affected. The PROVAR study also captures RHD

Table 2
Demographic and socioeconomic variables of children with normal and abnormal (borderline + definite RHD): univariate analysis.

Variable:	Normal (N = 5706)	Abnormal: borderline RHD (N = 221) + definite RHD (N = 30))	Odds-ratio	95% CI	p-value
Age (median [IQR])	13.0 [10.0/15.0]	14 [11.8/16.0]	1.14	1.10–1.20	<0.001*
Children >12 years (%)	61.4%	74.8%	1.84	1.38–2.47	<0.001*
Gender (% female)	53.9%	62.0%	1.38	1.06–1.79	0.016*
Type of property (% own)	80.0%	76.4%	1.25	0.90–1.74	0.19
Household members (median [IQR])	4 [4/5]	4 [4/5]	0.96	0.88–1.05	0.41
Household members <15 years (median [IQR])	2 [1/2]	1 [1/2]	0.80	0.70–0.92	0.001*
HDI (median [IQR])	0.768 [0.700/0.843]	0.764 [0.736/0.813]	1.67	0.32–8.60	0.54

Abbreviations: 95% CI: 95% confidence interval; IQR: interquartile range ([25/75]); HDI: Human Development Index; RHD: Rheumatic Heart Disease. *: $p < 0.05$. Note: in multivariate analysis, the only independent predictor of positive screening echocardiography was age (OR = 1.16, 95% CI: 1.10–1.22, $p < 0.001$).

Table 3
Detailed echocardiographic abnormal screening findings of the borderline and definite RHD cases.

Borderline RHD (N = 221, 37/1000)	
A. At least two morphological features of RHD of the MV without pathological MR or MS.	5 (2.3%)
B. Pathological MR.	181 (81.9%)
C. Pathological AR.	35 (15.8%)
Definite RHD (N = 30, 5/1000)	
A. Pathological MR and at least two morphological features of RHD of the MV.	17 (56.7%)
B. MS with mean gradient >4 mm Hg.	0
C. Pathological AR and at least two morphological features of RHD of the AV.	3 (10.0%)
D. Borderline disease of both the AV and MV.	10 (33.3%)

Abbreviations: AR: aortic regurgitation; AV: aortic valve; MR: mitral regurgitation; MS: mitral stenosis; MV: mitral valve; RHD: Rheumatic Heart Disease.

prevalence in adolescence (14 to 18 years old, 40% of the sample), where global data have been lacking. As predicted, RHD prevalence increased with age; however the degree of increase, which grew from 28/1000 in children less than 12 to an alarming 58/1000 in those greater than 14, was not anticipated.

The PROVAR study adds to the currently sparse echocardiographic prevalence data of RHD in Latin America. Our finding of 4.2% prevalence among socioeconomic disadvantaged children is similar to the 4.8% RHD prevalence observed among children in Leon, Nicaragua [20], a lower-middle income country. While the Nicaraguan study was preformed prior to the development of the WHF diagnostic criteria [13], the distribution of RHD severity was similar, with the majority of children showing evidence of early RHD: 88% of RHD cases in our study were borderline (vs. definite) and 91% of RHD cases in Nicaragua were "possible" (vs. probable or definite). This differs from the disease pattern seen in sub-Saharan Africa where 23% to 54% of RHD positive children have more advanced, definite RHD [15,18].

In contrast to Brazil, children in Peru showed a very low prevalence of RHD, 0.39% [21]. We believe some of this difference can be explained from the inclusion of all socioeconomic status strata in the Peruvian study, where over half of the included children attended private school and 35% of parents had education exceeding high-school level [21]. Additionally, we hypothesize that the streptococcal burden, and thus the chances of ARF in Minas Gerais, Brazil a tropical savanna climate, may be greater than that of Arequipa, Peru, a high-altitude, cool desert environment [22]. Higher streptococcal and ARF burden has been suggested as a key driver of early rheumatic mitral stenosis seen in sub-Saharan Africa [23], and may also account for the higher prevalence and earlier presentation of definite RHD seen in that region compared to Latin America.

Our study supports the finding that advancing age is an independent predictor of RHD presence and severity. In a recent meta-analysis of active RHD surveillance, Rothenbuhler and colleagues found that the annual incidence of RHD remained stable from 5–15 years, resulting in an additive effect on RHD prevalence, which increased from 4.7 per 1000 persons at 5 years to 21 per 1000 persons at 16 years [24]. As screening for RHD cannot be practically carried out on an annual basis, it is critical to identify the "ideal" age(s) for screening, which will necessarily be context-specific. Our data suggests that in the Brazilian context, an ideal time for first-screen might be between 12 and 14 years, when the prevalence of RHD has increased, but the number of definite RHD cases remains low. This recommendation is slightly older than that supported by one Ugandan study [17], again suggesting that presentation with advanced disease may occur later in Latin America. Our finding of female gender being a risk factor for latent RHD on univariate analysis is consistent with previously published data that show higher rates of both ARF and subclinical RHD in females [25,26].

We believe that the design of the PROVAR program is as important as the prevalence data it collected. We employed non-physician screeners, telemedicine, and integration of handheld echocardiography, each of which has implications for cost, scalability, and sustainability. Task-shifting of RHD screening away from physicians has been identified as a priority for developing sustainable screening programs [27]. Emerging research has shown non-experts, with limited training, to perform well in the screening environment (19–20). Our experience was very positive with task shifting, resulting in high quality imaging [28].

Telemedicine, utilized both for training of our non-expert field team and for remote cloud-based image interpretation, was a unique feature of the PROVAR program. The cloud systems used in PROVAR had technical features developed specifically for RHD screening, facilitating measurement and reporting. The ability to support a non-expert team remotely, and to transmit images from the field team to experts for interpretation, represents a new model for RHD outreach. While further implementation and cost studies are needed, this model may prove more acceptable in health systems where non-experts are not licensed to interpret echocardiograms (such as in Brazil), and could be more scalable, with centralized experts supporting multiple remote teams. As technology improves, smaller files and the possibility of uploads through 3G/4G cellphone connections from the field may further improve the feasibility of this model in other locations.

In our screening environment, handheld echocardiographic equipment was used interchangeably with standard portable echocardiography equipment. The functionality of handheld equipment is reduced compared to standard portable echocardiography equipment (specifically handheld devices lack spectral Doppler), necessitating slight alterations in the WHF criteria [15,29]. However, these devices have demonstrated acceptable accuracy for RHD detection (79–100% sensitivity and 87–93% specificity) [14,15] both with expert and non-expert operators [30,31]. In the PROVAR program, the considerably lower costs of handheld devices allowed a larger number of screeners working in parallel.

Important to any discussion surrounding echocardiographic screening for RHD, is the acknowledgement of our limited understanding of how often, at what rate, and by what risk factors latent RHD progresses to clinically significant heart disease. Four shorter-term studies (limited by small numbers, short follow-up periods (4–30 months), and for some, use of outdated diagnostic criteria) concluded definite RHD had high rates of persistence and progression while borderline RHD was more likely to stabilize and resolve [20,30,32–34]. However children with latent RHD did experience ARF in the follow-up period [32], and data from Australia showed children with borderline RHD are at higher risk of ARF and progression of valve disease compared to normal peers [35]. The longest follow-up to date, a recent 5-year follow-up study of South African children, showed both borderline and definite RHD to have a dynamic natural history [36]. Children from both categories showed improvement, stabilization, and worsening – some to symptomatic heart disease – over this period, though the study was not powered to adequately assess risk factors for progression. Thus, currently there is no consensus about the ideal follow-up strategy, or whether or not children with borderline RHD should receive secondary prophylaxis. More long term follow up data are required to inform best practices. In our program we followed the algorithm described in most studies to date, enrolling all positive cases in follow up but only prescribing Penicillin to definite cases [3,32,36].

Determining the risk to children found to have latent RHD is a top priority, as it has wide-reaching implications for the development of screening programs [10]. A multinational prospective registry of children with latent RHD is planned and may better answer this question [37]. Children identified with RHD through the PROVAR program are enrolled in a longitudinal clinical and echocardiographic follow-up study that may add valuable information about the natural history of latent RHD in Latin America. Only limited data are available on the cost-effectiveness strategies that include echocardiography screening and follow up; further evaluation is needed [38].

The findings of the PROVAR study highlight the need to develop RHD control strategies in Brazil – the world's 5th biggest population – and across Latin America. The echocardiographic prevalence found – far above previous estimates – warrants urgent attention from health authorities. Recent unexpected shortages of Penicillin, inconsistent quality of Penicillin, and data on suboptimal results of cardiac surgeries [39] further highlight the gap between available resources/expertise and clinical need.

Echocardiographic screening for RHD remains a research tool pending further implementation research, cost analysis, and determination of the impact of early RHD detection on prognosis. In order to gather essential epidemiological data, the PROVAR program utilized a large-scale vertical screening design. The features of PROVAR also make it a practical stepping-stone towards diagonal programming to integrate RHD screening within the Public Health System. Essentially, this would occur in parallel to strengthening systems for primary and secondary prevention. The PROVAR team is currently planning a pilot study of this model, the results of which will contribute to the planning of broad-based RHD action in Brazil. Our data, and the data gained though the integration study will also be a starting point for cost-effectiveness modeling of RHD control in Latin America.

6. Limitations

Despite efforts to maximize student participation, our prevalence data may be biased due to marginal student participation. The poorest of families, those with less education and literacy may be less likely to return a signed informed consent, which could lead to an underestimation of prevalence, assuming RHD is more common with decreasing socioeconomic status. In the future, use of community health workers to educate families about RHD and screening children in the context of the primary healthcare center, may overcome this limitation. This same bias may have affected our ability to demonstrate a significant association between RHD and socioeconomic status, as demographics were not collected from students lacking consent. Also, it was not feasible to collect more detailed socioeconomic variables, such as average house income, from children, as direct contact with the families was not possible. We also acknowledge that there are many variables that affect rates of RHD in a community and this data from Minas Gerais may not be generalizable to the remainder of Brazil and its neighbors, including gender distribution and HDI. Rigorous studies from other areas within and outside of Brazil are needed to create a complete picture of the RHD burden in Latin America and its association with socioeconomic indicators. Finally, follow-up confirmatory data of positive RHD cases is not immediately available, but will be part of a subsequent study.

7. Conclusions

The echocardiographic prevalence of RHD among socioeconomically disadvantaged Brazilian schoolchildren is comparable to rates seen in low-income countries. RHD prevalence is cumulative, and increases with age. The PROVAR program utilized a unique model of non-physician screeners, telemedicine, and handheld echocardiography that could be translated into a diagonal program within the primary healthcare structure of Brazil. Future studies will pilot this model, determine the longitudinal outcome of children identified with latent RHD, and examine costs. PROVAR has added to the compelling case for renewed investment in RHD prevention and early detection in Latin America.

Contributors

Bruno Nascimento, Andrea Beaton, Maria Carmo Nunes, Antonio Ribeiro and Craig Sable participated in the conception of the project. Adriana Diamantino, Kaciane Oliveira, Cassio Oliveira, Eduardo Lopes, Iara Castro and Vitória Rezende participated in the acquisition of data. Bruno Nascimento, Andrea Beaton, Zilda Maria Meira, Sandra Regina Castilho, Graziela Chequer, Taylor Landay, Allison Tompsett and Craig Sable analyzed and interpreted the data. Bruno Nascimento, Andrea Beaton and Craig Sable participated drafting the article and revising it critically for important intellectual content. Craig Sable, Maria do Carmo Nunes and Antonio Ribeiro approved the version to be submitted. All authors have approved the final article, and have no conflicts of interest do declare.

Funding

This study was funded by Verizon, USA.

The funder did not have any relationship with the conduct of the study, the collection, analysis, and interpretation of the data, and the preparation, review, or approval of this manuscript.

Conflicts of interest to disclose

None.

Acknowledgements

The PROVAR investigators would like to thank Verizon for supporting and funding the ongoing RHD educational and screening program in Brazil, General Electric for providing echocardiography equipment for this program, and Vitel Net for their collaboration and contribution to creating a RHD cloud platform. The Telehealth Network of Minas Gerais was funded by the State Government of Minas Gerais, by its Health Department (Secretaria de Estado da Saúde de Minas Gerais) and its research agency FAPEMIG (Fundação de Amparo à Pesquisa de Minas Gerais), and by the Brazilian Government, including the Health Ministry and the Science and Technology Ministry and its research and innovation agencies, CNPq (ConselhoNacional de Desenvolvimento Científico e Tecnológico) e FINEP (Financiadora de Estudos e Projetos). Dr. Ribeiro was supported in part by CNPq (Bolsa de produtividade em pesquisa, 309073/2011-1) and by FAPEMIG (Programa Pesquisador Mineiro, PPM-00161-13).

References

[1] J.R. Carapetis, A.C. Steer, E.K. Mulholland, M. Weber, The global burden of group a streptococcal diseases, Lancet Infect. Dis. 5 (2005) 685–694.
[2] Global burden of disease study C. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the global burden of disease study 2013, Lancet (2015).
[3] M. Mirabel, T. Fauchier, R. Bacquelin, M. Tafflet, A. Germain, C. Robillard, et al., Echocardiography screening to detect rheumatic heart disease: a cohort study of schoolchildren in French Pacific Islands, Int. J. Cardiol. 188 (2015) 89–95.
[4] K. Roberts, G. Maguire, A. Brown, D. Atkinson, B. Remenyi, G. Wheaton, et al., Echocardiographic screening for rheumatic heart disease in high and low risk Australian children, Circulation 129 (2014) 1953–1961.
[5] J.S. Morrow, Toward a more normative assessment of maldistribution: the Gini index, Inquiry 14 (1977) 278–292.
[6] T. Soubbotina, K.A. Sheram, Income inequality, in: T. Soubbotina (Ed.), Beyond Economic Growth, The World Bank, Washington - DC 2000, pp. 27–29.
[7] A.C. Steer, M.H. Danchin, J.R. Carapetis, Group A streptococcal infections in children, J. Paediatr. Child Health 43 (2007) 203–213.
[8] G.S. Ribeiro, S.Y. Tartof, D.W. Oliveira, A.C. Guedes, M.G. Reis, L.W. Riley, et al., Surgery for valvular heart disease: a population-based study in a Brazilian urban center, PLoS One 7 (2012), e37855.
[9] A.L. Ribeiro, B.B. Duncan, L.C. Brant, P.A. Lotufo, J.G. Mill, S.M. Barreto, Cardiovascular health in Brazil: trends and perspectives, Circulation 133 (2016) 422–433.
[10] K. Roberts, S. Colquhoun, A. Steer, B. Remenyi, J. Carapetis, Screening for rheumatic heart disease: current approaches and controversies, Nat. Rev. Cardiol. 10 (2013) 49–58.
[11] M.B. Alkmim, R.M. Figueira, M.S. Marcolino, C.S. Cardoso, M. Pena de Abreu, L.R. Cunha, et al., Improving patient access to specialized health care: the telehealth network of Minas Gerais, Brazil, Bull. World Health Organ. 90 (2012) 373–378.
[12] D. Engelman, E. Okello, A. Beaton, G. Selnow, B. Remenyi, C. Watson, et al., Evaluation of computer-based training for health workers in echocardiography for rheumatic heart disease, Glob. Health (2016).

[13] B. Remenyi, N. Wilson, A. Steer, B. Ferreira, J. Kado, K. Kumar, et al., World heart federation criteria for echocardiographic diagnosis of rheumatic heart disease–an evidence-based guideline, Nat. Rev. Cardiol. 9 (2012) 297–309.
[14] A. Beaton, T. Aliku, E. Okello, S. Lubega, R. McCarter, P. Lwabi, et al., The utility of handheld echocardiography for early diagnosis of rheumatic heart disease, J. Am. Soc. Echocardiogr. 27 (2014) 42–49.
[15] A. Beaton, J.C. Lu, T. Aliku, P. Dean, L. Gaur, J. Weinberg, et al., The utility of handheld echocardiography for early rheumatic heart disease diagnosis: a field study, Eur. Heart J. Cardiovasc. Imaging 16 (2015) 475–482.
[16] P.A. Harris, R. Taylor, R. Thielke, J. Payne, N. Gonzalez, J.G. Conde, Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support, J. Biomed. Inform. 42 (2009) 377–381.
[17] A. Beaton, E. Okello, P. Lwabi, C. Mondo, R. McCarter, C. Sable, Echocardiography screening for rheumatic heart disease in Ugandan schoolchildren, Circulation 125 (2012) 3127–3132.
[18] M.E. Engel, A. Haileamlak, L. Zuhlke, C.E. Lemmer, S. Nkepu, M. van de Wall, et al., Prevalence of rheumatic heart disease in 4720 asymptomatic scholars from South Africa and Ethiopia, Heart 101 (2015) 1389–1394.
[19] L.P. Miranda, P.A. Camargos, R.M. Torres, Z.M. Meira, Prevalence of rheumatic heart disease in a public school of Belo Horizonte, Arq. Bras. Cardiol. 103 (2014) 89–97.
[20] J.A. Paar, N.M. Berrios, J.D. Rose, M. Caceres, R. Pena, W. Perez, et al., Prevalence of rheumatic heart disease in children and young adults in Nicaragua, Am. J. Cardiol. 105 (2010) 1809–1814.
[21] E. Spitzer, J. Mercado, F. Islas, M. Rothenbuhler, R. Kurmann, F. Zurcher, et al., Screening for rheumatic heart disease among Peruvian children: a two-stage sampling observational study, PLoS One 10 (2015), e0133004.
[22] M.C. Peel, B.L. Finlayson, T.A. McMahon, Updated world map of the Köppen–Geiger climate classification, Hydrol. Earth Syst. Sci. 11 (2007) 1633–1644.
[23] H. Tadele, W. Mekonnen, E. Tefera, Rheumatic mitral stenosis in children: more accelerated course in sub-Saharan patients, BMC Cardiovasc. Disord. 13 (2013) 95.
[24] M. Rothenbuhler, C.J. O'Sullivan, S. Stortecky, G.G. Stefanini, E. Spitzer, J. Estill, et al., Active surveillance for rheumatic heart disease in endemic regions: a systematic review and meta-analysis of prevalence among children and adolescents, Lancet Glob. health 2 (2014) e717–e726.
[25] N.R. Shrestha, P. Karki, R. Mahto, K. Gurung, N. Pandey, K. Agrawal, et al., Prevalence of subclinical rheumatic heart disease in eastern Nepal, JAMA Cardiol. 1 (2016) 89–96.
[26] D.D. Sudeep, K. Sredhar, The descriptive epidemiology of acute rheumatic fever and rheumatic heart disease in low and middle- income countries, Am. J. Epidemiol. Infect. Dis. 1 (2013) 34–40.
[27] B.R. Nascimento, M.C.P. Nunes, E.L.V. Lopes, V.M.L.R. Rezende, T. Landay, A.L. Ribeiro, et al., Rheumatic heart disease echocardiographic screening: approaching practical and affordable solutions, Heart 102 (2016) 658–664.
[28] B.R. Nascimento, A.C. Diamantino, G.T.R. Pereira, E.L.V. Lopes, C.O. Miri, K.K.B. Oliveira, et al., Improving the practicality of echocardiographic screening for rheumatic heart disease: performance of non-expert users following completion of a standardized computer-based training curriculum, Circulation 132 (2015) (A18811-A).
[29] J.C. Lu, C. Sable, G.J. Ensing, C. Webb, J. Scheel, T. Aliku, et al., Simplified rheumatic heart disease screening criteria for handheld echocardiography, J. Am. Soc. Echocardiogr. 28 (2015) 463–469.
[30] M. Mirabel, R. Bacquelin, M. Tafflet, C. Robillard, B. Huon, P. Corsenac, et al., Screening for rheumatic heart disease: evaluation of a focused cardiac ultrasound approach, Circ. Cardiovasc. Imaging 8 (2015).
[31] M. Ploutz, J.C. Lu, J. Scheel, C. Webb, G.J. Ensing, T. Aliku, et al., Handheld echocardiographic screening for rheumatic heart disease by non-experts, Heart 102 (2016) 35–39.
[32] A. Beaton, E. Okello, T. Aliku, S. Lubega, P. Lwabi, C. Mondo, et al., Latent rheumatic heart disease: outcomes 2 years after echocardiographic detection, Pediatr. Cardiol. 35 (2014) 1259–1267.
[33] M. Bhaya, R. Beniwal, S. Panwar, R.B. Panwar, Two years of follow-up validates the echocardiographic criteria for the diagnosis and screening of rheumatic heart disease in asymptomatic populations, Echocardiography 28 (2011) 929–933.
[34] A. Saxena, S. Ramakrishnan, A. Roy, S. Seth, A. Krishnan, P. Misra, et al., Prevalence and outcome of subclinical rheumatic heart disease in India: the RHEUMATIC (rheumatic heart Echo utilisation and monitoring actuarial trends in Indian children) study, Heart 97 (2011) 2018–2022.
[35] M. Remond, D. Atkinson, A. White, A. Brown, J. Carapetis, B. Remenyi, et al., Are minor echocardiographic changes associated with an increased risk of acute rheumatic fever or progression to rheumatic heart disease? Int. J. Cardiol. 198 (2015) 117–122.
[36] L. Zühlke, M.E. Engel, C.E. Lemmer, M. Van de Wall, S. Nkepu, A. Meiring, et al., The natural history of latent rheumatic heart disease in a 5 year follow-up study: a prospective observational study, BMC Cardiovasc. Disord. 16 (2016) 1–6.
[37] A. Saxena, L. Zuhlke, N. Wilson, Echocardiographic screening for rheumatic heart disease: issues for the cardiology community, Glob. Heart 8 (2013) 197–202.
[38] J.P. Zachariah, M. Samnaliev, Echo-based screening of rheumatic heart disease in children: a cost-effectiveness Markov model, J. Med. Econ. 18 (2015) 410–419.
[39] A.L. Ribeiro, S.P. Gagliardi, J.L. Nogueira, L.M. Silveira, E.A. Colosimo, Lopes do Nascimento CA. Mortality related to cardiac surgery in Brazil, 2000-2003, J. Thorac. Cardiovasc. Surg. 131 (2006) 907–909.