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ORIGINAL ARTICLE

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Two-year evolution of latent rheumatic heart disease in Malawi

Amy Sanyahumbi MD[1] | Andrea Beaton MD[2] | Danielle Guffey MS[3] | Mina C. Hosseinipour MD, MPH[4] | Melissa Karlsten MPH[1] | Charles G. Minard PhD[3] | Daniel J. Penny MD, PhD[1] | Craig A. Sable MD[5] | Peter N. Kazembe MBChB[6]

[1]Division of Pediatric Cardiology, Department of Pediatrics, Baylor College of Medicine, Texas Children's Hospital, Houston, Texas

[2]Department of Pediatric Cardiology, Heart Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

[3]Dan L Duncan Institute for Clinical and Translational Research, Baylor College of Medicine, Houston, Texas

[4]Department of Infectious Disease, University of North Carolina Project, University of North Carolina, Lilongwe, Malawi

[5]Department of Pediatric Cardiology, Children's National Heart Institute, Children's National Medical Center, Washington, District of Columbia

[6]Department of Pediatrics, Baylor College of Medicine Clinical Center of Excellence, Lilongwe, Malawi

Correspondence
Amy Sanyahumbi, Division of Pediatric Cardiology, Department of Pediatrics, Baylor College of Medicine, Texas Children's Hospital, 6621 Fannin St., 19th floor, Houston, TX 77030.
Email: aesims@bcm.edu

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Abstract

Background: In *asymptomatic* children, screening echocardiography has been used to attempt to diagnose rheumatic heart disease (RHD) at an early stage (latent RHD). World Heart Federation guidelines have standardized categorization of "definite," "borderline," or no RHD by echo findings. The progression of RHD diagnosed through echo screening is not known. In 2014, we screened 1450 schoolchildren in Malawi.

Objective: Our objective was to evaluate 2-year RHD evolution among those diagnosed through screening.

Methods: Two-year follow-up echocardiograms of those diagnosed with latent RHD were read by a primary, secondary, then third reader if there was disagreement. Progression or regression of both definite and borderline groups were tabulated. Penicillin adherence, age, gender, number in home, and household income were compared between those with definite RHD who regressed to borderline and those that stayed definite. We utilized the local system used to track HIV defaulters in order to bring participants back into care. Comparisons were made using Fisher's exact and Wilcoxon rank-sum tests.

Results: Of the 39 with borderline RHD, 1 was lost to follow-up (2.6%), 1 progressed to definite (2.6%), 19 remained borderline (48.7%), 17 (43.6%) regressed to normal, and 1 was reclassified as mitral valve prolapse (2.6%). Of the 11 with definite RHD, 6 (54.5%) remained definite, 4 regressed to borderline (36.4%), and 1 regressed to normal (9.1%). Two of 11 with definite RHD had penicillin adherence above 80% for the 2-year follow-up period. There were no differences in adherence, gender, age, household income, or number in household between those with definite RHD that regressed to borderline and those who did not ($P > .19$).

Conclusions: Borderlines had a very low progression rate to definite RHD. A strength of our study was a high retention rate (98%). Longer follow-up is needed to determine expected disease evolution.

KEYWORDS

echocardiography, global health, pediatric cardiology, rheumatic heart disease, screening

1 | INTRODUCTION

Rheumatic heart disease (RHD) is the leading cause of cardiac morbidity and mortality in young people worldwide. In 2015, there were an estimated 33.4 million prevalent clinical cases with 319,400 deaths and 10.5 million disability adjusted life years.[1]

An estimated 169,000 cases of RHD exist in Malawi.[2] RHD is preventable, yet continues to cause devastation in low-resourced settings, such as Malawi. The REMEDY study, a multinational registry in low and middle-income countries,[3] as well as other studies,[4-6] showed that most people with RHD in LMIC present with advanced disease and have a poor prognosis.

Benzathine penicillin G (BPG) injections, given every 3-4 weeks, have been shown to prevent RHD progression in clinically symptomatic children.[7] In asymptomatic children, echocardiography has been used as a screening tool to diagnose RHD at an early stage in high-risk populations, with the intent that early diagnosis and intervention could prevent RHD progression.[8]

World Heart Federation (WHF) guidelines, published in 2012, have standardized echocardiographic screening criteria for latent RHD.[9] "Latent" RHD describes echocardiographic evidence of RHD in people with no known history of acute rheumatic fever (ARF) and no clinical symptoms. Using echocardiography criteria only, children are diagnosed as having definite, borderline, or no RHD. The progression of RHD valve lesions in asymptomatic children diagnosed through echo screening is not known, nor is it known if BPG is effective in preventing progression of lesions diagnosed in this manner. In particular, it is still unknown whether borderline RHD represents true early RHD and whether this diagnosis requires follow-up and secondary prophylaxis with benzathine penicillin injections.

Malawi is the poorest country with published RHD prevalence data.[10] In 2014, we performed echocardiographic screening for RHD on 1450 children ages 5 through 16 years in 3 schools and surrounding communities in the central region of Malawi.[11] In this manuscript, we present the echocardiography results after 2-years of follow-up of those diagnosed positive in the initial screening.

2 | METHODS

The Institutional Review Boards of Baylor College of Medicine, University of North Carolina, and Malawi National Health Sciences Research Committee approved the study. At the initial screening in 2014, children were diagnosed as having definite, borderline, or no RHD by WHF Criteria.[9] Echocardiographic studies were obtained using a Philips CX50 (Best, The Netherlands) portable echocardiography machine with a transducer frequency range of 1-5 MHz by a pediatric cardiologist (AS) or a trained ultrasonographer under the guidance of the pediatric cardiologist. Children diagnosed as having definite or borderline RHD were followed with yearly echocardiograms. All data were collected using a HIPAA-compliant web-based database system that was managed by Baylor College of Medicine research informatics team.

Children with definite RHD were prescribed BPG injections to be given every 4 weeks as per the standard of care for children with clinical RHD in Malawi. Children with borderline RHD were not prescribed monthly BPG. For the 2-year follow-up, each echocardiogram was read by a primary (AS) and secondary reader (AB). A third reader served as a tiebreaker if there was disagreement (CS). The same methodology for reading echocardiograms was followed for the original study. Adherence was calculated for those with definite RHD that were prescribed BPG by dividing the number of injections received by the number prescribed. Adherence to penicillin was calculated over the entire 2-year follow-up period. BPG adherence, age, gender, number in home, and household income were compared between those with definite RHD who regressed to borderline or normal and those that stayed definite. These variables were not compared in the borderline group because only one participant progressed to definite RHD. Comparisons were made using Fisher's exact and Wilcoxon rank-sum tests.

We employed the tracking system for HIV defaulters to trace participants who did not come to their follow-up appointment. At enrollment, we collected detailed location information of every participant, and were given permission to call and track participants if they did not come to follow-up appointments. Participants were called and asked to come to the follow-up appointment. If participants did not come to the appointment and were not reachable by phone, a nurse tracker employed by the Baylor HIV clinic used the directions originally given by the participants to go to their house and ask them to come to their appointment.

3 | RESULTS

In 2014, 39 children were diagnosed with borderline RHD, and 11 were diagnosed with definite RHD. 2-year follow-up echocardiograms were performed a mean of 716 days after initial echo. Of the 39 with borderline RHD, 1 was lost to follow-up (2.6%), and 1 was re-classified as mitral valve prolapse (2.6%). Of the remaining 37, 1 progressed to definite (3%, 95% CI: 0.1%, 14%), 19 remained borderline (51%, 95% CI: 34%, 68%), and 17 (46%, 95% CI: 29%, 63%) regressed to normal (Figure 1).

Of the 11 with definite RHD, 6 (55%, 95% CI: 23%, 83%) remained definite, and 5 regressed to borderline or normal (45%, 95% CI: 17%, 77%) (Figure 2). Two of the children could be considered

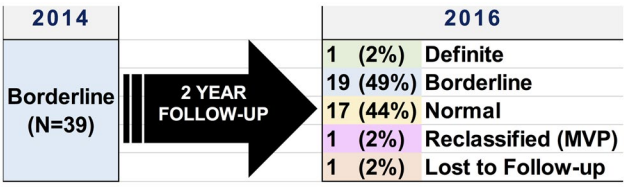

FIGURE 1 Borderline 2-year follow-up outcomes

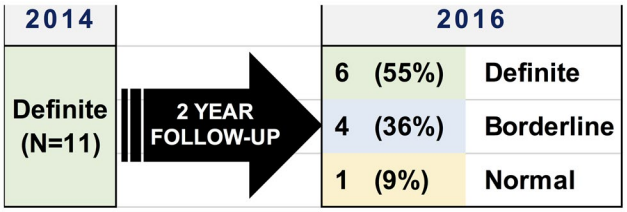

FIGURE 2 Definite 2-year follow-up outcomes

"missed clinical" RHD because one had moderate MR and one had severe MR at diagnosis. These both stayed definite at the 2-year follow-up point.

Only 2 of 11 children with definite RHD (18%) had >80% BPG adherence for the entire two years of follow-up. Five of 11 children with definite RHD had penicillin adherence above 80% during year 2. At the 1-year point, it was discovered that the health centers did not have a reliable supply of benzathine penicillin and often children would come for their injections but the health center would be out of stock. The study then supplied a year's worth of benzathine penicillin directly to participants. This did improve adherence, but it was then discovered that health centers often did not have syringes to give the BPG.

We did not find any significant differences in previous year adherence, gender, age, household income, or number in household between those with definite RHD that regressed to borderline and those who did not (Table 1, $P \geq .19$). Although it was not significant (likely because of our small numbers), the children who regressed to borderline did have a median adherence 11% points better than those who stayed definite. Also, notable but not significant, those that regressed to borderline or normal were an average of 1.6 years older than those who did not.

Of those with borderline RHD, most originally met criteria by having pathological mitral regurgitation (36 of 39, 92.3%), while two met criteria by having morphological changes of the mitral valve (5.1%), and one (2.6%) met criteria by having pathological aortic regurgitation. Of the 2 children that had morphologic changes of the mitral valve, 1 remained borderline, and 1 regressed to normal. The child who had borderline RHD with pathologic aortic regurgitation remained borderline after 2 years. All children with definite RHD met criteria by having pathologic MR with two pathologic features of the mitral valve, so definite criteria associated with regression could not be evaluated.

Table 2 compares our results with other published RHD progression studies. Children in Malawi with borderline RHD showed less progression to definite than in other published studies ($P = .03$), although the confidence intervals overlap with two of the four studies. Definite regression rates were similar to other published studies.

4 | DISCUSSION

Understanding the natural history of latent, echo-detected RHD is critical in evaluating the utility of echocardiographic screening programs. Malawi's 2016 GNI per capita of $320 is less than that of South Africa ($5480), Uganda ($680), or Ethiopia ($660), which have been sites of previous WHF criteria based RHD screening studies.[10] People with advanced RHD in Malawi are burdened with substantial disability due to the lack of in-country cardiac surgery, small numbers of physicians, and limited medical facilities. Prevention of severe RHD is essential in this population. There is a critical need to understand the progression of RHD lesions in children with latent RHD in order to evaluate the potential benefit of implementing widespread echo screening. As Malawi is the poorest country in which echo screening has taken place, our findings regarding progression and regression of RHD are noteworthy.

Overall, the participants in our study had poor adherence to BPG, with only 18% having >80% adherence for the 2-year period. A major reason for the poor adherence was that health centers would run out of BPG (even though the health centers were supplied with BPG by the study) or syringes for BPG administration. Adherence improved to 45% over the second year once BPG was directly supplied to

TABLE 1 Children with initial definite category: Associations with regression

	All	Remained definite	Regressed to borderline/normal	
	N = 11	6 (55%)	5 (45%)	*P* value
Male, *n* (%)	5 (45%)	4 (67%)	1 (20%)	.24
2-year adherence Median (25th, 75th)	0.58 (0.23, 1)	0.58 (0.23, 0.96)	0.69 (0.38, 1)	.56
Age at enrollment Median (25th, 75th)	9.97 (8.2, 13.1)	9.17 (7.7, 13.7)	10.8 (9.4, 12.5)	.72
Monthly household income ($) Median (25th, 75th)	15 (0, 50)	40 (0, 150)	1 (0, 15)	.19
Number in household Median (25th, 75th)	6 (4, 9)	6 (4, 11)	6 (4, 6)	.57

TABLE 2 Borderline and definite evolution

Borderline evolution								
Country	**Author**	**Year**	***n***	**Definite**	**Borderline**	**Normal**	**Average time period (yrs)**	**Overall retention rate**
Malawi	Current article	2018	37	3% (95% CI: 0.1, 14)	51% (95% CI: 34, 68)	46% (95% CI: 29, 63)	2	98%
Fiji	Engelman[12]	2016	17	24%[a]	64%[a]	12%[a]	7.5	73%
New Caledonia	Bertaina[13]	2017	25	8%[a]	60%[a]	32%[a]	1.9	100%
South Africa	Zuhlke[14]	2016	34	21%[a]	21%[a]	59%[a]	2.6	83%
Uganda	Beaton[15]	2017	164	9%[a]	44%[a]	46%[a]	2.4	Unknown

Definite evolution						
Country	**Author**	**Published**	**n**	**Definite**	**Borderline + normal**	**Average follow-up time (years)**
Malawi	Current article	2018	11	55% (95% CI: 23%, 83%)	45% (95% CI: 17%, 77%)	2
Fiji	Engelman[12]	2016	20	70%[a]	30%[a]	7.5
South Africa	Zuhlke[14]	2016	10	70%[a]	30%[a]	2.6
Uganda	Beaton[15]	2017	42	55%[a]	45%[a]	2.4

[a]No confidence intervals published for these studies.

parents, but most children still had poor adherence. Poor adherence to BPG is a common problem. Secondary prevention with 4-weekly BPG injections has been shown to prevent RHD progression and improve RHD outcomes in children with clinical RHD, but the efficacy of BPG in preventing progression among children with latent RHD is as of yet unclear. Previous studies have shown only 20%-65% of people with clinical RHD received an adequate amount of prescribed injections to prevent further episodes of ARF.[16-20] These numbers are consistent with the poor adherence that we observed in this study. Improving BPG adherence would likely improve outcomes in children with RHD and steps to improve adherence, such as ensuring access to BPG and syringes, should be implemented.

Our numbers are too small to make conclusions about association of subtype of RHD with progression or regression. As only one participant diagnosed with borderline RHD progressed to definite RHD, our study highlights the need for longitudinal studies to evaluate the clinical significance of borderline RHD.[21] Our study may suggest that borderline RHD may not represent a clinical concern in this population. In addition, it is clear that if screening is to continue in a systematic way, that there needs to be a unified criteria-based system for grading of progression of definite lesions. The WHF criteria provide clear criteria to determine if borderline RHD progresses (to definite) or regresses (to normal). However, there are currently no standard published criteria for determining whether definite RHD has progressed, which makes comparisons between studies difficult.

A strength of our study was a high retention rate (98%), higher than most other published studies where retention ranged from 73% to 100%,[12-15] thereby allowing a near complete evaluation of 2-year outcomes. Even for the one child who did not have follow-up echo, we were able to determine she was generally well and attending boarding school. Our retention strategy leveraging existing HIV defaulter tracing services may be adopted by other RHD programs to allow optimal evaluation of longitudinal outcomes.

5 | LIMITATIONS

The main limitation of our study is that it is a relatively small sample size from one area of one country. The small sample size leads to large confidence intervals. As such, our study is not powered to detect risk factors for progression or regression.

6 | CONCLUSION

This study adds to the body of knowledge about RHD progression. We found a low risk of progression from borderline to definite RHD among this cohort of Malawian children followed for 2 years. We will plan to follow this cohort for at least 5 years, then they will be assimilated into the clinical cardiology clinic if disease is still present. Longer follow-up of a larger number of children or a randomized controlled trial is needed to determine expected disease evolution of latent RHD.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest with the contents of this article.

AUTHOR CONTRIBUTIONS

Concept/design, data collection, data analysis/interpretation, drafting of article, critical revision of article, approval of article, statistics, secured funding: Amy Sanyahumbi

Data analysis/interpretation, critical revision of article, approval of article: Andrea Beaton, Danielle Guffey, Melissa Karlsten

Concept/design, data analysis/interpretation, critical revision of article, approval of article: Mina Hosseinipour, Craig A. Sable

Data analysis/interpretation, critical revision of article, approval of article, statistics: Charles G. Minard

Concept/design, critical revision of article, approval of article, secured funding: Daniel J Penny

Concept/design, critical revision of article, approval of article: Peter N. Kazembe

ORCID

Amy Sanyahumbi https://orcid.org/0000-0002-5545-5729

Daniel J. Penny https://orcid.org/0000-0002-8426-0381

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