






ORIGINAL RESEARCH

# Active Case Finding for Rheumatic Fever in an Endemic Country

Emmy Okello, MBChB, MMed, PhD; Emma Ndagire, MBChB, MMed; Jenifer Atala, RN; Asha C. Bowen, MD, PhD; Marc P. DiFazio, MD; Nada S. Harik, MD; Chris T. Longenecker , MD; Peter Lwabi , MBChB, MMed; Meghna Murali, MPH; Scott A. Norton, MD; Isaac Otim Omara, RN; Linda Mary Oyella, RN; Tom Parks, MD, PhD; Jafesi Pulle, RN; Joselyn Rwebembera , MBChB; Rachel J. Sarnacki, BA; Christopher F. Spurney, MD; Elizabeth Stein, BS; Laura Tochen, MD; David Watkins, MD; Meghan Zimmerman , MD; Jonathan R. Carapetis, MD, PhD; Craig Sable, MD; Andrea Beaton , MD

**BACKGROUND:** Despite the high burden of rheumatic heart disease in sub-Saharan Africa, diagnosis with acute rheumatic fever (ARF) is exceedingly rare. Here, we report the results of the first prospective epidemiologic survey to diagnose and characterize ARF at the community level in Africa.

**METHODS AND RESULTS:** A cross-sectional study was conducted in Lira, Uganda, to inform the design of a broader epidemiologic survey. Key messages were distributed in the community, and children aged 3 to 17 years were included if they had either (1) fever and joint pain, (2) suspicion of carditis, or (3) suspicion of chorea, with ARF diagnoses made by the 2015 Jones Criteria. Over 6 months, 201 children met criteria for participation, with a median age of 11 years (interquartile range, 6.5) and 103 (51%) female. At final diagnosis, 51 children (25%) had definite ARF, 11 (6%) had possible ARF, 2 (1%) had rheumatic heart disease without evidence of ARF, 78 (39%) had a known alternative diagnosis (10 influenza, 62 malaria, 2 sickle cell crises, 2 typhoid fever, 2 congenital heart disease), and 59 (30%) had an unknown alternative diagnosis.

**CONCLUSIONS:** ARF persists within rheumatic heart disease–endemic communities in Africa, despite the low rates reported in the literature. Early data collection has enabled refinement of our study design to best capture the incidence of ARF and to answer important questions on community sensitization, healthcare worker and teacher education, and simplified diagnostics for low-resource areas. This study also generated data to support further exploration of the relationship between malaria and ARF diagnosis in rheumatic heart disease/malaria-endemic countries.

**Key Words:** epidemiology ■ pediatrics ■ rheumatic heart disease

Rheumatic heart disease (RHD) is the most common cardiovascular disease among children and young adults worldwide. More than 40 million people were living with RHD and about 300 000 individuals died from RHD in the year 2017.<sup>1</sup> The accepted pathogenesis of RHD requires group A streptococcal infection(s), which triggers the systemic inflammatory condition acute rheumatic fever (ARF), leading to acquired chronic cardiac valve disease. In spite of the large burden of RHD in Africa and other low-resource settings, diagnosis of acute ARF is rare.<sup>1,2</sup>

Poor health-seeking behavior, underdiagnosis,<sup>3</sup> and differences in clinical manifestations<sup>4</sup> may contribute to the low rates of ARF presentation in low-resource settings but have not been adequately investigated. A recent update to the American Heart Association Jones Criteria,<sup>5</sup> the most widely recognized criteria for ARF diagnosis, provides provisions for less stringent ARF criteria in moderate-/high-risk regions. Less stringent criteria may provide higher sensitivity for ARF detection but have not been systematically studied.

Here, we report the first results from our American Heart Association Strategically Focused Research

Correspondence to: Andrea Beaton, MD, Cincinnati Children's Hospital Medical Center, Cincinnati, OH. E-mail: andrea.beaton@cchmc.org

For Sources of Funding and Disclosures, see page 9.

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## CLINICAL PERSPECTIVE

### What Is New?

- This is the first prospective epidemiologic survey to diagnose and characterize acute rheumatic fever at the community level in Africa.

### What Are the Clinical Implications?

- Acute rheumatic fever persists within rheumatic heart disease–endemic communities in Africa, despite the low rates reported in the literature.

## Nonstandard Abbreviations and Acronyms

<b>ARF</b>	acute rheumatic fever
<b>RHD</b>	rheumatic heart disease

Network, reporting the first prospective study in Africa employing active case finding for ARF. Active case finding through widespread community sensitization and access to high-quality diagnostics may overcome barriers to ARF diagnosis, closing the gap between high RHD prevalence and low ARF diagnostic rates. These data have informed the design and power of our larger ongoing longitudinal study to determine ARF incidence and longitudinal outcomes of children with ARF in Uganda.

## METHODS

This was a 6-month prospective cross-sectional study of ARF in Lira, Uganda. The data that support the findings of this study are available from the corresponding author upon reasonable request.

### Study Setting

Uganda is an equatorial country in East Africa, home to ≈44 million people. Lira, one of 116 districts, is located in the Northern Region of Uganda and is home to just over 400 000 people, 54% of whom are under 18 years of age and 66% of whom live on <\$1.90 per day (compared with 34% in Uganda as a whole). The district is mainly rural, and 89% of households rely on subsistence farming.<sup>6</sup> This study was based at Lira Regional Referral Hospital, where a ARF clinic was established for evaluation of children, aged 3 to 17 years, demonstrating signs and symptoms of ARF. A community-engaged approach including focus groups and interviews with key stakeholder was used in our study design, which informed recruitment materials and approaches as well as health

education for those evaluated. Key stakeholders and people living with RHD were used to inform the community of these results following our larger epidemiologic survey.

### Community Sensitization

To address some of the main reasons for low ARF diagnosis, specifically poor health-seeking behavior and low knowledge about the signs/symptoms of ARF, a community sensitization campaign was launched before study enrollment. The campaign used radio messaging, posters, village health teams, and direct school-based and clinic-based education to raise awareness about the signs of ARF in the community with focused key messaging based on target audience (Table 1, Figure 1).

### Case Referral and Enrollment

A toll-free hotline for case referral from healthcare facilities, schools, or community health workers was established. Walk-in cases and self-referrals were also welcomed. Children met inclusion criteria if they were between the ages of 3 and 17 years and met 1 of 3 additional clinical presentations consistent with a suspected ARF diagnosis:

1. Fever ( $\geq 38^{\circ}\text{C}$  oral or  $\geq 37.5^{\circ}\text{C}$  axillary or history of tactile fever in the last 48 hours), and any joint involvement (monoarthritis, monoarthralgia, polyarthritis, polyarthralgia).
2. Suspicion of acute rheumatic carditis (cardiac murmur suspicious for mitral or aortic regurgitation with or without signs of acute left heart failure [breathlessness, poor perfusion, orthopnea], or suspicion of pericardial effusion [chest pain worse when supine, tachycardia at rest, pericardial rub]).
3. Suspicion of chorea (any abnormal involuntary non-rhythmic movement).

Children were excluded if they had a confirmed alternative diagnosis at time of presentation, including septic arthritis, connective tissue or rheumatologic conditions, viral arthropathy, sickle cell crisis, joint trauma, malaria, infective endocarditis, myocarditis, and congenital mitral or aortic valve disease that was responsible for the presenting symptoms.

The parent or guardian of children meeting enrollment criteria freely provided written consent for participation. Children of at least 8 years of age also freely provided written assent. This study was approved by the Makerere University School of Medicine Research and Ethics Committee, Children's National Hospital, Cincinnati Children's Hospital Medical Center, and the Uganda National Council for Science and Technology.

**Table 1. Key Educational Messages Used for Community Sensitization**

Common messaging	Not all patients who present with fever and joint pain have malaria. Fever and joint pain could indicate a problem that can damage the heart called ARF. Abnormal involuntary movements can happen in ARF. A research program is now available in your district to better understand ARF. Free medical testing is available in your district to diagnose ARF and to understand more about this condition.
Community & village health teams	If your child (3–17 y), or another child you know, has fever and joint pain or if he/she begins to have abnormal involuntary movements, take him/her to the nearest healthcare facility and ask about this study. If your child meets criteria for possible ARF, he/she will be sent to the regional referral hospital for further evaluation and your transport and care will be paid. Proper recognition and treatment of ARF can protect the heart from damage.
Providers at health centers II, III, and IV	Children (3–17 y) who present with fever or history of fever in the past 48 h and any joint complaint (monoarthritis, monoarthralgia, polyarthritis, or polyarthralgia) should be considered to have suspected ARF until disproven. Children who present with new-onset abnormal involuntary movements should be considered to have suspected ARF until disproven. When a suspected ARF case is detected, please call the ARF hotline (number provided) to discuss the case with a research nurse, who will confirm the child meets enrollment criteria. If the child meets enrollment criteria, he/she will be invited to come to the regional referral hospital for further evaluation and care. Transport to the regional referral hospital and evaluation will be provided at no cost to the patient's family.
Providers at the regional referral and national referral hospitals	Above messaging for providers PLUS: ARF can present as acute carditis, typically affecting the left-sided heart valves. Children presenting with fever and a murmur consistent with mitral or aortic regurgitation or signs/symptoms of acute left-sided heart failure (with or without joint pain) or pericardial effusion should also be referred for possible study inclusion.

ARF indicates acute rheumatic fever.

## Data and Sample Collection

A study nurse recorded demographic information, including information on socioeconomic status,<sup>7</sup> history, and physical examination, and sent the results of diagnostic tests (see Table 2). If a child received a positive rapid antigen Strep A test or if the local team saw definitive evidence of rheumatic carditis on echocardiogram, a single dose of benzathine penicillin G was given while awaiting final results of diagnostic tests. Results of the history, physical examination, and several laboratory tests (point-of-care malaria, HIV, and Strep A) tests were available immediately for review by the medical officer or clinical officer at the outpatient or inpatient department. The health officer evaluated the patient and determined a diagnosis and treatment plan according to the usual clinical practice. Final clinical diagnosis and treatment were recorded for all participants.

Our exam method allowed for digital video to be recorded at the point of medical service, and then later sent securely to reviewers in the United States for confirmation of a diagnosis of chorea, an often subtle and variable movement disorder. Although this method precluded real-time instructions for the patient's examiner, it provided objective exam findings consistently confirming chorea by both of our neurologists.

Echocardiograms were obtained using a limited RHD protocol<sup>8</sup> focusing on left-sided inflow and outflow valves by research nurses who had completed standardized training in person and on the computer (<http://www.wiredhealthresources.net/>), and demonstrated competency in RHD. Echocardiograms were obtained using handheld ultrasound machines (General Electric Vscan, Milwaukee, WI), transferred securely via cloud

technology, and viewed remotely using proprietary software. ECGs were performed on General Electric MAC 800 machines, and images were uploaded directly into Research Electronic Data Capture for remote viewing.

All participants were asked to return to the clinic 7 days after initial presentation to receive a definitive study diagnosis, which was made through remote chart review by the investigative team to reduce bias. Possible study diagnoses included definite diagnosis, suspected diagnosis, known alternative diagnosis (after diagnostic evaluation), or unknown alternative diagnosis. Children with a diagnosis of definite RHD or RHD without evidence of ARF were enrolled in the Ugandan National/RHD Registry.

## Acute Case Definition

Enrolled children were diagnosed with definite ARF, possible ARF, known alternative diagnosis detected during ARF evaluation, or unknown alternative diagnosis (Table 3). The 2015 revision of the Jones Criteria<sup>5</sup> was used to guide the diagnosis of ARF in moderate-/high-risk populations. Patients were defined as having recurrent ARF if they had echocardiographic evidence of established RHD and met criteria for ARF.<sup>5</sup> We used the 80% upper limit of normal cutoff values for antistreptolysin O (389 IU/mL) and antideoxyribonuclease B (568 IU/mL) titers that were established specifically for the Uganda population in a recent study (for 5–14-year-olds).<sup>10</sup>

## Diagnostic Overlap Category

Per the Jones Criteria,<sup>5</sup> ARF is a diagnosis of exclusion; thus, children with a confirmed alternative diagnosis were categorized as “known alternative” diagnosis,

# JOINT PAIN + FEVER CAN BE: RHEUMATIC FEVER

Malaria is not the only cause of joint pain and fever.

Joint pain and fever can indicate **Acute Rheumatic Fever.**

Two atipa peen keken aye kelo arem me wang mwot kede lyeto ento twero bedo anyut me **two adunu nyo two itao.**

**Acute Rheumatic Fever can damage the heart.**

**Two adunu nyo two itao twero balo adunu ni woko.**

If your child **(3-17 yrs)** has joint pain and fever take them to the nearest health center for evaluation.

Cwal atini **(me mwaka 3 nio 18)** matye kede arem me wang mwot kede lyeto I ot yat ma cok kedi wek opim.

**FREE EVALUATIONS IN LIRA REGIONAL REFERRAL HOSPITAL**  
Dakatal adwong me Lira  
TYE ME NONO

**0800-201900**

**Figure 1. Poster used during community sensitization campaign.**  
Shown in English. A Luganda and a Luo version were used for this project.

reported here as a subcategory of diagnostic overlap. As an exception to this practice, children with carditis and diagnostic overlap were classified as definite ARF, reported here as definite ARF+diagnostic overlap (Table 3). Children who met the definition of ARF but also met an alternative diagnosis were included in both the ARF and the alternative diagnosis categories.

### Statistical Analysis

Data were entered into Research Electronic Data Capture, an electronic web-based research data capture tool hosted at Children's National.<sup>11</sup> A probability-based enrollment, limited to 6 months, was used to generate this early data. Data were largely descriptive, summarized by number and percentage or median and interquartile range as appropriate.

**Table 2. Diagnostic Workup for Suspected ARF**

	Details	Processing and Reporting
Demographics	Age, sex, type of housing (permanent/impermanent), number of people in household, number <15 y in household, if applicable type of school (day or boarding), district of primary residence, WAMI Index <sup>7</sup> (household SES)	N/A
Past medical history	History of RHD, recent sore throat or impetigo, any chronic medical conditions (sickle cell, HIV, etc), any chronic medications, hospitalizations, surgeries	N/A
Current clinical history	Detailed history to include onset, duration, and description of symptoms and any medications or traditional medicine taken in the 7 d before evaluation. Complete review of systems to identify other signs/symptoms not mentioned	N/A
Family history	First-degree relatives with known history of or RHD	N/A
Physical exam	HEENT exam (eg, rhinorrhea, pharyngitis), cardiac exam (eg, murmur, gallop, rub), respiratory exam (eg, work of breathing, lung sounds), skin exam (eg, rash, impetigo, scabies), musculoskeletal exam (eg, joint pain, swelling, limited range of motion), and neurological evaluation (eg, chorea maneuvers)	If neurological abnormality was suspected, the neurological exam was video recorded and sent to neurology team (United States) via telemedicine for review and returned in 48 h. If a skin changes (rash or lesions) were present, a photo was taken and reviewed by the dermatology team (United States) with return of results in 48 h
ECG	12-lead ECG: measurement of PR interval	Telemedicine review by investigative team (United States) within 48 h
Echocardiogram	Focused echocardiogram <sup>8</sup> : standard portable echocardiography for left-sided valve assessment (2D, color Doppler, spectral Doppler)	Telemedicine review by investigative team (United States) within 48 h. Modified diagnostic criteria for <sup>5</sup> and RHD, <sup>9</sup> absence of spectral Doppler
Venipuncture	POC malaria	Manufacturer's instructions (CareStart)
	POC HIV	Manufacturer's instructions (Determine)
	CBC	MINDRAY/HUMAN
	ESR	HumaSRate
	CRP	Manufacturer's instructions (Icroma)
	Blood smear, malaria	Thick and thin blood smears were prepared and stained with 5% Giemsa and read by a laboratory technician (MBN)
	Viral PCR (eg, Chikungunya, O'nyong'nyong, Zika, Dengue)	Standard protocol, commercial test kit
	Antistreptolysin O Titers	Manufacturer's instructions (Icroma)
	Antideoxyribonuclease B titers	Completed on the nephelometer at PathWest (Australia)
Throat swab	POC Strep A testing and send-out throat culture	Manufacturer's instructions (Fisher Scientific), MBN Clinical Laboratory
Nasal swab	Influenza PCR	Nylon flocked swab, vortexed in a tube of viral transport media tested via real-time quantitative reverse transcription-polymerase chain reaction (qRT-PCR) using the AgPath-ID One-Strep RT-PCR Kit

ARF indicates acute rheumatic fever; CBC, complete blood count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HEENT, head; eyes, ears, nose, throat; N/A, not applicable; PCR, polymerase chain reaction; POC, point of care; RHD, rheumatic heart disease; RT-PCR, real-time polymerase chain reaction; SES, socioeconomic status; and WAMI, water and sanitation, 8 selected assets, maternal education, and household income.

## RESULTS

### Enrollment

From June to November 2017, 577 children presented to the ARF evaluation clinic. Of these, 201 (35%) met criteria for participation and 376 (65%) were excluded (Figure 2). Participants had a median age of 11 years (interquartile range, 6.5) and 103 (51%) were female (Table 4). The majority of children  $\geq 5$  years of age (149/174; 86%) were enrolled in school. Nearly half of

participants presented by self-referral (42%), with the rest referred from various levels of the healthcare system (50%) and a small proportion referred from school (7%).

The most common qualifying clinical pattern was fever and joint involvement in the past 48 hours (85%). More than half of children (61%) had received treatment in the week before presentation, including 18% who had received  $\geq 1$  antibiotics and 26% who had received nonsteroidal anti-inflammatory drugs. Severe anemia

**Table 3. Operational Definitions for ARF Diagnosis**

Category	Operational Definition
Definite ARF	Meets full Jones Criteria <sup>5</sup> for the diagnosis of ARF in moderate-/high-risk populations including evidence of recent streptococcal infection (throat culture or rapid group A streptococcal test in those with sore throat, elevated antistreptolysin O or antideoxyribonuclease B titer [population normal]) plus 1 of the following: (1) 2 major criteria, (2) 1 major and 2 minor criteria, (3) chorea (no need to show streptococcal evidence), (4) fulminant rheumatic carditis (no need to show streptococcal evidence) AND no known alternative diagnosis for presenting symptoms
Diagnostic overlap	Meets criteria for definite ARF with carditis AND has a confirmed alternative diagnosis (see “known alternative diagnosis”)
Possible ARF	Patients who fulfilled the clinical criteria for ARF including either (1) 2 major criteria or (2) 1 major and 2 minor criteria but did not have raised antistreptococcal antibody titers as defined by our upper limit of normal
Known alternative diagnosis	Confirmed alternative diagnosis for the presenting symptoms
Diagnostic overlap	Meets criteria for known alternative diagnosis, but also meets criteria for definite ARF without carditis
Unknown alternative diagnosis	No confirmed alternative diagnosis as the source of presenting complaint

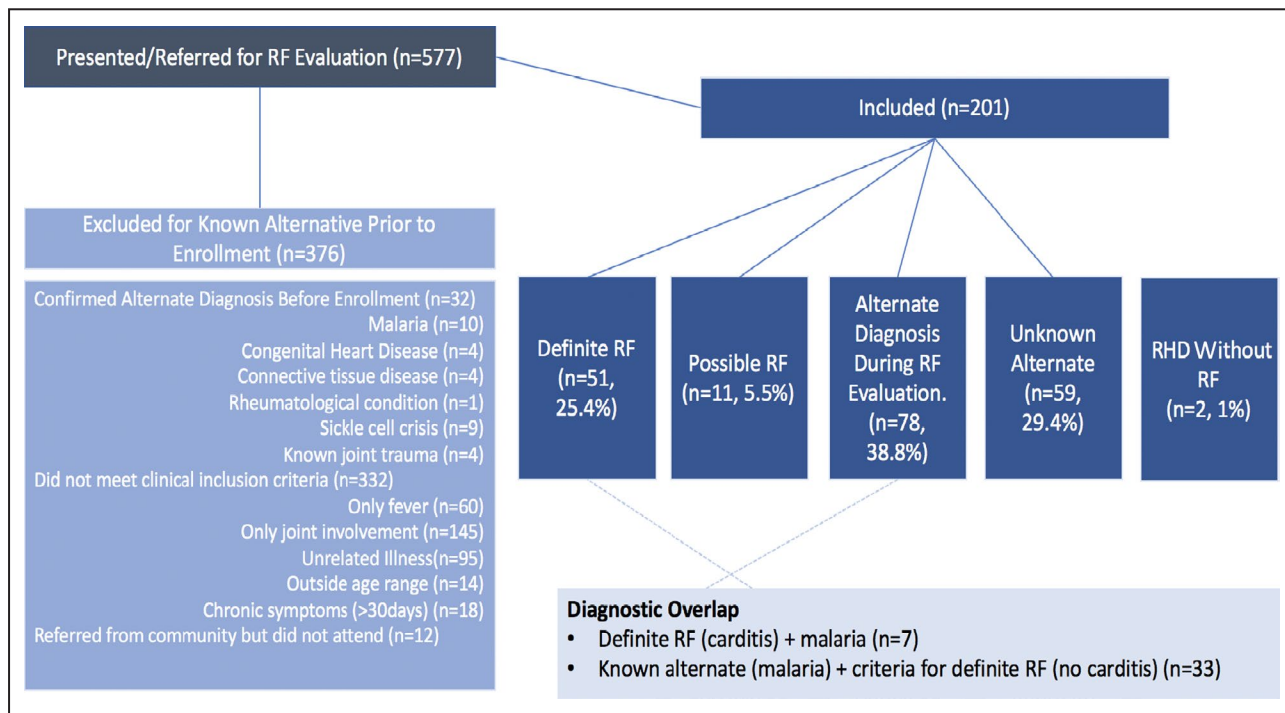
ARF, acute rheumatic fever.

(hemoglobin <7 g/dL) was rare (5%), though moderate anemia (hemoglobin 7–11 g/dL) was relatively common, affecting 40 of 201 enrolled children (20%). HIV tests were positive in 5 (2.5%) of children, all of which were previously unknown diagnoses. Overall, 8 children (4%) were admitted to the hospital for heart failure, and 3, all with severe carditis and confirmed ARF, died (1.5%) from rheumatic carditis during the 6-month study.

As a final diagnosis, 51 children (25%) had definite ARF, 11 (6%) had possible ARF, 2 (1%) had RHD without evidence of ARF, 78 (39%) had a known alternative diagnosis (10 influenza, 62 malaria, 2 sickle cell crises, 2 typhoid fever, 2 congenital heart disease), and 59 (30%) had an unknown alternative diagnosis.

Diagnostic overlap was observed in 7 children with definite ARF with carditis who also had evidence of malaria and in 33 children with a known alternative diagnosis (of malaria) who also met criteria for ARF without carditis (Figure 2).

For children diagnosed with definite ARF, elevations in antideoxyribonuclease B were more common than elevations in antistreptolysin O titers. Nearly all children had at least 1 major joint criterion, and slightly less than half (41%) had carditis. In our sample, Sydenham chorea was an uncommon presentation, diagnosed in only 2 children (4%). Additionally, subcutaneous nodules were rare, and erythema marginatum was not seen (Table 5).



**Figure 2. ARF case enrollment and categorization.**

RF indicates rheumatic fever.

**Table 4. Demographic Features, Referral Patterns, and Clinical History for Children Included in This Study**

Demographics	
Age in y, median (IQR)	11 (6.5)
Sex (female), n (%)	103 (51.2)
Housing (semipermanent, n,%)	110 (54.7)
No. of people in the home, median (IQR)	7 (5)
No. of additional children <15 y, median (IQR)	4 (2)
Referral patterns	
Referral source, n (%)	
HCII	29 (14.4)
HCIII	31 (15.4)
HCIV	17 (8.5)
Lira Regional Referral Hospital Inpatient Department	3 (1.5)
Lira Regional Referral Hospital Outpatient Department	20 (10.0)
School	13 (6.5)
Self-referral	85 (42.3)
Unknown	3 (1.5)
Inclusion criteria, n (%)	
Fever+joint pain	171 (85.0)
Suspicion of carditis	10 (5.0)
Joint pain+suspicion of carditis	15 (7.5)
Suspicion of chorea	5 (2.5)
History, n (%)	
Sore throat in the past 4 wk	31 (15)
Skin infection in the past 4 wk	1 (0.5)
Child with prior diagnosis of ARF	6 (3.0)
Child with prior diagnosis of RHD	1 (0.5)
Family history (first-degree relative) ARF/RHD	7 (3.5)
Taken medication <1 wk prior to presentation, n (%)	122 (60.7%)
≥1 antibiotic	22 (18)
Paracetamol	79 (64.8)
NSAID	32 (26.2)
Antimalarial	18 (14.8)
Unknown	11 (9.0)
Labs, n (%)	
Positive POC group <i>Astreptococcus</i>	41 (20.4)
Positive malaria POC or blood smear	86 (42.8)
Positive POC HIV	5 (2.5)
Severe anemia (hemoglobin <7 g/dL)	5 (2.5)
Moderate anemia (hemoglobin 7–11 g/dL)	40 (20.0)
Influenza	10 (5.0)
Alphaviruses	0 (0)
Initial disposition (admitted to Lira Regional Referral Hospital), n (%)	8 (4.0)

ARF indicates acute rheumatic fever; HC, health center; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug; POC, point of care; and RHD, rheumatic heart disease.

Of the 21 children diagnosed with acute rheumatic carditis, 1 child had a moderate pericardial effusion (5%), 4 had left ventricular dilation (19%; 1 mild, 3 moderate), and all had preserved left ventricular systolic function. Pathological mitral regurgitation<sup>5</sup> was seen in 18 (86%; 9 trivial/mild, 4 moderate, 5 severe), and pathological aortic regurgitation<sup>5</sup> was seen in 12 (57%; 7 trivial/mild and 5 moderate). Eight cases showed evidence of chronic RHD,<sup>9</sup> indicating possible recurrent rheumatic fever (38%), but none of these children had a known history of prior ARF/RHD.

## DISCUSSION

To our knowledge, this is the first time that active case finding, as compared with passive surveillance at tertiary centers<sup>12</sup> or retrospective chart review,<sup>13</sup> was used to collect community-level data on ARF in Africa. Our study design used a combination of community mobilization and a dedicated ARF clinic to recruit cases of possible ARF and to provide comprehensive diagnostic evaluation and treatment, which are rarely available in low-resource settings. While these data were collected to plan a larger study to characterize incidence and progression of ARF in Uganda, they contribute independently as evidence that ARF persists within low-resource RHD-endemic settings, despite the rarity of clinical diagnosis.

Data on acute ARF in RHD-endemic countries are exceedingly sparse.<sup>14</sup> Despite the large burden of RHD in Africa, incidence and clinical characteristics of ARF have been described in only 5 populations since 1991. In all 5 populations—Algeria,<sup>15</sup> Nigeria,<sup>16</sup> Cameroon,<sup>17</sup> the Eastern Cape of South Africa,<sup>18</sup> and Sudan<sup>12</sup>—data consist of a small number of children (n=4–66) presenting for diagnosis exclusively at tertiary referral hospitals. Recent multinational RHD registries, Un registre des valvulopathies rhumatismales en Afrique de l'Ouest et Centrale (A registry of rheumatic heart disease in Western and Central Africa) (VALAFRIC)<sup>19</sup> (which includes patients with RHD from Western and Central Africa) and Global Rheumatic Heart Disease Registry (REMEDY)<sup>20</sup> (which largely capture patients with RHD from sub-Saharan Africa), have added substantial understanding to presentation and outcomes of chronic RHD on the continent, but were not designed to capture ARF.

Indeed, the diagnosis of ARF in resource-limited settings has myriad challenges. The first obstacle is lack of public awareness of ARF and RHD, even in settings where RHD is endemic. A cross-sectional study of adults and children in Cameroon revealed that 95% of interviewees did not know what caused RHD, and 82% had never heard of the condition.<sup>21</sup> Efforts to institute public ARF/RHD awareness are ongoing in Zambia<sup>22</sup> through

**Table 5. Breakdown of Jones Criteria for Children With Definite ARF**

	Definite ARF (n=51)
Streptococcal evidence, n (%)	
Elevated antistreptolysin O titers	22 (43.1)
Elevated antideoxyribonuclease B	41 (80.4)
Rapid group A streptococcal test*	16 (31.4)
Throat culture†	5 (9.8)
Major criteria, n (%)	
Carditis	21 (41.2)
Joint involvement	50 (98.0)
Polyarthritis	24 (47.0)
Polyarthralgia	23 (45.0)
Monoarthritis	3 (5.9)
Subcutaneous nodules	1 (2.0)
Erythema marginatum	0 (0)
Chorea	2 (3.9)
Minor criteria, n (%)	
Fever	51 (100)
Monoarthralgia	0 (0)
Elevated markers of inflammation	47 (92.1)
Erythrocyte sedimentation rate >30 mm/h	35 (68.6)
C-reactive protein >5 mg/L	31 (60.8)
Prolonged PR interval‡	4 (7.8)

ARF indicates acute rheumatic fever.

\*12/16 also had serological evidence of streptococcal exposure.

†4/5 also had serological evidence of streptococcal exposure.

‡Three of these children also had echocardiographic carditis; PR interval not counted as a minor criterion toward fulfillment of the Jones Criteria.

RHD week and related public health outreach activities and in South Africa through the ASAP (Awareness, Surveillance, Advocacy and Prevention) program<sup>23</sup> and ARF week. In this study, we used a combination of radio messaging, teacher education, and posters to raise community awareness. Ongoing work is in process to assess the efficacy of these strategies.

The second obstacle to ARF diagnosis is lack of awareness of ARF and RHD among healthcare workers. In Sudan, pediatric physicians showed only average knowledge of the prevention of ARF/RHD.<sup>24</sup> In Zambia, 112 healthcare workers, 15% of whom had not heard of RHD, participated in a novel RHD training curriculum with immediate improvements in knowledge around RHD diagnosis and management.<sup>22</sup> Further work is needed to better integrate ARF/RHD into the core curriculum and continuing education of community healthcare workers, nurses, and physicians in resource-limited RHD-endemic settings. Leveraging existing educational outreach platforms such as *Helping Babies Breathe* in Zambia<sup>22</sup> may provide additional access to practicing providers. Our larger study will assess referral patterns for ARF

in Uganda, following education of frontline healthcare workers and educators to assess the impact of direct ARF education in symptom recognition. These data will be critical for developing strong ARF surveillance systems. To enable replication of our success in active ARF case finding outside of a focused, well-resourced research program, ARF/RHD may need to be made notifiable public health conditions.

The third obstacle, and perhaps the largest challenge to healthcare systems seeking to improve ARF diagnosis, is the technical ability to make the diagnosis of ARF in a resource-limited setting. Because there is no single diagnostic test for ARF, diagnosis depends on fulfilling a set of clinical, laboratory, ECG, and echocardiographic criteria. While many clinical features are readily identifiable, access to laboratory and diagnostic testing is severely limited in much of sub-Saharan Africa, in particular outside of tertiary care settings.<sup>25</sup> The 2015 Jones Criteria make a provision for the diagnosis of possible ARF in settings where diagnostic testing is limited.<sup>5</sup> Though specificity may be lowered, healthcare workers in RHD-endemic settings should try to balance the consequences of missed ARF and progression to RHD and overtreating false-positive cases.<sup>26</sup> Ongoing work within our research team is seeking to determine whether ARF diagnosis can be adequately detected at lower tiers of the Ugandan healthcare system where echocardiography and advanced laboratory testing are not readily available.

A fourth hurdle to ARF diagnosis is overlap with other common conditions. Because no single diagnostic test exists, ARF is largely a disease of exclusion. If another diagnosis can explain the presenting symptoms, then ARF is ruled out.<sup>5</sup> However, this becomes challenging in a tropical environment where malaria is also endemic and incidental malaria parasitemia is common; in Uganda the prevalence of malaria parasitemia in school-aged children is around 35%.<sup>27</sup> In our study, we saw substantial diagnostic overlap between ARF and malaria, as 40 children had laboratory confirmation of malaria and also met criteria for definite ARF. In this initial study, those with laboratory confirmation of malaria and carditis were treated for malaria and placed on secondary prophylaxis for ARF, while those without carditis were treated for malaria and remain in close longitudinal follow-up. In practical terms, a positive point-of-care malaria test, readily available in community settings, will likely be regarded as conclusive, and any further workup that might identify cases of ARF would likely be abandoned. Sickle cell disease can also mimic the symptoms of ARF and also have associated mitral regurgitation and pulmonary hypertension. Sickle cell crisis should be ruled out in all children presenting with fever and joint pain. Diagnostic algorithms for fever in tropical settings will need to



consider this situation carefully to improve ARF case detection at reasonable cost.

Finally, diagnosis of ARF in this setting was complicated by the high rates of premedication with anti-inflammatory drugs. As anti-inflammatory medications are rapidly effective in reducing joint symptoms, self-prescription can mask the severity of both joint manifestations and fever.<sup>5</sup> In our cohort, around one quarter of children had taken a nonsteroidal anti-inflammatory drug before presentation. In this study, we did not modify diagnostic criteria if prior medication was used. Thus, we could have false-negative diagnoses among children who had taken nonsteroidal anti-inflammatory drugs, for example, before presentation. Longitudinal follow-up will help determine if sensitivity was inappropriately lowered by strictly employing the Jones Criteria.

This data collection was too short to determine incidence (will be addressed in larger study) but provided new information about ARF clinical presentation in Uganda. First, we saw a lower rate of chorea (4%) than described from pooled data from other global populations (12.9%).<sup>14</sup> This may be largely explained by our health messaging campaign that emphasized fever and joint pain among the community but provided education about abnormal movements only to healthcare workers. Second, we saw lower rates of carditis (41%) than previously reported. Globally, ~60% of children with ARF demonstrate evidence of carditis,<sup>14</sup> and the Nigerian series showed that 98% had carditis.<sup>16</sup> This difference may be explained by the revision of the Jones Criteria, which allowed monoarthritis and polyarthralgia as major criteria, improving the sensitivity for detection of less severe ARF presentations as has been described in Australia.<sup>28</sup> Another explanation may be that less severe cases were captured in the community as compared with previous study at tertiary facilities.

There are several limitations to this study that will be overcome with the larger epidemiologic cohort. The total number of positive ARF cases was modest but represents the largest ARF study to date in Uganda and confirms a high, underappreciated burden; the larger study anticipates recruitment of several hundred children with ARF enabling more robust clinical characterization. We cannot determine annual incidence from these initial data as community sensitization was conducted in parallel and penetrance of the messaging not assessed.

Our data show that acute ARF persists within RHD-endemic communities in Africa, despite the low rates reported in the literature. These early data have enabled refinement of our study design to best capture the incidence of ARF and to answer important questions on community sensitization, healthcare worker and teacher education, and simplified diagnostics for low-resource areas. This study also generated new

research questions, urging further exploration of the relationship between malaria and ARF diagnosis in RHD-/malaria-endemic countries. Nevertheless, closing the gap between ARF incidence and RHD prevalence remains a critical challenge in RHD control.

## ARTICLE INFORMATION

Received January 24, 2020; accepted June 3, 2020.

### Affiliations

From the Uganda Heart Institute, Kampala, Uganda (E.O., E.N., J.A., P.L., I.O.O., L.M.O., J.P., J.R.); Telethon Kids Institute, Perth, Western Australia, Australia (A.C.B., J.R.C.); Children's National Hospital, Washington, DC (E.N., M.P.D., N.S.H., M.M., S.A.N., R.J.S., C.F.S., L.T., M.Z., C.S.); Case Western Reserve University School of Medicine, Cleveland, OH (C.T.L.); London School of Hygiene & Tropical Medicine, London, United Kingdom (T.P.); University of Washington, Seattle, WA (E.S., D.W.); Cincinnati Children's Hospital Medical Center, Cincinnati, OH (A.B.); and Cincinnati University School of Medicine, Cincinnati, OH (A.B.).

### Sources of Funding

This study was funded by the American Heart Association Children's Strategically Focused Research Network Grant #17SFRN33670607 and by DEL-15-011 to THRIVE-2. The DELTAS Africa Initiative is an independent funding scheme of the African Academy of Sciences' Alliance for Accelerating Excellence in Science in Africa and supported by the New Partnership for Africa's Development Planning and Coordinating Agency with funding from the Wellcome Trust grant #107742/Z/15/Z and the UK government. The views expressed in this publication are those of the author(s) and not necessarily those of African Academy of Sciences, New Partnership for Africa's Development Planning and Coordinating Agency, Wellcome Trust, or the UK government. The authors did not enter into any agreements with these funders that limited their ability to complete the research as planned and had full control of the primary data.

### Disclosures

None.

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