Active Case Finding for Rheumatic Fever in an Endemic Country

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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 2017.1 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.1,2

Poor health-seeking behavior, underdiagnosis,3 and differences in clinical manifestations4 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,5 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...
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. 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 (≥38°C oral or ≥37.5°C axillary or history of tactile fever in the last 48 hours), and any joint involvement (monoarthritis, monoarthritis, polyarthritis, polyarthritis).
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.
Data and Sample Collection
A study nurse recorded demographic information, including information on socioeconomic status,7 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 examination, it provided objective exam findings consistently confirming chorea by both of our neurologists.

Echocardiograms were obtained using a limited RHD protocol8 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 investigational 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 Criteria5 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.5 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).10

Diagnostic Overlay Category
Per the Jones Criteria,5 ARF is a diagnosis of exclusion; thus, children with a confirmed alternative diagnosis were categorized as “known alternative” diagnosis,
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.

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

**Statistical Analysis**

Data were entered into Research Electronic Data Capture, an electronic web-based research data capture tool hosted at Children’s National. 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.
Okello et al. Active Case Finding for Rheumatic Fever in Uganda

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 ≥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 ≥1 antibiotics and 26% who had received nonsteroidal anti-inflammatory drugs. Severe anemia

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* (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 |
| 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**: 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** and RHD,^ 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 Titters | 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.
(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).

### Table 3. Operational Definitions for ARF Diagnosis

| Category                          | Operational Definition                                                                                                                                                                                                 |
|-----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Definite ARF                      | Meets full Jones Criteria² 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.

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

RF indicates rheumatic fever.
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 was seen in 18 (86%; 9 trivial/mild, 4 moderate, 5 severe), and pathological aortic regurgitation was seen in 12 (57%; 7 trivial/mild and 5 moderate). Eight cases showed evidence of chronic RHD, 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 or retrospective chart review, 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. 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, Nigeria, Cameroon, the Eastern Cape of South Africa, and Sudan—the 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 (VALAFRIC) (which includes patients with RHD from Western and Central Africa) and Global Rheumatic Heart Disease Registry (REMEDY) (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. Efforts to institute public ARF/RHD awareness are ongoing in Zambia through

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

| Demographics                  | Age in y, median (IQR) | Sex (female), n (%) | Housing (semipermanent, n,%) | No. of people in the home, median (IQR) | No. of additional children <15 y, median (IQR) |
|-------------------------------|------------------------|---------------------|-----------------------------|----------------------------------------|-----------------------------------------------|
| Referral patterns             |                        |                     |                             |                                        |                                               |
| 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)             |                     |                             |                                        |                                               |
| Suspicition of carditis       | 10 (5.0)               |                     |                             |                                        |                                               |
| Joint pain+suspicition of carditis | 15 (7.5) | | | | |
| Suspicition 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 Astreptoccus | 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.
RHD week and related public health outreach activities and in South Africa through the ASAP (Awareness, Surveillance, Advocacy and Prevention) program23 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.24 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.22 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 Zambia22 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.25 The 2015 Jones Criteria make a provision for the diagnosis of possible ARF in settings where diagnostic testing is limited.26 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 overtreatment of false-positive cases.26 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.5 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%.27 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 remained in close longitudinal follow-up. In practical terms, a positive point-of-care malaria test, readily available.

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

| Minor criteria, n (%) | Definite ARF (n=51) |
|----------------------|--------------------|
| Fever                | 51 (100)           |
| Monoarthritis        | 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.
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. 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%). 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, and the Nigerian series showed that 98% had carditis. 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. 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 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.

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.

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None.

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