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ORIGINAL RESEARCH

Rheumatic Heart Disease in the United States: Forgotten But Not Gone

Results of a 10 Year Multicenter Review

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BACKGROUND: Recent evaluation of rheumatic heart disease (RHD) mortality demonstrates disproportionate disease burden within the United States. However, there are few contemporary data on US children living with acute rheumatic fever (ARF) and RHD.

METHODS AND RESULTS: Twenty-two US pediatric institutions participated in a 10-year review (2008–2018) of electronic medical records and echocardiographic databases of children 4 to 17 years diagnosed with ARF/RHD to determine demographics, diagnosis, and management. Geocoding was used to determine a census tract-based socioeconomic deprivation index. Descriptive statistics of patient characteristics and regression analysis of RHD classification, disease severity, and initial antibiotic prescription according to community deprivation were obtained. Data for 947 cases showed median age at diagnosis of 9 years; 51% and 56% identified as male and non-White, respectively. Most (89%) had health insurance and were first diagnosed in the United States (82%). Only 13% reported travel to an endemic region before diagnosis. Although 96% of patients were prescribed secondary prophylaxis, only 58% were prescribed intramuscular benzathine penicillin G. Higher deprivation was associated with increasing disease severity (odds ratio, 1.25; 95% CI, 1.08–1.46).

CONCLUSIONS: The majority of recent US cases of ARF and RHD are endemic rather than the result of foreign exposure. Children who live in more deprived communities are at risk for more severe disease. This study demonstrates a need to improve guideline-based treatment for ARF/RHD with respect to secondary prophylaxis and to increase research efforts to better understand ARF and RHD in the United States.

Key Words: acute rheumatic fever ■ deprivation ■ pediatric ■ rheumatic heart disease ■ socioeconomic status ■ United States

Worldwide, rheumatic heart disease (RHD) remains one of the most common cardiovascular diseases with 40.5 million prevalent cases resulting in ≈305 000 deaths annually.[1–3] Acute rheumatic fever (ARF) incidence and RHD prevalence vary greatly across the globe, occurring most commonly

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CLINICAL PERSPECTIVE

What Is New?

- This article characterizes recent pediatric cases of acute rheumatic fever and rheumatic heart disease in the United States, the majority of which are endemic.
- Although most children with acute rheumatic fever/rheumatic heart disease are receiving echocardiograms and secondary prophylaxis, only about half are receiving benzathine penicillin G, the gold standard.

What Are the Clinical Implications?

- Children living in deprived communities are at risk for more severe disease; increased research is needed to understand and care for children in the United States at highest risk of acute rheumatic fever and rheumatic heart disease.

Nonstandard Abbreviations and Acronyms

ARF	acute rheumatic fever
BPG	benzathine penicillin G
DI	deprivation index
RHD	rheumatic heart disease

in low- and middle-income countries.[2] Although ARF was the leading cause of mortality in 5- to 20-year-olds in the United States during the 1920s, the annual incidence of ARF in the United States today is low (<2 cases per 100 000 school-aged children compared with up to 150 cases per 100 000 worldwide).[4–6] These data may lead to the conclusions that ARF and RHD are diseases of the past in the United States and other high-income countries. However, this view does not take persistent inequities into account. Recent geographic evaluation based on RHD mortality has demonstrated pockets of disproportionate disease burden; some coincide with elevated rates of poverty and disadvantage, but this is not true in all regions.[7,8] As mortality captures only a fraction of those affected by RHD and lags behind diagnosis by decades, it fails to accurately capture children currently affected by this disease. There is little contemporary data on children living with ARF and RHD within the United States. The role socioeconomic status plays in current pediatric cases is similarly unknown. This study describes the demographics, clinical features, and cardiac involvement of pediatric ARF/RHD in the United States over the past 10 years and examines the association with community deprivation.

METHODS

Study Design

Sixty US institutions (including all 59 Accreditation Council for Graduate Medical Education accredited cardiology fellowship programs) were invited to participate in a 10-year review (2008–2018) of the electronic medical record and echocardiography databases of pediatric patients ages 4 to 17 with a diagnosis of ARF or RHD. Patients with congenital heart disease were excluded. Diagnostic *International Classification of Diseases, Ninth Revision* and *Tenth Revision* (*ICD-9*, *ICD-10*) codes were used to identify children with ARF and RHD in both the inpatient and outpatient setting. Primary institutional review board approval was obtained from Cincinnati Children's Hospital Medical Center, and all participating centers also received secondary institutional review board approval except for 1 institution that relied on Cincinnati Children's Hospital Medical Center institutional review board. The de-identified data that support the findings of this study are available on request from the corresponding author with appropriate human subject protections assured.

Patient Characteristics and Operational Definitions for Key Outcomes

Electronic medical record chart abstraction and review of echocardiographic databases enabled gathering demographic characteristics, presenting features, echocardiographic findings at presentation, and treatment with secondary antibiotic prophylaxis. Apart from changes in antibiotic regimens for secondary prophylaxis, data focused on features at time of presentation and did not collect longitudinal data. Study data were collected and managed using REDCap electronic data capture tools hosted at Cincinnati Children's Hospital Medical Center.[9,10] Echocardiographic data was gathered from nonstandardized reports at each center; no images were reviewed, and no components were independently reclassified.

Disease Severity

Based upon the echocardiographic findings at presentation, subjects were classified as having either mild, moderate, or severe disease (Table 1). If the mitral and aortic valve were affected in varying degrees, the more significant pathology was used to define overall disease severity.

Appropriate Secondary Prophylaxis

For this study, as recommended by the American Heart Association and other international guidelines, benzathine penicillin G (BPG) was considered the

Table 1. Disease Severity Based on Severity of Cardiac Involvement at Time of Presentation

	Mitral or Aortic Regurgitation	Left Ventricular Dysfunction	Mitral Stenosis
Mild or no cardiac involvement	Normal, trivial, or mild	…	…
Moderate cardiac involvement	Mild to moderate, Moderate	None or mildly diminished	…
Severe cardiac involvement	Moderate to severe, Severe	> mildly diminished	Present (any degree)

gold standard for RHD prophylaxiss.[11–13] Based on a subject's disease classification at presentation (ARF versus RHD) in addition to echocardiographic findings at presentation, subjects were classified in accordance with the American Heart Association guidelines for secondary prophylaxis duration (Table 2).[11] If the recommended duration of antibiotic prophylaxis was less than that advised by the American Heart Association guidelines, it was considered inadequate duration.

Exposures/Predictors

Travel Exposure

An endemic region was defined as a country with an "estimated childhood mortality secondary to RHD >0.15 deaths per 100 000 population among children 5 to 9 years old," as defined by the Global Burden of Disease.[2] Travel exposure was determined by any documented travel before diagnosis as noted in the medical record. Given limitations of the electronic medical record, time spent in the endemic region could not be determined.

Deprivation Index

The previously published deprivation index (DI) was employed to capture community socioeconomic context.[14] Using Health Insurance Portability and Accountability Act-compliant software, the street address for each subject was geocoded to a corresponding census tract. The related tract was characterized by the DI, enumerated using 6 variables related to material deprivation obtained from the 2015 American Community Survey: (1) fraction of population with income in past 12 months below poverty level, (2) median household income in past 12 months in 2015 inflated-adjusted dollars, (3) fraction of population 25 and older with educational attainment of at least high school graduation (includes general educational development equivalency), (4) fraction of population with no health insurance coverage, (5) fraction of households receiving public assistance income or food stamps or Supplemental Nutrition Assistance Program in the past 12 months, and (6) fraction of houses that are vacant. The DI ranges from 0 to 1, with 1 reflecting the greatest community deprivation. Whereas the DI is a measure of community deprivation, census tracts tend to be homogenous and therefore served as reasonable proxy for individual (or household) deprivation. Geocoding and DI derivation was completed at Cincinnati Children's using Decentralized Geomarker Assessment for Multi-Site Studies,[14] except for 2 institutions who performed their own geocoding on site using the same software.

Statistical Analysis

Descriptive statistics were used to enumerate the distribution of key variables. Independent sample *t* tests and chi-square tests were used to test for differences in participant characteristics according to disease classification, disease severity, and DI dichotomized at the national average. Fisher's exact tests are reported for categorical variables where the expected cell counts do not exceed 5 in more than 80% of cells. Multivariable logistic regression was used to obtain odds ratios (ORs) and 95% CIs for RHD classification at presentation according to a 1 SD increase in participant DI. Ordinal logistic regression (cumulative logit) was used to obtain an OR for increasing disease severity (mild, moderate, severe). Multinomial logistic regression was used to obtain ORs for initial antibiotic prescription. Covariates thought to potentially confound the association between the DI and outcomes of interest were selected a priori and included biological sex, age at diagnosis, race, ethnicity, and insurance type. The percentage of missing values across the variables considered for regression ranged from 0% to 12%. Incomplete variables were multiply imputed (n=50 data sets) using full conditional specification as implemented by the default settings in mice version 3.9.0.[15] Variables entered into the imputation model included sex, age at diagnosis, race, ethnicity, insurance type, DI, RHD classification, RHD severity, and initial antibiotic prescription. Estimates were obtained for each imputed data set using the base R logistic regression (glm), MASS version 7.3.51[16] polr, and nnet version 7.3.14[16] multinomial logistic regression functions and combined using Rubin's rules. Potential nonlinear associations were examined using restricted cubic splines but not retained as inclusion of additional terms did not improve model fit as determined by the Akaike information criterion. Therefore, ORs are presented in all models for a 1 SD change in the DI. Analyses were conducted using R version 4.0.0,[17] JMP Version 14.0 (Cary, NC), and STATA MP version 13.0 (College Station, TX).

Table 2. Guideline Based Duration for Prophylaxis and Criteria for Inadequate Duration of Prophylaxis

AHA Category	AHA Recommended Duration of Prophylaxis	Participant Classification at Presentation	Participant Echocardiographic Findings	Criteria for Inadequate Duration of Prophylaxis
Rheumatic fever without carditis	5 y or until 21 y of age (whichever is longer)	ARF	Normal or regurgitation	Anything <21 y of age
Rheumatic fever with carditis but NO residual valvular disease	10 y or until 21 y of age (whichever is longer)	ARF	Normal or regurgitation	Anything <21 y of age
Rheumatic fever with carditis and residual heart disease	10 y or until 40 y of age (whichever is longer)	ARF	Any mitral stenosis	Anything <40 y of age
Rheumatic fever with carditis and residual heart disease	10 y or until 40 y of age (whichever is longer)	Rheumatic heart disease	Anything but Normal	Anything <40 y of age

AHA indicates American Heart Association; and ARF, acute rheumatic fever.

RESULTS

Participant Characteristics

Data were collected for 947 children from 22 institutions (37% participation); enrollment by site varied significantly (from 7 to 132 subjects) (Table S1 and Figure S1). Across all cases, the median age at diagnosis was 9 years (interquartile range 7–12), with half identifying as male (487, 51%) and three-quarters identifying as non-Hispanic (700, 74%). Almost half identified as White (420, 44%). Most spoke English as their primary language (792, 84%) or had a parent who spoke English as a primary language (609, 82%). The majority of children had health insurance (846, 89%), with slightly over half covered by Medicaid or Medicare (450, 53%). Subjects were largely diagnosed in the United States (82%), rather than abroad (Table 3).

Travel Exposure

Only 124 (13%) had known travel to an endemic region before diagnosis of ARF/RHD. The most frequently identified regions included the Pacific Islands (58, 37%) and Africa (33, 21%) (Figure). Those with RHD at time of diagnosis were more likely to report travel to an endemic region compared with those who presented with ARF (P=0.02; Table 3).

Presentation

Clinical Findings in Acute Rheumatic Fever

At time of presentation, nearly three-quarters of cases were diagnosed at the time of ARF (684, 72%). The most commonly cited major Jones criteria were carditis (336, 49%), polyarthritis (208, 30%), and Sydenham chorea (254, 37%), whereas the most commonly cited minor criteria were fever (330, 48%) and elevated inflammatory markers (315, 46%) (Table 4). Of these, 96% had an echocardiogram performed with the most common pathological findings of mitral regurgitation (417, 64%) and aortic regurgitation (221, 34%). Rarely was there associated left ventricular (10, 1.5%) or right ventricular (2, 0.3%) systolic dysfunction (Table 5).

Clinical Findings in Chronic Rheumatic Heart Disease

Having missed the diagnosis of ARF, 27% (258) were diagnosed with chronic RHD as their first presentation. Of these, one-third (35%) recalled a previous history consistent with ARF, though the diagnosis was not made. All had an echocardiogram. As in ARF, mitral regurgitation (228, 88%) and aortic regurgitation

Table 3. Participant Characteristics

	All (n=947)	Acute Rheumatic Fever (n=684)	Rheumatic Heart Disease (n=258)	*P* value
Sex				0.048
Male	487 (51.4%)	365 (53.4%)	119 (46.1%)	
Female	460 (48.6%)	319 (46.6%)	139 (53.9%)	
	N=904	N=661	N=239	
Age at diagnosis, y, median (interquartile range)	9 (7–12)	9 (7–12)	10 (7–13)	0.001
Race				<0.001
American Indian or Alaska Native	39 (4.1%)	22 (3.2%)	17 (6.6%)	
Asian	43 (4.5%)	26 (3.8%)	17 (6.6%)	
Black	172 (18.1%)	98 (14.3%)	73 (28.3%)	
Native Hawaiian or other Pacific Islander	65 (6.9%)	39 (5.7%)	26 (10.1%)	
White	420 (44.4%)	354 (51.8%)	63 (24.4%)	
Other	143 (15.1%)	101 (14.8%)	41 (15.9%)	
Unknown	65 (6.9%)	44 (6.4%)	21 (8.1%)	
Ethnicity				0.83
Hispanic or Latino	161 (17.0%)	115 (16.8%)	46 (17.8%)	
Non-Hispanic or Latino	700 (74.0%)	503 (73.5%)	193 (74.8%)	
Unknown	85 (9.0%)	66 (9.6%)	19 (7.4%)	
Primary language				<0.001
English	792 (83.6%)	595 (87.0%)	193 (74.8%)	
Spanish	82 (8.7%)	54 (7.9%)	28 (10.9%)	
Other	62 (6.5%)	26 (3.8%)	35 (13.6%)	
Unknown	11 (1.2%)	9 (1.3%)	2 (0.8%)	
Has health insurance	846 (89.3%)	612 (89.5%)	229 (88.8%)	0.22
	N=846	N=612	N=229	
Type of health insurance				0.004
Private	344 (40.7%)	267 (43.6%)	75 (29.1%)	
Medicaid or Medicare	450 (53.2%)	304 (49.7%)	144 (55.8%)	
Both	3 (0.4%)	1 (0.2%)	0 (0%)	
Unknown	49 (5.8%)	40 (6.5%)	10 (3.9%)	
Diagnosed in the United States				<0.001
Yes	780 (82.4%)	599 (87.6%)	177 (68.6%)	
No	119 (12.6%)	52 (7.6%)	66 (25.6%)	
Unknown	48 (5.1%)	33 (4.8%)	15 (5.8%)	
	N=747	N=543	N=256	
Parent primary language English	609 (81.5%)	462 (85.1%)	193 (74.8%)	<0.001
Prior travel to endemic region	124 (13.0%)	53 (7.7%)	70 (27.1%)	0.02

n (%) unless otherwise indicated.

(131, 51%) were the most common pathological findings. Mitral stenosis was found in 19% of patients (Table 5).

Disease Severity

Disease severity was determined for the 872 participants who had echocardiographic data, of which 452 (52%) had mild disease, 188 (22%) had moderate disease, and 232 (27%) had severe disease. Those who identified their race as White had less severe disease ($P<0.001$); there was no difference in disease severity with respect to ethnicity (Hispanic or Latino versus non-Hispanic or Latino, $P=0.79$). Possessing health insurance and type of health insurance (commercial versus public) were not associated with disease severity ($P=0.51$ and $P=0.55$, respectively). Severe disease was more likely if either the subject or subject's parental primary language was not English ($P=0.001$ and $P=0.047$,

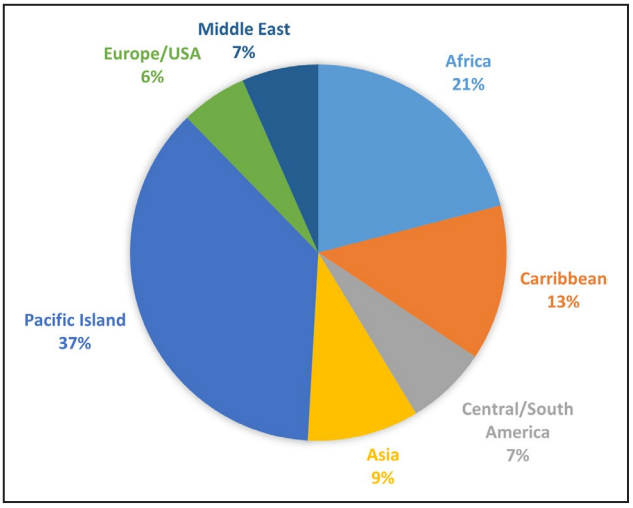

Figure 1. Travel exposure.
Breakdown of region traveled to for the 157 participants with travel exposure.

respectively) compared with subjects whose primary language was English (Table 6).

Management

Secondary Prophylaxis

Although almost all patients were prescribed secondary prophylaxis (913, 96%), only half (527, 58%) were prescribed intramuscular benzathine penicillin G (BPG); 318 (35%) received oral penicillin and 68 (7%) were prescribed other antibiotics (Table 4). Subjects with no insurance or public insurance were more likely to receive BPG therapy versus oral therapy (62% and 64%, respectively, versus 53% for private insurance, P=0.01). Although the reason for choosing oral antibiotics over BPG was known in fewer than half the cases (144, 39%), patient or family preference was the most commonly cited reason (107, 74%), followed by patient allergy (32, 22%). The type of secondary prophylaxis was changed in 18% (171) of subjects, with 7% (13) switching from initial nonpenicillin prophylaxis to penicillin prophylaxis. In these cases, patients frequently had a preceding documented allergy to penicillin, but after further evaluation (often by allergy/immunology), the patient was cleared to receive penicillins and thus transitioned to BPG.

Duration of Prophylaxis

Seventeen percent of patients were advised a prophylactic duration shorter than the American Heart Association guidelines recommend (Table 2).

Deprivation Index

The DI was calculated for 871 (92%) of cases. Of the 76 addresses that could not be geocoded, the address was either missing (3), international (2), a PO box (44), listed as general delivery (1), or not recognized (26). The mean DI in our cases was 0.39±0.15, slightly higher than the national population-weighted mean DI of 0.37 for those <18 years old.[18] Using the national mean DI of 0.375, cases were assigned to a less deprived (DI <0.375) and more deprived (DI ≥0.375) group. Comparing characteristics between these groups demonstrated that increased community deprivation was associated with identifying as non-White (66% versus 42%, P<0.001), Hispanic- or Latino ethnicity (25% versus 11%, P<0.001), less frequently speaking English as a primary language (76% versus 90%, P<0.001), having Medicaid or Medicare insurance (70% versus 34%, P<0.001), and less likely to be diagnosed in the United States (79% versus 85%, P=0.008). Higher deprivation was associated with increasing disease severity (OR, 1.25; 95% CI, 1.08–1.46) and higher likelihood of BPG when compared with enteral penicillin prescription (OR, 0.67; 95% CI, 0.56–0.8) in models adjusted for participant sex, age at diagnosis, race, ethnicity, and insurance type (Table 7).

DISCUSSION

Through a 10-year retrospective case review, our data capture the contemporary picture of pediatric ARF and RHD in the United States. The use of primary source data, not previously employed at a national level, has allowed a more comprehensive and nuanced look at these cases. The addition of deprivation index highlights that ARF and RHD continue as diseases of health inequity, with children living in more deprived communities at increased risk of severe RHD.

Caution must be employed when interpreting the demographics of our cases. Although our sample is large, it was not collected in a representative manner and may not reflect the demographics of children with ARF/RHD living in the United States as a whole. Still, it is worth noting that there was a higher than expected percentage of children identifying as Black, or Indigenous (American Indian or Alaskan Native and Native Hawaiian or other Pacific Islander), which is consistent with previously reported increased risk for both population subgroups within the United States,[5,6] as well as the increased risk seen in Indigenous populations in Australia, New Zealand, and Canada.[19–22] Combined, these data suggest that more intensive surveillance, including active screening, could help characterize and develop plans to mitigate the risk in these vulnerable US communities.

It is also worth noting, that the majority of children diagnosed with ARF or RHD were diagnosed in the United States (>80%), spoke English as their primary language (>80%), and had health insurance (nearly

Table 4. Presentation at Diagnosis and Management

Reported Findings for Those with ARF Presentation (n=684)	
Major criteria	
Carditis	336 (49.1%)
Polyarthritis	208 (30.4%)
Sydenham chorea	254 (37.1%)
Subcutaneous nodules	24 (3.5%)
Erythema marginatum	59 (8.6%)
Minor criteria	
Fever	330 (48.2%)
Elevated C-reactive protein and/or erythrocyte sedimentation rate	315 (46.1%)
Prolonged PR interval on electrocardiogram	63 (9.2%)*
Arthralgia	131 (19.2%)†
Secondary Prophylaxis	
Prescribed secondary prophylaxis	
Yes	913 (96.4%)
No	23 (2.4%)
Unknown	11 (1.2%)
Initial antibiotic choice for secondary prophylaxis (n=913, prescribed secondary prophylaxis)	
BPG, intramuscular	527 (57.7%)
Oral penicillin	318 (34.8%)
Macrolide	24 (2.6%)
Sulfadiazine	8 (0.9%)
Other	20 (2.2%)
Unknown	16 (1.8%)
Reason for not using BPG (n=370, prescribed a known alternate)	
Patient/family preference	107 (28.9%)
Patient allergy	32 (8.6%)
Other	5 (1.4%)
Unknown	226 (61.1%)
Secondary prophylaxis prescription changed (n=913, prescribed secondary prophylaxis)	171 (18.7%)

n (%) unless otherwise indicated. ARF indicates acute rheumatic fever; and BPG, benzathine penicillin G.

*Only 16 without echocardiographic carditis counted toward ARF diagnosis.

†Without arthritis.

90%). Furthermore, 87% had no travel history to an endemic region, indicating a continued domestic burden of ARF and RHD. This has important implications for provider awareness and appropriate use of primary and secondary prevention. Additionally, the continued domestic case burden highlights that diagnosis and treatment of symptomatic streptococcal sore throat can never prevent all cases of ARF. A group A streptococcal vaccine, in contrast, could help eliminate new cases of ARF both here and around the world.[13,23,24]

This study also gives important insight into the clinical presentation of ARF and RHD in the United States. Chorea was exceedingly common in this population (37% of those presenting with ARF), as compared with the <10% to 30% of ARF cases globally,[25–33] including recent studies in the United States.[5,6] It will be important in future studies to determine if high rates of chorea reflect true distribution of ARF presentations or if more mild joint presentations are being missed, skewing the percentages higher for chorea as a primary presentation.

Another important clinical finding is that a significant number of children captured through this study presented with chronic RHD, one-quarter with severe disease, who may require cardiac catheterization or surgery in the future. Late presentation results in the missed opportunity to have maximum benefit from secondary antibiotic prophylaxis, which prevents group A streptococcal infections and recurrent ARF. Further research should be undertaken to study provider and parent awareness of ARF, as education might improve early ARF diagnosis and reduce the number of children presenting with late stage RHD.

These data highlight the successful implementation of evidence-based diagnostic recommendations for ARF and RHD in the United States. As newly recommended by the 2015 Jones criteria, children in this study were exceedingly likely to have had an echocardiogram as part of their diagnostic work-up (97%). As half of these cases predate these recommendations, high rates of echocardiography may also reflect the near universal access to echocardiography in US tertiary facilities (where case recruitment occurred). However, there was inconsistent reporting of echocardiographic findings and frequent use of nonstandardized definitions for grading severity of valvular and features of RHD. Future emphasis should be placed on standardization of echocardiographic evaluation for children with RHD including the American Society of Echocardiography and American Heart Association guidelines,[34–36] the revised Jones criteria from 2015,[26] and the 2012 World Heart Federation Guidelines for the Echocardiographic Diagnosis of Rheumatic Heart Disease[37] to allow for a unified definition and ability to compare data across countries and continents using a standardized criteria for RHD diagnosis.

There was also substantial variation from guideline-based care on the type and duration of secondary prophylaxis.[11] Despite the fact that BPG is recommended as first-line prevention, having greater efficacy than oral penicillin in preventing recurrent ARF,[12,13] only 58% of the cases was prescribed BPG. Family preference was the most common reason cited for not prescribing BPG. It is worth noting that those living in more deprived areas were more likely to be prescribed BPG than oral penicillin, perhaps perceived by clinicians to be at higher risk. Our data highlight variability in the recommended duration of secondary prevention,

Table 5. Echocardiographic Data

	All (n=947)	Acute Rheumatic Fever (n=684)	Rheumatic Heart Disease (n=258)
Echocardiogram performed	917 (96.8%)	656 (95.9%)	258 (100%)
Mitral stenosis	73 (8.0%)	24 (3.7%)	49 (19.0%)
Mild	38 (52.0%)	17 (70.8%)	21 (42.8%)
Moderate	21 (28.8%)	5 (20.8%)	16 (32.7%)
Severe	6 (8.2%)	1 (4.2%)	5 (10.2%)
Data on quantification not available	8 (11.0%)	1 (4.2%)	7 (14.3%)
Mitral regurgitation	645 (70.3%)	417 (63.6%)	228 (88.4%)
< Moderate	277 (42.9%)	206 (49.4%)	71 (31.1%)
Moderate	219 (34.0%)	137 (32.8%)	82 (36.0%)
Severe	144 (22.3%)	72 (17.3%)	72 (31.6%)
Data on quantification not available	5 (0.8%)	2 (0.5%)	3 (1.3%)
Aortic stenosis	21 (2.3%)	3 (0.5%)	18 (7.0%)
< Moderate	17 (80.9%)	2 (66.7%)	15 (83.3%)
Moderate	3 (14.3%)	1 (33.3%)	2 (11.1%)_
Severe	0 (0%)	0 (0%)	0 (0%)
Data on quantification not available	1 (4.8%)	0 (0%)	1 (5.6%)
Aortic regurgitation	352 (38.4%)	221 (33.7%)	131 (50.8%)
< Moderate	191 (54.3%)	136 (61.5%)	55 (42.0%)
Moderate	102 (29.0%)	58 (26.2%)	44 (33.6%)
Severe	55 (15.6%)	24 (10.9%)	31 (23.7%)
Data on quantification not available	4 (1.1%)	3 (1.4%)	1 (0.7%)
Pulmonary hypertension	66 (7.2%)	27 (4.1%)	39 (15.1%)
Reduced left ventricular systolic function	27 (2.9%)	10 (1.5%)	17 (6.6%)
Mildly reduced	16 (59.3%)	6 (60.0%)	10 (58.8%)
Moderately reduced	7 (25.9%)	2 (20.0%)	5 (29.4%)
Severely reduced	4 (14.8%)	2 (20.0%)	2 (11.8%)
Reduced right ventricular systolic function	9 (1.0%)	2 (0.3%)	7 (2.7%)
Pericardial effusion	81 (8.8%)	51 (7.8%)	30 (11.6%)
Trace/small	66 (87.6%)	40 (78.4%)	26 (86.7%)
Moderate	9 (6.7%)	7 (13.7%)	2 (6.7%)
Large	4 (3.8%)	3 (5.9%)	1 (3.3%)
Present but not quantified	2 (1.9%)	1 (2.0%)	1 (3.3%)

n (%) unless otherwise indicated.

with shorter than recommended[11] durations in 17% of cases based on presenting features and severity of cardiac involvement. Together, these data suggest that increased clinician and parental education is needed to ensure that children living with ARF and RHD in the United States receive guideline-based care.

Finally, these data support that RHD remains a disease characterized by inequity among children living in the United States. Greater community socioeconomic deprivation was associated with having more severe valvular involvement, which could reflect living conditions such as overcrowding, poor sanitation, and poor hygiene, which are long recognized factors that increase exposure to group A streptococcal disease.[13,38,39] It is worth noting that this finding contrasts that of a recent study on children hospitalized for ARF, finding no statistically significant differences in socioeconomic status. That study, however, was limited by its sole use of insurance status as a proxy for socioeconomic status.[5] The deprivation index provides a more multidimensional assessment of one's contextual living environment, and our conclusions support the findings that ARF and RHD outcomes remain inequitable globally and nationally.[1]

Limitations

There are several limitations in our data stemming from our pragmatic recruitment strategy based on tertiary hospital programs. First, our data may not be representative of patients and clinical practices outside of major

Table 6. Disease Severity

	Mild (n=452)	Moderate (n=188)	Severe (n=232)	*P* value
Sex				0.03
Male	245 (54.2%)	98 (52.1%)	101 (43.5%)	
Female	207 (45.8%)	90 (47.9%)	131 (56.5%)	
	N=436	N=180	N=222	
Age at diagnosis, y, median (interquartile range)	9 (7–12)	10 (8–12)	10 (7–13)	0.11
Race				<0.001
American Indian or Alaska Native	17 (3.8%)	14 (7.4%)	8 (3.4%)	
Asian	14 (3.1%)	9 (4.8%)	17 (7.3%)	
Black	58 (12.8%)	37 (19.7%)	61 (26.3%)	
Native Hawaiian or other Pacific Islander	30 (6.6%)	11 (5.9%)	24 (10.3%)	
White	235 (52.0%)	80 (42.6%)	71 (30.6%)	
Other	64 (14.2%)	23 (5.1%)	39 (16.8%)	
Unknown	34 (7.5%)	14 (7.4%)	12 (5.2%)	
Ethnicity				0.79
Hispanic or Latino	73 (16.2%)	29 (15.4%)	42 (18.1%)	
Non-Hispanic or Latino	339 (75.0%)	139 (73.9%)	172 (74.1%)	
Unknown	40 (8.8%)	20 (10.6%)	18 (7.8%)	
Primary language				0.001
English	392 (86.7%)	155 (82.4%)	183 (78.9%)	
Spanish	36 (8.0%)	20 (10.6%)	18 (7.8%)	
Other	17 (3.8%)	13 (6.9%)	28 (12.1%)	
Unknown	7 (1.5%)	0 (0%)	3 (1.3%)	
	N=436	N=176	N=226	
Has health insurance	407 (90.0%)	165 (87.8%)	206 (88.8%)	0.51
	N=399	N=170	N=222	
Type of health insurance				0.64
Private	167 (36.9%)	69 (36.7%)	79 (34.1%)	
Medicaid or Medicare	201 (44.5%)	90 (47.9%)	123 (53.0%)	
Both	2 (0.4%)	0 (0%)	0 (0%)	
Unknown	37 (8.2%)	6 (3.2%)	4 (1.7%)	
Diagnosed in the United States				0.09
Yes	381 (84.3%)	164 (87.2%)	186 (80.2%)	
No	54 (11.9%)	18 (9.6%)	38 (16.4%)	
Unknown	17 (3.8%)	6 (3.2%)	8 (3.4%)	
	N=354	N=161	N=182	
Parent primary language English	297 (65.7%)	133 (70.7%)	137 (59.1%)	0.047
Travel exposure before diagnosis				0.02
Yes	65 (14.4%)	29 (15.4%)	53 (22.8%)	
No	68 (15.0%)	32 (17.0%)	45 (19.4%)	
Unknown	319 (70.6%)	127 (67.6%)	134 (57.8%)	
Travel to endemic region	49 (10.8%)	25 (13.3%)	45 (19.4%)	0.31
Prescribed secondary prophylaxis				0.43
Yes	437 (96.7%)	181 (96.3%)	224 (96.6%)	
No	9 (2.0%)	7 (3.7%)	5 (2.2%)	
Unknown	6 (1.3%)	0 (0%)	3 (1.2%)	

(*Continued*)

Table 6. Continued

	N=430	N=180	N=221	
Initial antibiotic choice for secondary prophylaxis				0.09
BPG, intramuscular	231 (53.7%)	118 (65.5%)	142 (64.2%)	
Oral penicillin	172 (40.0%)	52 (28.9%)	67 (30.3%)	
Macrolid	10 (2.3%)	6 (3.3%)	7 (3.2%)	
Sulfadiazine	5 (1.2%)	1 (0.6%)	2 (0.9%)	
Other	12 (2.8%)	3 (1.7%)	3 (1.4%)	
	N=80	**N=27**	**N=32**	
Reason for not using BPG				0.130
Patient/family preference	62 (77.5%)	20 (74.1%)	22 (68.8%)	
Patient allergy	16 (20%)	4 (14.8%)	10 (31.2%)	
Other	2 (2.5%)	3 (11.1%)	0 (0%)	

n (%) unless otherwise indicated. BPG indicates benzathine penicillin G.

medical centers. Second, although we invited participation from all programs with a pediatric cardiology fellowship, only 37% of invited institutions participated. Although we recruited nearly 1000 patients, increasing the internal validity of our data, there were some geographic areas of our country that were not well represented, such as the West, and thus certain populations may be underrepresented or not captured. Given this, we could not compare population characteristics, such as race or ethnicity, to overall US population characteristics to confidently identify groups at higher risk.

Retrospective review of data led to several additional limitations. Data on travel to an endemic region did not include specifications on the nature of exposure (for example, limited travel exposure versus prior residence in endemic region); thus we are unable to comment on whether participants were immigrants from an endemic region or merely went to visit. We collected echocardiographic data only at presentation and are not able to comment on the longitudinal progression or regression of cardiac disease. In addition to our population limitations, DI is a measure of community-level deprivation and cannot be used to extrapolate individual risk prediction and we cannot rule out the potential for unmeasured factors to have resulted in residual confounding when estimating the association between neighborhood deprivation and outcomes of interest.

Table 7. Odds Ratios and 95% CIs for RHD Classification, Severity, and Initial Therapy According to a 1 SD Increase in the DI (n=871)

	OR (95% CI)	AOR (95% CI)
Model 1: RHD classification at presentation*	1.33 (1.14–1.54)	1.13 (0.95–1.34)
Model 2: disease severity at presentation†	1.34 (1.18–1.53)	1.25 (1.08–1.46)
Model 3: initial antibiotic therapy‡		
Macrolide	0.70 (0.45–1.09)	0.79 (0.48–.30)
None	0.88 (0.58–1.35)	0.93 (0.57–1.51)
Other	0.48 (0.28–0.84)	0.64 (0.33–1.26)
Oral penicillin	0.65 (0.56–0.76)	0.67 (0.56–0.80)
Sulfa	0.60 (0.28–1.30)	1.07 (0.43–2.64)

AOR adjusted for sex, age at diagnosis, race, ethnicity, and insurance type. Missing data imputed using n=50 imputations. SD increase in DI index is 0.147 units. AOR indicates adjusted odds ratio; CI, confidence interval; DI, deprivation index; OR, odds ratio; and RHD, rheumatic heart disease.

*OR obtained from logistic regression.

†OR obtained from ordinal regression.

‡OR obtained from multinomial logistic regression. Estimates provided for each therapy when compared with benzathine penicillin G (intramuscular penicillin).

CONCLUSIONS

ARF and RHD are characterized by equity gaps in the United States as well as around the world. Children who newly acquire ARF and RHD in the United States are, for the most part, exposed to group A streptococcal disease and experiencing the sequelae within the United States and not abroad. There is room to improve evidence-based treatment for ARF and RHD in the United States, both through provider and parent education. Further study of high-risk populations in the United States could better target these educational efforts and provide the opportunity to strengthen primary prevention for our most vulnerable children.

ARTICLE INFORMATION

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Supplementary Material

Table S1
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. Participant Enrollment by Site.

Site	Total Enrolled (n)
Duke Children's Hospital & Health Center	7
Nicklaus Children's Hospital	7
University of Florida Health, Shands Children's Hospital	11
Yale New Haven Medical Center	17
Morgan Stanley Children's Hospital of New York Presbyterian, Columbia University Medical Center	17
Nationwide Children's Hospital	19
University of Mississippi	21
Children's Mercy Hospital	23
University of Rochester Medical Center	26
University of Arkansas for Medical Sciences	31
University of New Mexico	34
Washington University School of Medicine, St. Louis	39
Ann & Robert H. Lurie Children's Hospital of Chicago	41
Monroe Carell Jr Children's Hospital at Vanderbilt	45
Children's Healthcare of Atlanta, Emory University	49
Texas Children's Hospital	52
Nemours.Alfred I. DuPont Hospital for Children	56
Children's Hospital at Montefiore	67
Boston Children's Hospital	72
Children's National Hospital	80
Cincinnati Children's Hospital Medical Center	101
Seattle Children's Hospital	132

Figure S1. Participating Sites.