ORIGINAL ARTICLE

Secondary Antibiotic Prophylaxis for Latent Rheumatic Heart Disease

Andrea Beaton, M.D., Emmy Okello, Ph.D., Joselyn Rwebembera, M.Med., Anneke Grobler, Ph.D., Daniel Engelman, Ph.D., Juliet Alepere, B.A., Lesley Canales, B.A., Jonathan Carapetis, Ph.D., Alyssa DeWyer, B.S., Peter Lwabi, M.Med., Mariana Mirabel, Ph.D., Ana O. Mocumbi, Ph.D., Meghna Murali, M.P.H., Miriam Nakitto, M.P.H., Emma Ndagire, M.Med., Maria C.P. Nunes, Ph.D., Isaac O. Omara, B.N.S., Rachel Sarnacki, B.A., Amy Scheel, B.S., Nigel Wilson, Ph.D., Meghan Zimmerman, M.D., Liesl Zühlke, Ph.D., Ganesan Karthikeyan, M.D., Craig A. Sable, M.D., and Andrew C. Steer, Ph.D.

ABSTRACT

BACKGROUND

Rheumatic heart disease affects more than 40.5 million people worldwide and results in 306,000 deaths annually. Echocardiographic screening detects rheumatic heart disease at an early, latent stage. Whether secondary antibiotic prophylaxis is effective in preventing progression of latent rheumatic heart disease is unknown.

METHODS

We conducted a randomized, controlled trial of secondary antibiotic prophylaxis in Ugandan children and adolescents 5 to 17 years of age with latent rheumatic heart disease. Participants were randomly assigned to receive either injections of penicillin G benzathine (also known as benzathine benzylpenicillin) every 4 weeks for 2 years or no prophylaxis. All the participants underwent echocardiography at baseline and at 2 years after randomization. Changes from baseline were adjudicated by a panel whose members were unaware of the trial-group assignments. The primary outcome was echocardiographic progression of latent rheumatic heart disease at 2 years.

RESULTS

Among 102,200 children and adolescents who had screening echocardiograms, 3327 were initially assessed as having latent rheumatic heart disease, and 926 of the 3327 subsequently received a definitive diagnosis on the basis of confirmatory echocardiography and were determined to be eligible for the trial. Consent or assent for participation was provided for 916 persons, and all underwent randomization; 818 participants were included in the modified intention-to-treat analysis, and 799 (97.7%) completed the trial. A total of 3 participants (0.8%) in the prophylaxis group had echocardiographic progression at 2 years, as compared with 33 (8.2%) in the control group (risk difference, –7.5 percentage points; 95% confidence interval, –10.2 to –4.7; P<0.001). Two participants in the prophylaxis group had serious adverse events that were attributable to receipt of prophylaxis, including one episode of a mild anaphylactic reaction (representing <0.1% of all administered doses of prophylaxis).

CONCLUSIONS

Among children and adolescents 5 to 17 years of age with latent rheumatic heart disease, secondary antibiotic prophylaxis reduced the risk of disease progression at 2 years. Further research is needed before the implementation of population-level screening can be recommended. (Funded by the Thrasher Research Fund and others; GOAL ClinicalTrials.gov number, NCT03346525.)

The authors' affiliations are listed in the Appendix. Dr. Beaton can be contacted at andrea.beaton@cchmc.org or at Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave., Cincinnati, OH 45229.

Drs. Beaton and Okello contributed equally to this article.

This article was published on November 13, 2021, at NEJM.org.

N Engl J Med 2022;386:230-40.
DOI: 10.1056/NEJMoa2102074

Rheumatic heart disease is a chronic valvular heart disease caused by rheumatic fever, which develops after untreated *Streptococcus pyogenes* infection.[1] More than 40.5 million people worldwide are estimated to be living with rheumatic heart disease, and approximately 306,000 deaths from rheumatic heart disease occur annually.[2]

Secondary antibiotic prophylaxis is the cornerstone of management of rheumatic fever and rheumatic heart disease.[3] Intramuscular penicillin G benzathine (also known as benzathine benzylpenicillin) has been found to be more effective than oral antibiotic agents in preventing streptococcal pharyngitis, and its use is associated with a lower incidence of recurrence of rheumatic fever.[4] Studies of rheumatic fever cohorts suggest that prophylaxis allows for regression of valvular damage[5,6] and may prevent death from rheumatic heart disease.[7]

However, rheumatic fever is diagnosed infrequently in low-resource settings for several reasons, including limited health-seeking behavior, varied presentations, and overlap with other common illnesses, such as malaria and viral infections.[8] Rather, most patients receive the diagnosis of rheumatic heart disease when the disease is advanced and complications have developed.[9] Late diagnosis is associated with high mortality at a young age,[9] in part owing to the missed opportunity to benefit from prophylaxis. If patients can be identified early, the period between initial valvular damage and clinical disease affords an opportunity for intervention and improved outcomes.

Latent rheumatic heart disease, which is a relatively new concept, is detected by means of screening surveys that involve echocardiography.[10,11] Children with latent rheumatic heart disease have mild valvular changes that do not cause symptoms and are often clinically undetectable. A systematic review and meta-analysis of studies across several continents showed a worldwide pooled prevalence of latent rheumatic heart disease of 1.3%.[12] In 2012, standardized criteria for the diagnosis of latent rheumatic heart disease were established; these criteria included categories of borderline disease and definite disease for persons younger than 20 years of age.[13]

In order to justify echocardiographic screening, evidence that secondary prophylaxis improves outcomes for children and adolescents with latent rheumatic heart disease is needed. Despite dozens of published studies on echocardiographic screening, such data are lacking. In the absence of evidence, practice varies from provision of prophylaxis to active surveillance.[14-16] To address this knowledge gap, we conducted a trial in Northern Uganda referred to as Gwoko Adunu pa Lutino (GOAL), meaning "protect the heart of a child."

A Quick Take is available at NEJM.org

METHODS

DESIGN AND OVERSIGHT

We conducted a randomized, controlled trial to evaluate secondary prophylaxis with intramuscular penicillin G benzathine, as compared with no prophylaxis, in Ugandan children and adolescents with latent rheumatic heart disease. The trial was conducted in Gulu, Uganda, from July 2018 through October 2020.[17] Details of the trial design are described in the protocol, available with the full text of this article at NEJM.org.

The trial was approved by the institutional review board at Makerere University School of Medicine and at Children's National Medical Center, with additional approvals from the Uganda National Council for Science and Technology and the National Drug Authority in Uganda, and was conducted in accordance with Good Clinical Practice guidelines.[18] A seven-member advisory board was involved in the design of the trial and provided oversight during the conduct of the trial. We held two general community engagement meetings and two focus groups to develop plans for recruitment, consent or assent, and retention. Parents or guardians provided written informed consent, and assent was obtained from children and adolescents older than 7 years of age.[17]

TRIAL POPULATION

Primary and secondary schools in Gulu and surrounding districts were selected for screening (Fig. 1). Children and adolescents 5 to 17 years of age were invited to participate. Participants with abnormal screening echocardiograms were referred for clinical evaluation and detailed echocardiography (Vivid q or Vivid iq [General Electric]). Participants who had a new diagnosis of latent rheumatic heart disease were approached for inclusion in the trial. Participants with moderate or severe disease[19] were not eligible for the trial; however, prophylactic treatment was initi-

Figure 1. GOAL Trial Site in Northern Uganda.

Shown is the location of the GOAL trial site in the Gulu District (region 1), as well as the surrounding districts in which additional participants were residing (the Pader District [region 2], the Oyam District [region 3], the Nwoya District [region 4], and the Amuru District [region 5]).

ated, and the participants were referred for ongoing follow-up, in accordance with standard recommendations. Participants were also excluded if they had a history of rheumatic fever, rheumatic heart disease, or other structural or functional heart disease; had a known penicillin allergy; had a predisposition to bleeding; or were receiving prophylaxis with an antibiotic for other indications. A second round of exclusion occurred after randomization, when a consensus panel adjudicated the confirmatory echocardiograms that had been obtained at enrollment; details of this process are described below.

RANDOMIZATION

Participants were stratified at enrollment according to 2012 World Heart Federation category,[13] and randomization was performed in permuted blocks, with participants assigned in equal numbers to either the prophylaxis group or the control group. The randomization scheme was designed by an independent statistician and embedded within the randomization module of REDCap, a Web-based electronic data capture system.[17,20] Two designated members of the research staff enrolled participants after consent or assent was obtained, at which time the trial-group assignment was revealed automatically.

INTERVENTION

Participants in the prophylaxis group received intramuscular penicillin G benzathine every 4 weeks for 2 years (a total of 26 injections), with an acceptable window of 24 to 32 days between injections. Injections of penicillin G benzathine were administered by trial staff who were trained in best practices.[21] Participants in the control group received no prophylaxis and no placebo.[17]

A case-management and peer-group strategy that has been described previously[17] was used to maximize retention of participants in both groups. (Details regarding the strategies used to retain participants in the trial and to achieve high adherence to the injections are provided in the Supplementary Appendix, available at NEJM.org.) With the onset of the coronavirus disease 2019 (Covid-19) pandemic in Uganda in March 2020, peer-group meetings halted, and administration of prophylaxis shifted to community health centers that were supported by GOAL staff. During this period, participants in the control group received telephone calls from their case managers twice monthly but were not seen in person.

OUTCOMES

The primary outcome was echocardiographic progression of latent rheumatic heart disease at 2 years.[13] All the participants underwent standard echocardiography (during which 15 images were obtained) at enrollment and at 2 years (trial completion). We assembled a four-member consensus panel to evaluate and classify echocardiograms at both time points on the basis of the 2012 World Heart Federation criteria.[22] The echocardiograms obtained at enrollment and at 2 years were presented side by side to the panel, with random right or left display. The members of the panel, who were unaware of the trial-group assignments and the timing of the echocardiograms, determined whether the images were "the same," "right worse," or "left worse," according to strict definitions (see the Supplementary Appendix).[13] These data were subsequently unblinded by a single research coordinator and

categorized as progression, regression, or no change. The secondary outcome was echocardiographic regression of latent rheumatic heart disease at 2 years.

ADVERSE EVENTS

Adverse events were recorded for participants in the prophylaxis group. These data were collected on a monthly basis through interviews with participants and parents and with the use of a standard checklist. Participants in whom a penicillin allergy or anaphylaxis developed received care in accordance with standard guidelines,[23,24] and prophylaxis in these participants was changed to oral erythromycin (250 mg twice daily). All the participants in both trial groups underwent limited echocardiography at 13 months to monitor for the development of moderate or severe rheumatic heart disease; clinical care was adjusted as needed for any participants who had such progression of disease. Participants in the control group who had a midtrial echocardiogram that showed moderate or severe disease began receiving prophylaxis with penicillin G benzathine every 4 weeks; however, the final echocardiograms that were obtained at 2 years were still presented in a blinded fashion to the consensus panel for determination of outcome.[25] An independent data and safety monitoring board oversaw the safety of the trial.

STATISTICAL ANALYSIS

On the basis of previous natural-history cohorts, we estimated that progression would occur in 7.5 to 12.5% of the participants in the prophylaxis group and in 15 to 25% of the participants in the control group over the course of 2 years.[11,26] To determine an appropriate sample size, we used the lowest percentages within these ranges in each trial group (7.5% and 15%, respectively). We estimated that a total sample of 916 participants would provide the trial with 90% power to detect a significant difference in the primary outcome between the trial groups at a two-sided alpha level of 0.05, using a chi-square test. This calculation was based on an estimated 20% attrition, including 10% from the initial echocardiographic adjudication and 10% for other reasons.

Efficacy was evaluated in the modified intention-to-treat population, which included all children and adolescents who had undergone randomization, who had been assessed on the basis of the consensus-panel adjudication of baseline echocardiograms as having borderline or definite disease, and who had final echocardiograms at 2 years. The percentages of participants who had echocardiographic progression or regression, along with 95% confidence intervals, were calculated for each group. These percentages were compared between the groups with the use of a generalized linear model with an identity link and binomial distribution; adjustment was made for the baseline disease category (borderline or definite) to estimate the differences between the groups. We also determined risk ratios, which we adjusted for baseline disease category using a generalized linear model. Analyses of the primary and secondary outcomes were planned to be performed with the use of multiple imputation if more than 10% of the data were missing.

We performed one subgroup analysis of the primary and secondary outcomes to assess whether baseline disease category (borderline disease or definite disease) influenced the effectiveness of the prophylaxis, using the same generalized linear model as that described above, with baseline disease category included as an interaction term. The widths of the confidence intervals were not adjusted for multiple comparisons, so the intervals should not be used to infer definitive treatment effects for the subgroup analysis or for the analysis of the secondary outcome.

RESULTS

TRIAL POPULATION

A total of 102,200 children and adolescents 5 to 17 years of age had screening echocardiograms. On the basis of these echocardiograms, 3327 children and adolescents were initially assessed as having latent rheumatic heart disease; 926 of the 3327 subsequently received a positive diagnosis on the basis of confirmatory echocardiography and were determined to be eligible for the trial. Of these 926 persons, 10 declined to participate. After consent or assent to participate was obtained for each of the remaining 916 persons, all underwent randomization (Fig. 2). The consensus panel review of the confirmatory echocardiograms that had been obtained at enrollment led to the exclusion of 98 participants (10.7%) owing to reclassification (77 as normal, 15 as alternative diagnosis, and 6 as moderate or

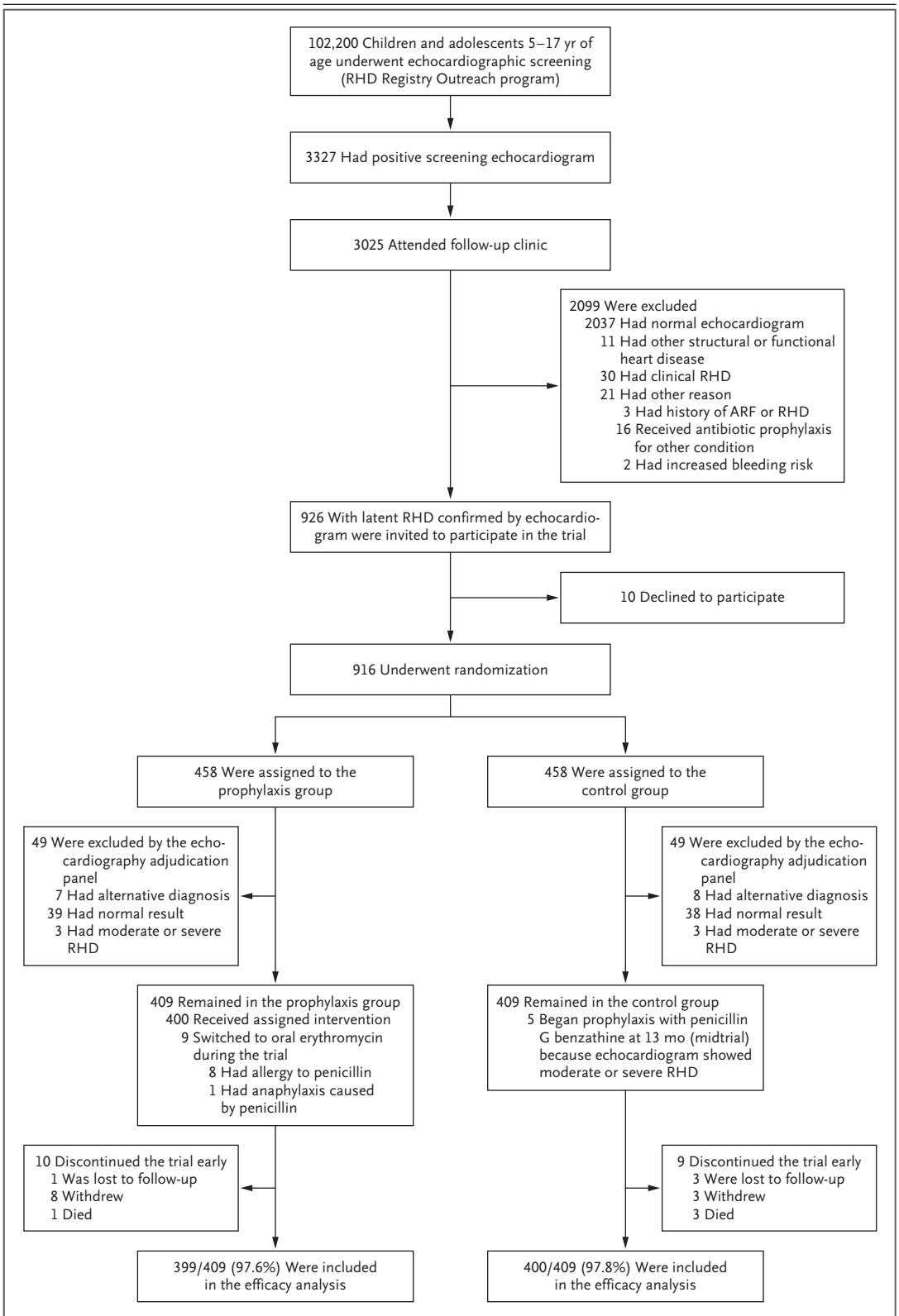

Figure 2. Enrollment, Randomization, and Follow-up.

ARF denotes acute rheumatic fever, and RHD rheumatic heart disease.

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Variable	Prophylaxis (N = 409)	Control (N = 409)
Rheumatic heart disease category — no. (%)†		
Borderline	328 (80.2)	339 (82.9)
Definite	81 (19.8)	70 (17.1)
Age at enrollment — yr		
Mean	12.6±2.8	12.5±2.9
Distribution — no. (%)		
<12	156 (38.1)	159 (38.9)
≥12	253 (61.9)	250 (61.1)
Sex — no. (%)		
Male	176 (43.0)	188 (46.0)
Female	233 (57.0)	221 (54.0)
Type of housing — no. (%)		
Permanent	75 (18.3)	88 (21.5)
Semipermanent	333 (81.4)	315 (77.0)
Data missing	1 (0.2)	6 (1.5)
Median duration of maternal education (IQR) — yr	5 (3–7)	5 (3–7)
No. of persons living in household	7.9±3.5	7.9±3.2
No. of persons <15 yr of age living in household	3.7±2.0	3.8±1.8
Type of school — no. (%)		
Day	357 (87.3)	356 (87.0)
Boarding	52 (12.7)	52 (12.7)
Data missing	0	1 (0.2)
WAMI index‡	0.3±0.1	0.3±0.1
Sore throat reported in previous 4 wk — no. (%)	78 (19.1)	67 (16.4)
Skin infection reported in previous 4 wk — no. (%)	26 (6.4)	26 (6.4)
At least 1 first-degree family member with previous diagnosis of acute rheumatic fever — no. (%)	5 (1.2)	6 (1.5)
At least 1 first-degree family member with previous diagnosis of rheumatic heart disease — no. (%)	12 (2.9)	7 (1.7)

* Plus–minus values are means ±SD. IQR denotes interquartile range. Percentages may not total 100 because of rounding.

† The category was determined by a four-member consensus panel on the basis of the 2012 World Heart Federation criteria.[22]

‡ The WAMI (water and sanitation, assets, maternal education, and household income) index[13] is a measure of socioeconomic status; scores range from 0 to 1, with lower scores indicating worse status.

severe disease). The remaining 818 participants (409 in each group) composed the modified intention-to-treat population. Sociodemographic and clinical variables at baseline were similar in the two groups (Table 1).

A total of 799 participants (97.7%) completed the trial: 399 in the prophylaxis group and 400 in the control group. Among the 19 participants (2.3%) who discontinued the trial early, 4 were lost to follow-up, 11 requested withdrawal from the trial, and 4 died from non–trial-related causes (Fig. 2).

Among the 399 participants in the prophylaxis group who were included in the modified intention-to-treat analyses and who completed the trial, a total of 10,284 of the 10,374 scheduled injections (99.1%) were administered, with 10,250 (98.8%) given within the acceptable window. Of the 90 missed injections, 77 were missed at the onset of the Covid-19 pandemic,

Table 2. Effect of Trial Group on Progression and Regression of Latent Rheumatic Heart Disease at 2 Years.*

Outcome	Prophylaxis (N=399)	Control (N=400)	Risk Difference (95% CI)	P Value	Risk Ratio (95% CI)
			percentage points		
Progression — no. (% [95% CI])	3 (0.8 [0.2 to 2.3])	33 (8.2 [5.9 to 11.4])	−7.5 (−10.2 to −4.7)	<0.001	0.09 (0.03 to 0.29)
Regression — no. (% [95% CI])	195 (48.9 [44.0 to 53.8])	191 (47.8 [42.9 to 52.7])	1.5 (−5.4 to 8.4)		1.03 (0.89 to 1.19)

* A total of 799 participants (399 in the prophylaxis group and 400 in the control group) completed the trial and had data available for the primary and secondary outcomes. Our statistical analysis plan specified that we would perform analyses of the primary and secondary outcomes using multiple imputation to adjust for the effect of missing data if more than 10% of the data were missing. Since only 3% of the data from the primary outcome assessments were missing, we analyzed the observed data, which led to the exclusion of participants with missing data. The risk difference and risk ratio were adjusted for rheumatic heart disease category, which was determined by the consensus panel at baseline. The widths of the confidence intervals have not been adjusted for multiple comparisons, so the intervals should not be used to infer definitive treatment effects.

when all transportation was abruptly halted. Among all the participants in the modified intention-to-treat population, antistreptococcal antibiotic use for indications other than latent rheumatic heart disease was similar in the two groups; 252 participants (61.6%) in the prophylaxis group received 579 courses of treatment, and 230 participants (56.2%) in the control group received 571 courses. No episodes of suspected rheumatic fever were identified.

PRIMARY OUTCOME

In total, 3 of 399 (0.8%) participants in the prophylaxis group had echocardiographic progression of latent rheumatic heart disease at 2 years, as compared with 33 of 400 (8.2%) participants in the control group (risk difference, −7.5 percentage points; 95% confidence interval [CI], −10.2 to −4.7; P<0.001) (Table 2). Among the participants who had progression, 3 of 3 (100.0%) in the prophylaxis group and 16 of 33 (48.5%) in the control group had progression to moderate or severe rheumatic heart disease. The number of children or adolescents with latent rheumatic heart disease who would need to receive prophylaxis to prevent 1 child or adolescent from having progression was 13 (95% CI, 10 to 21).

SECONDARY OUTCOME

A total of 195 participants (48.9%) in the prophylaxis group and 191 participants (47.8%) in the control group had echocardiographic regression of latent rheumatic heart disease at 2 years (risk difference, 1.5 percentage points; 95% CI, −5.4 to 8.4) (Table 2). Among the 386 participants who had regression, 363 (94.0%) had a normal echocardiogram at the end of the trial.

In a subgroup analysis of the primary and secondary outcomes among participants who had had definite latent rheumatic heart disease at baseline, 2 of 81 participants (2.5%) in the prophylaxis group had echocardiographic progression at 2 years, as compared with 8 of 67 participants (11.9%) in the control group (risk difference, −9.5 percentage points; 95% CI, −17.9 to −1.0). Among the participants who had had borderline latent rheumatic heart disease at baseline, 1 of 318 (0.3%) in the prophylaxis group had echocardiographic progression at 2 years, as compared with 25 of 333 (7.5%) in the control group (risk difference, −7.2 percentage points; 95% CI, −10.1 to −4.3) (Table S5 in the Supplementary Appendix).

SAFETY OUTCOMES

Adverse events reported in the prophylaxis group are summarized in Table 3. Two participants had serious adverse events that were attributable to receipt of prophylaxis. In 1 of these participants (0.2% of the participants in the prophylaxis group, which represents <0.1% of the injections administered), symptoms of anaphylaxis (chest tightness and shortness of breath) developed 3 minutes after the injection of penicillin G benzathine; the symptoms resolved with a single intramuscular dose of epinephrine. The other participant had a sciatic nerve injury with paresthesia that ameliorated over the course of several months.

In total, 290 participants (63.3%) in the pro-

Table 3. Adverse Events in the Prophylaxis Group.*

Adverse Event	Any Grade		Grade 3 or 4	
	no. of participants (%)	*no. of events*	*no. of participants (%)*	*no. of events*
Any adverse event	296 (64.6)	828	6 (1.3)	6
Pain, limp, or swelling	236 (51.5)	575	3 (0.7)	3
Pain	220 (48.0)	508	3 (0.7)	3
Limp	99 (21.6)	140	2 (0.4)	2
Swelling	139 (30.3)	265	1 (0.2)	1
Skin rash or hives	68 (14.8)	77	1 (0.2)	1
Redness, bruising, or bleeding	14 (3.1)	17	0	0
Redness	2 (0.4)	2	0	0
Bruising	0	0	0	0
Bleeding	11 (2.4)	12	0	0
Other	95 (20.7)	159	2 (0.4)	2

* Data are reported for all 458 participants who were randomly assigned to the prophylaxis group. Individual participants could be counted in more than one adverse event category. Adverse events were classified as follows: grade 1, is present but manageable; grade 2, interferes with daily activities; grade 3, prevents the ability to participate in daily activities; or grade 4, is life-threatening or persistent or causes significant disability or incapacity. In this trial, all adverse events of grade 4 were considered to be serious adverse events. Among the adverse events of grade 1 or 2, eight (1.7% of the participants in the prophylaxis group) were allergic reactions to penicillin G benzathine. Among the adverse events of grade 3 or 4, the two events classified as "other" were serious adverse events of grade 4 (anaphylaxis and sciatic nerve injury, occurring in one participant each).

phylaxis group reported 823 mild adverse events that occurred after injection, including pain, limp, and localized leg swelling. Eight participants (1.7%) had a delayed hypersensitivity rash associated with penicillin G benzathine; prophylaxis in these participants was subsequently changed to erythromycin. Under the assumption of zero adverse events in the control group (data in the control group not collected in this trial), the number of children or adolescents with latent rheumatic heart disease who would need to receive prophylaxis to cause harm ranged from 77 (95% CI, 43 to 372) (if only adverse events of grade 3 or 4 were included in the calculation) to 2 (95% CI, 1 to 2) (if all grades of events, the majority of which were minor pain, limp, or swelling at the injection site, were included).

Five participants in the control group were found to have moderate or severe rheumatic heart disease on the basis of the midtrial echocardiograms, and prophylaxis was initiated in these participants. Four participants died from non–trial-related causes during the trial period (1 in the prophylaxis group and 3 in the control group). Details are provided in the Supplementary Appendix.

DISCUSSION

This randomized trial investigated the effectiveness of secondary antibiotic prophylaxis in modifying the natural history of latent rheumatic heart disease. We observed a significant reduction in the risk of disease progression in the prophylaxis group. Across both groups, more than half the participants who had progression had moderate or severe rheumatic heart disease at the end of the trial, a finding that suggests important clinical and public health implications. Antibiotic prophylaxis did not significantly reduce the risk of disease regression.

Preventing the development of severe rheumatic heart disease is important because severe valve dysfunction is largely untreatable by medical management.[27] The question of whether echocardiographic screening should be implemented in children and adolescents has been discussed by the rheumatic heart disease research community on the basis of population-

screening criteria developed by the World Health Organization and the Council of Europe and remains controversial.[28-31] Factors in support of screening include the obvious burden of disease, a detectable latent phase, and the availability of a suitable screening test.[23] Results from this trial showed that prophylaxis with penicillin G benzathine every 4 weeks for 2 years can reduce the risk of progression of latent disease, a finding that provides new evidence in favor of screening.

Among the more than 100,000 children and adolescents who underwent screening echocardiography in this trial, approximately 900 were identified as being eligible for the trial; this indicates that more than 100 persons would need to be screened to identify 1 person eligible for the intervention studied. The overall incidence of progression was lower than anticipated, a result that may reflect the rigorous conditions of our trial, as compared with the observational natural-history data that informed our assumptions. Specifically, we used strict inclusion criteria that excluded children or adolescents with more advanced latent forms of rheumatic heart disease, and we used robust criteria for defining progression.

We estimated that 13 children or adolescents with latent rheumatic heart disease would need to be treated to prevent disease progression in 1 person at 2 years. In general, an acceptable number of persons who would need to be treated for prevention of disease varies, based on the severity of the condition to be prevented and the risk and burden of the intervention.[32] In low-resource settings, symptomatic rheumatic heart disease has an annual case fatality rate approaching 10%.[9] Although mild adverse events were common in our trial, serious adverse events attributable to secondary antibiotic prophylaxis occurred in 1 in 200 participants and anaphylaxis occurred in 1 in 10,000 injections, consistent with previously reported international data.[13]

However, these trial data alone are not sufficient justification for adoption of a screening policy. A number of barriers to achieving high adherence in a real-world setting exist, including a lack of retention in care, a lack of availability of medication, a lack of access to transportation, social stigma, pain associated with intramuscular injection, and a limited understanding of the disease, and these factors are largely unaccounted for in a clinical trial setting.[33,34] Furthermore, fear of serious adverse events and death contributes to the reluctance of health care workers and patients to consider the use of secondary prophylaxis,[35] and increasing the number of children and adolescents receiving antibiotic prophylaxis arouses concern about worsening community antibiotic resistance. Although such resistance is not an issue for the causative agent of rheumatic heart disease (given that *S. pyogenes* remains universally susceptible to penicillin), the resistance of other bacteria could be affected.[36] We think that this risk is relatively low, since penicillin is a narrow-spectrum antibiotic and the number of children and adolescents with latent rheumatic heart disease is small. In order to effectively scale secondary prophylaxis, these practical challenges need to be better understood and addressed.

There are also critical health system issues to consider before implementation of a population-based screening strategy. Screening, diagnosis, clinical follow-up, treatment, and program management require substantial strengthening of health systems and the workforce.[37-39] Our trial involved highly specialized interpretation of echocardiographic imaging, as well as skilled staff to administer injections of secondary antibiotic prophylaxis. At scale, it is likely that health care personnel with less training would implement screening activities and prophylaxis administration, which could increase the likelihood of misdiagnosis and related adverse events, respectively. Furthermore, retention in care of patients with rheumatic heart disease is critical to achieving adequate treatment adherence,[40] and the highly successful strategies used in our trial (e.g., the use of peer groups and case managers, as well as reimbursement of travel expenses) would be challenging and expensive to implement at scale. Both of these issues could be compounded by the longer duration of clinical follow-up required (typically at least 5 years as compared with our 2-year research end point).

The secondary outcome of this trial was echocardiographic regression of latent rheumatic heart disease, which occurred in nearly half the participants in both trial groups. Although the percentage of participants who had regression was higher than anticipated, it is not entirely unexpected.[41] Rheumatic heart disease, even in its classic form after the occurrence of rheumatic fever, follows a heterogeneous course.[42]

However, the high incidence of regression seen in this trial arouses the concern that if screening in children and adolescents were adopted, a proportion of those treated would not be expected to benefit. Further study is needed to determine the efficacy, outcomes, and cost-effectiveness of alternative approaches, including secondary prophylaxis with oral penicillin and regular echocardiographic follow-up to monitor for progression in persons not receiving prophylaxis.

Initial regression may not imply lifelong protection. Rheumatic fever or progression of rheumatic heart disease may develop later in some children and adolescents.[42] Further research is needed to identify subcategories of latent rheumatic heart disease that may pose a higher risk to children and adolescents than other subcategories and to refine recommendations for the duration of prophylaxis, including the safety of discontinuing prophylaxis in persons with normalization of echocardiographic findings.

In the GOAL trial, secondary antibiotic prophylaxis reduced the risk of progression of latent rheumatic heart disease in children and adolescents. Although further research is needed to assess real-world implementation, population-based screening and initiation of prophylaxis may eventually prove to be integral components of the National Rheumatic Heart Disease action plans envisioned by the World Health Assembly in 2017 in a resolution on rheumatic heart disease.[43]

Supported by the Thrasher Research Fund, Gift of Life International, Children's National Hospital Foundation (Zachary Blumenfeld Fund and Race for Every Child [Team Jocelyn]), the Elias–Ginsburg Family, Wiley Rein, Philips Foundation, AT&T Foundation, Heart Healers International, the Karp Family Foundation, Huron Philanthropies, and the Cincinnati Children's Hospital Heart Institute Research Core.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

This article is dedicated to the late Professor Bongani Mayosi, an original investigator of the GOAL trial. Professor Mayosi was a mentor, colleague, and friend who inspired and guided rheumatic heart disease research as part of his life's work toward a more equitable future for Africa and the world.

APPENDIX

The authors' affiliations are as follows: Cincinnati Children's Hospital Medical Center, and the Department of Pediatrics, University of Cincinnati School of Medicine — both in Cincinnati (A.B.); Uganda Heart Institute (E.O., J.R., J.A., P.L., M.N., E.N., I.O.O.), and the Department of Medicine, Makerere University (E.O.) — both in Kampala, Uganda; Children's National Hospital, Washington, DC (L.C., M. Murali, R.S., C.A.S.); Murdoch Children's Research Institute (A.G., D.E., A.C.S.), and Melbourne Children's Global Health, Royal Children's Hospital (D.E., A.C.S.), Melbourne, and Telethon Kids Institute, Perth Children's Hospital, University of Western Australia, Perth (J.C.) — all in Australia; Virginia Tech Carilion School of Medicine, Roanoke, VA (A.D.W.); Assistance Publique–Hôpitaux de Paris, Université de Paris, and Cardio-Oncologie, Hôpital Européen Georges-Pompidou — both in Paris (M. Mirabel); Instituto Nacional de Saúde, Maputo, Mozambique (A.O.M.); Universidade Federal de Minas Gerais, Belo Horizonte, Brazil (M.C.P.N.); Emory University School of Medicine, Atlanta (A.S.); Green Lane Paediatric and Congenital Cardiac Service, Starship Children's Hospital, Auckland, New Zealand (N.W.); Geisel School of Medicine, Dartmouth–Hitchcock Medical Center, Lebanon, NH (M.Z.); the Division of Paediatric Cardiology, Department of Paediatrics, Red Cross War Memorial Children's Hospital, and the Division of Cardiology, Department of Medicine, Groote Schuur Hospital — both in Cape Town, South Africa (L.Z.); and All India Institute of Medical Sciences, New Delhi, India (G.K.).

REFERENCES

1. Carapetis JR, Beaton A, Cunningham MW, et al. Acute rheumatic fever and rheumatic heart disease. Nat Rev Dis Primers 2016;2:15084.
2. Roth GA, Mensah GA, Johnson CO, et al. Global burden of cardiovascular diseases and risk factors. 1990–2019: update from the GBD 2019 study. J Am Coll Cardiol 2020;76:2982-3021.
3. Gewitz MH, Baltimore RS, Tani LY, et al. Revision of the Jones criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: a scientific statement from the American Heart Association. Circulation 2015;131:1806-18.
4. Spinetto H, Lennon D, Horsburgh M. Rheumatic fever recurrence prevention: a nurse-led programme of 28-day penicillin in an area of high endemnicity. J Paediatr Child Health 2011;47:228-34.
5. Stollerman GH, Rusoff JH, Hirschfeld I. Prophylaxis against group A streptococci in rheumatic fever — the use of single monthly injections of benzathine penicillin G. N Engl J Med 1955;252:787-92.
6. Tompkins DG, Boxerbaum B, Liebman J. Long-term prognosis of rheumatic fever patients receiving regular intramuscular benzathine penicillin. Circulation 1972;45:543-51.
7. Majeed HA, Batnager S, Yousof AM, Khuffash F, Yusuf AR. Acute rheumatic fever and the evolution of rheumatic heart disease: a prospective 12 year follow-up report. J Clin Epidemiol 1992;45:871-5.
8. Karthikeyan G, Guilherme L. Acute rheumatic fever. Lancet 2018;392:161-74.
9. Zühlke L, Karthikeyan G, Engel ME, et al. Clinical outcomes in 3343 children and adults with rheumatic heart disease from 14 low- and middle-income countries: two-year follow-up of the Global Rheumatic Heart Disease Registry (the REMEDY study). Circulation 2016;134:1456-66.
10. Marijon E, Ou P, Celermajer DS, et al. Prevalence of rheumatic heart disease detected by echocardiographic screening. N Engl J Med 2007;357:470-6.
11. Beaton A, Okello E, Aliku T, et al. Latent rheumatic heart disease: outcomes 2 years after echocardiographic detection. Pediatr Cardiol 2014;35:1259-67.
12. Rothenbühler M, O'Sullivan CJ, Stortecky S, et al. Active surveillance for rheumatic heart disease in endemic regions: a systematic review and meta-analysis of prevalence among children and adolescents. Lancet Glob Health 2014;2(12):e717-e726.

13. Reményi B, Wilson N, Steer A, et al. World Heart Federation criteria for echocardiographic diagnosis of rheumatic heart disease — an evidence-based guideline. Nat Rev Cardiol 2012;9:297-309.
14. Bacquelin R, Tafflet M, Rouchon B, et al. Echocardiography-based screening for rheumatic heart disease: what does borderline mean? Int J Cardiol 2016;203:1003-4.
15. Karthikeyan G. Measuring and reporting disease progression in subclinical rheumatic heart disease. Heart Asia 2016;8:74-5.
16. Saxena A, Zühlke L, Wilson N. Echocardiographic screening for rheumatic heart disease: issues for the cardiology community. Glob Heart 2013;8:197-202.
17. Beaton A, Okello E, Engelman D, et al. Determining the impact of benzathine penicillin G prophylaxis in children with latent rheumatic heart disease (GOAL trial): study protocol for a randomized controlled trial. Am Heart J 2019;215:95-105.
18. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:c332.
19. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63(22):e57-e185.
20. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) — a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377-81.
21. Russell K, Nicholson R, Naidu R. Reducing the pain of intramuscular benzathine penicillin injections in the rheumatic fever population of Counties Manukau District Health Board. J Paediatr Child Health 2014;50:112-7.
22. Scheel A, Mirabel M, Nunes MCP, et al. The inter-rater reliability and individual reviewer performance of the 2012 World Heart Federation guidelines for the echocardiographic diagnosis of latent rheumatic heart disease. Int J Cardiol 2021;328:146-51.
23. Simons FE, Ebisawa M, Sanchez-Borges M, et al. 2015 update of the evidence base: World Allergy Organization anaphylaxis guidelines. World Allergy Organ J 2015;8:32.
24. Banks TA, Tucker M, Macy E. Evaluating penicillin allergies without skin testing. Curr Allergy Asthma Rep 2019;19:27.
25. Gerber MA, Baltimore RS, Eaton CB, et al. Prevention of rheumatic fever and diagnosis and treatment of acute Streptococcal pharyngitis: a scientific statement from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, the Interdisciplinary Council on Functional Genomics and Translational Biology, and the Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. Circulation 2009;119:1541-51.
26. Engelman D, Mataika RL, Ah Kee M, et al. Clinical outcomes for young people with screening-detected and clinically-diagnosed rheumatic heart disease in Fiji. Int J Cardiol 2017;240:422-7.
27. Kumar RK, Antunes MJ, Beaton A, et al. Contemporary diagnosis and management of rheumatic heart disease: implications for closing the gap: a scientific statement from the American Heart Association. Circulation 2020;142(20):e337-e357.
28. Zühlke L, Mayosi BM. Echocardiographic screening for subclinical rheumatic heart disease remains a research tool pending studies of impact on prognosis. Curr Cardiol Rep 2013;15:343.
29. Zühlke LJ, Beaton A, Engel ME, et al. Group A streptococcus, acute rheumatic fever and rheumatic heart disease: epidemiology and clinical considerations. Curr Treat Options Cardiovasc Med 2017;19:15.
30. Recommendation no. R (94) 11 on screening as a tool of preventative medicine. In: Text of the Council of Europe on Bioethical Matters. Vol 1. Strasbourg, France: Council of Europe, 2014:49-54.
31. Roberts K, Colquhoun S, Steer A, Reményi B, Carapetis J. Screening for rheumatic heart disease: current approaches and controversies. Nat Rev Cardiol 2013;10:49-58.
32. Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. BMJ 1995;310:452-4.
33. Kevat PM, Reeves BM, Ruben AR, Gunnarsson R. Adherence to secondary prophylaxis for acute rheumatic fever and rheumatic heart disease: a systematic review. Curr Cardiol Rev 2017;13:155-66.
34. Engelman D, Ah Kee M, Mataika RL, et al. Secondary prevention for screening detected rheumatic heart disease: opportunities to improve adherence. Trans R Soc Trop Med Hyg 2017;111:154-62.
35. Marantelli S, Hand R, Carapetis J, Beaton A, Wyber R. Severe adverse events following benzathine penicillin G injection for rheumatic heart disease prophylaxis: cardiac compromise more likely than anaphylaxis. Heart Asia 2019;11(2):e011191.
36. Steer A, Danchin M. Primary prevention of rheumatic fever in children: key factors to consider. S Afr Med J 2014;104:156-7.
37. Saxena A. Task shifting rheumatic heart disease screening to non-experts. Lancet Glob Health 2016;4(6):e349-e350.
38. Nascimento BR, Beaton AZ, Nunes MC, et al. Echocardiographic prevalence of rheumatic heart disease in Brazilian schoolchildren: data from the PROVAR study. Int J Cardiol 2016;219:439-45.
39. Engelman D, Kado JH, Reményi B, et al. Focused cardiac ultrasound screening for rheumatic heart disease by briefly trained health workers: a study of diagnostic accuracy. Lancet Glob Health 2016;4(6):e386-e394.
40. Longenecker CT, Morris SR, Aliku TO, et al. Rheumatic heart disease treatment cascade in Uganda. Circ Cardiovasc Qual Outcomes 2017;10(11):e004037.
41. Zühlke L, Engel ME, Lemmer CE, et al. The natural history of latent rheumatic heart disease in a 5 year follow-up study: a prospective observational study. BMC Cardiovasc Disord 2016;16:46.
42. Bland EF, Duckett Jones T. Rheumatic fever and rheumatic heart disease: a twenty year report on 1000 patients followed since childhood. Circulation 1951;4:836-43.
43. Executive Board, 141st session: resolutions and decisions, annexes, summary records. Geneva: World Health Organization, 2017 (https://apps.who.int/iris/bitstream/handle/10665/272288/B141_REC1-en.pdf?sequence=1&isAllowed=y).