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Mass Treatment with Single-Dose Azithromycin for Yaws

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ABSTRACT

BACKGROUND

Mass treatment with azithromycin is a central component of the new World Health Organization (WHO) strategy to eradicate yaws. Empirical data on the effectiveness of the strategy are required as a prerequisite for worldwide implementation of the plan.

METHODS

We performed repeated clinical surveys for active yaws, serologic surveys for latent yaws, and molecular analyses to determine the cause of skin ulcers and identify macrolide-resistant mutations before and 6 and 12 months after mass treatment with azithromycin on a Papua New Guinean island on which yaws was endemic. Primary-outcome indicators were the prevalence of serologically confirmed active infectious yaws in the entire population and the prevalence of latent yaws with high-titer seroreactivity in a subgroup of children 1 to 15 years of age.

RESULTS

At baseline, 13,302 of 16,092 residents (82.7%) received one oral dose of azithromycin. The prevalence of active infectious yaws was reduced from 2.4% before mass treatment to 0.3% at 12 months (difference, 2.1 percentage points; P<0.001). The prevalence of high-titer latent yaws among children was reduced from 18.3% to 6.5% (difference, 11.8 percentage points; P<0.001) with a near-absence of high-titer seroreactivity in children 1 to 5 years of age. Adverse events identified within 1 week after administration of the medication occurred in approximately 17% of the participants, included nausea, diarrhea, and vomiting, and were mild in severity. No evidence of emergence of resistance to macrolides against *Treponema pallidum* subspecies *pertenue* was seen.

CONCLUSIONS

The prevalence of active and latent yaws infection fell rapidly and substantially 12 months after high-coverage mass treatment with azithromycin, with the reduction perhaps aided by subsequent activities to identify and treat new cases of yaws. Our results support the WHO strategy for the eradication of yaws. (Funded by Newcrest Mining and International SOS; YESA-13 ClinicalTrials.gov number, NCT01955252.)

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Yaws, an infectious disease caused by *Treponema pallidum* subspecies *pertenue*, affects mainly children in poor rural communities in tropical countries. This bacterium is transmitted by direct skin-to-skin, nonsexual contact and causes a chronic, relapsing disease that is characterized by highly contagious primary and secondary cutaneous lesions and by noncontagious tertiary destructive lesions of the bones.[1] Cases are reported currently in 12 countries in Africa, Asia, and the western Pacific region, and 42 million people are estimated to be at risk for yaws.[2]

A major campaign in the 1950s and 1960s to eradicate yaws by means of community-wide treatment with long-acting, injectable penicillin reduced the number of cases of the disease by 95% worldwide; however, yaws was not eradicated.[3] The discovery that a single dose of oral azithromycin is at least as effective as injectable penicillin G benzathine[4] prompted the World Health Organization (WHO) to develop a new azithromycin-based treatment policy in 2012 (the Morges strategy).[5] The recommendation is initial mass treatment of the entire population (often called total community treatment) with a single dose of oral azithromycin, followed by resurveys every 6 months in a targeted treatment program to detect and treat newly identified persons with active yaws and their contacts.

A Quick Take animation is available at NEJM.org

The Morges strategy has several advantages over previous campaigns, including oral versus parenteral administration of the drug[6] and mass treatment regardless of prevalence of yaws in the community versus selective treatment of active cases, without treatment of latent cases, which can develop into infectious yaws lesions.[7,8] In earlier campaigns, it was neglect of latent infection that resulted in the rapid return of the disease.[9] This risk is greatly reduced by the new mass treatment recommendation.[10,11]

Empirical data on the effectiveness of the Morges strategy to stop the transmission of yaws in a geographically defined area are required as a prerequisite for worldwide implementation of the plan. Data to determine the burden of yaws in a community include the prevalence of active infectious yaws (i.e., skin ulcers or papilloma) and the prevalence of seroreactivity among patients without active yaws; these data indicate, respectively, the extent to which yaws transmission is occurring and the extent of the latent or hidden infection in the community.[12] We used clinical surveys, serologic surveys, and etiologic studies of skin ulcers to measure the effect of mass azithromycin treatment on the community burden of yaws.

Methods

Study Setting and Participants

From April 2013 through May 2014, we conducted a longitudinal study in all the villages of Lihir Island, New Ireland Province, Papua New Guinea. Lihir Island consists of 28 villages with a range of 400 to 600 inhabitants each, and the estimated population in 2013 was 16,092 according to a regularly updated census. All the villages have been reported to have a relatively high prevalence of active yaws (range, 0.5 to 3.8%),[13] and mass treatment with azithromycin had never been attempted before our baseline surveys. An increased number of active yaws cases is observed during the wet season (January through June).

The implementation of the Morges elimination strategy in the villages started after baseline assessment surveys, in accordance with standards advocated by the WHO.[5] During the initial mass treatment program, everyone older than 2 months of age in the study villages was offered azithromycin (Medopharm) at a single oral dose of 30 mg per kilogram of body weight, up to a maximum dose of 2 g. Pregnant women and people with a known allergy to macrolides were offered penicillin G benzathine at a dose of 50,000 U per kilogram, administered intramuscularly. The WHO provided generic azithromycin, which was purchased at full cost from Medopharm.

The initial mass treatment program was followed every 6 months by a targeted treatment program, in which surveys were performed that consisted of clinical examination of the resident population, with treatment of all persons with active clinical cases and their contacts (household members, classmates, and playmates). Between those surveys, patients with active yaws who presented to a health care facility (passive case finding) and their close contacts were treated.

Treatment was provided without cost to the study participants. Passive surveillance for adverse events was undertaken throughout the study at the Lihir Medical Center and all peripheral health posts. Specific training for health

care staff was conducted before the interventions began, with a special emphasis on reporting any allergic event or any other adverse event that was deemed to be possibly related to the intervention, with the use of a standard case-report form for adverse events. We also performed household surveys 1 week after the initial distribution of the antibiotic agents to monitor for potential adverse events in 60 randomly selected households from 28 villages.

All the participants, or their parent or guardian, provided oral informed consent for screening and treatment. In addition, we obtained written informed consent from persons with suspected active yaws before their enrollment in clinical surveys and etiologic studies of ulcers and from parents or guardians of children recruited for serologic surveys; we obtained verbal agreement from the children. The study protocol was approved by the Medical Research Advisory Committee of the Papua New Guinea National Department of Health (approval number, 12.36). Full details of the study conduct are provided in the protocol, available with the full text of this article at NEJM.org. The sponsors of the study had no role in the design of the study, the collection, analysis, or interpretation of the data, or the writing of the manuscript. The first author had full access to all the study data and had the final responsibility for the decision to submit the manuscript for publication.

PROCEDURES

Primary-outcome indicators were the prevalence of serologically confirmed active infectious yaws in the entire population and the prevalence of latent yaws with high-titer seroreactivity (rapid plasma reagin [RPR], ≥1:16) in a subgroup of children 1 to 15 years of age, at baseline and at 6 and 12 months. Secondary-outcome indicators included the proportion of ulcers caused by *T. pallidum* subspecies *pertenue*, as assessed with the use of a polymerase-chain-reaction (PCR) assay, and the proportion of yaws samples with genetic mutations associated with macrolide resistance at each time point.

Clinical surveys for active infectious yaws lesions were undertaken in the entire resident population. Active yaws is usually a visible disease; hence clinical surveys provide useful knowledge. We undertook screening examination of all the villagers, using the WHO yaws-pictorial guide.[14] A clinical diagnosis of active infectious lesions was based on chronic (symptomatic for >2 weeks) solitary or multiple ulcers or papillomas (Fig. S1 and S2 in the Supplementary Appendix, available at NEJM.org).[15] Serologic confirmation of treponemal infection with the use of a *T. pallidum* hemagglutination assay (TPHA) and RPR testing was performed in persons with active lesions. In resurveys at 6 and 12 months, persons with new cases of active yaws were classified as absentees from initial treatment surveys; previously untreated visitors, returning laborers, or migrants with clinically active lesions; or previously treated local residents. For previously treated persons, we performed a meticulous inquiry to find the source of reinfection.

Serologic screening to detect latent yaws was conducted in a subgroup of asymptomatic children 1 to 15 years of age in six randomly selected villages (chosen with the use of computer-generated random numbers). Because the random sample was regenerated at each survey, villages might have been chosen repeatedly. The age criteria for inclusion in the serologic surveys were intended to reduce the likelihood of reactive serologic findings related to venereal syphilis. Venous blood samples were obtained from assenting children for TPHA and qualitative and quantitative RPR testing.

All asymptomatic children with a reactive TPHA and an RPR titer of at least 1:2 were classified as having latent yaws; those with a high RPR titer (≥1:16) were classified as having high-titer latent yaws. Children with latent yaws with high titers would be more likely than those with low titers to have a clinical reactivation with active lesions.[9] We classified asymptomatic children according to age (1 to 5 years vs. 6 to 15 years). Seroreactivity in young children (1 to 5 years of age) can indicate recent infection, because these children are new entrants in the potential pool of susceptible persons. The WHO criteria to certify the interruption of transmission include no young children with RPR seroreactivity and no new cases of active yaws for 3 consecutive years.[5]

All serologic tests for syphilis were performed at the Lihir Medical Center laboratory, with external quality-control testing (i.e., 5% of positive and negative samples) performed at Sullivan Nicolaides Pathology in Queensland, Australia. The laboratory scientists were unaware of the antibiotic coverage and clinical outcomes.

PCR surveillance was performed by analysis of swabs obtained during clinical surveys from each participant with papillomatous or ulcerative lesions. The PCR methods have been described previously.[16] After every survey, we forwarded 90 randomly selected specimens to the laboratory at the University of Washington, Seattle, for molecular testing with the use of PCR to detect *T. pallidum* DNA,[17-19] a molecular signature specific to subspecies *pertenue* (confirming yaws infection),[19] evidence of mutations conferring resistance to azithromycin,[20] and *Haemophilus ducreyi* DNA, which may coexist with yaws as a cause of skin ulcers.[16]

STATISTICAL ANALYSIS

We double-entered data in Access software, version 14.0 (Microsoft), with discrepancies checked against original forms. Using Stata software, version 13.1 (StataCorp), we calculated the prevalence of active yaws, assessing everyone in the study population at three time points. We estimated the prevalence of latent yaws in subgroups of children in randomly selected villages. We calculated that a sample of 875 children would provide the study with 80% power to estimate the prevalence of high-titer latent yaws with a precision of 1.5%, at a two-sided significance level of 5%. We assumed that the prevalence of high-titer latent yaws at 12 months would be 5%.[10] We estimated that this sample size would provide the study with 100% power to detect a prevalence difference of 11.8 percentage points between baseline and the 12-month follow-up.

We estimated the prevalence ratio for the comparison of active and latent yaws at three time points using a log-binomial regression model. We evaluated the decline in the prevalence of PCR-detected infection over time using a multinomial logistic-regression model. A P value of less than 0.05 was considered to indicate statistical significance. All P values are two-sided.

RESULTS

STUDY POPULATION

At baseline, we examined 13,490 of the 16,092 residents (83.8%). Of the 13,490 participants examined, 13,302 received azithromycin, 177 received penicillin G benzathine, and 11 declined treatment. Treatment with oral drugs was observed directly. The overall rate of treatment coverage during the mass treatment program was 83.8%, and all the study villages had a coverage rate of more than 70.0%.

No severe adverse events attributable to the study drug were reported by means of passive surveillance during the study. Active surveillance of 316 participants from 60 households yielded 54 participants (17.1%) who reported adverse events (all mild), including 30 (9.5%) with nausea or abdominal pain, 25 (7.9%) with diarrhea, and 15 (4.7%) with vomiting (Table S1 in the Supplementary Appendix).

Coverage rates of screening for active cases during the targeted treatment program in 28 villages were 81.8% at 6 months and 82.2% at 12 months. The most common reasons for absence during treatment and follow-up were travel and work.

CHANGES IN THE PREVALENCE OF ACTIVE DISEASE

The prevalence of infectious active yaws fell from 2.4% at baseline to 0.3% at 6 months and remained at 0.3% at 12 months (difference from baseline, 2.1 percentage points; 95% confidence interval [CI], 1.9 to 2.4; P<0.001) (Table 1). In all the surveys, the community burden of yaws-

Table 1. Prevalence of Clinically Active Yaws.

Time Point	No. of Persons Examined	Serologically Confirmed Active Yaws		Clinically Suspected Lesions with Negative Serologic Findings	
		No. of Persons (%)	Prevalence Ratio (95% CI)*	No. of Persons (%)	Prevalence Ratio (95% CI)*
Baseline	13,490	323 (2.4)	1.00	367 (2.7)	1.00
6 mo	13,166	44 (0.3)	0.14 (0.10–0.19)	77 (0.6)	0.22 (0.17–0.27)
12 mo	13,204	34 (0.3)	0.11 (0.08–0.15)	82 (0.6)	0.23 (0.18–0.29)

* The prevalence ratio was calculated by means of the log-binomial regression model. The baseline prevalence is the reference value. P<0.001 for the comparison with baseline.

related ulcers was disproportionately borne by children 15 years of age or younger (Fig. 1). Similarly, there was a decline in the proportion of participants with clinically suspicious lesions and negative serologic findings, with significant reductions from 2.7% at baseline to 0.6% at 12 months (difference, 2.1 percentage points; 95% CI, 1.8 to 2.4; P<0.001). Because *H. ducreyi* is also a major pathogen in skin ulcers on Lihir Island,[17] mass treatment probably also reduced the burden of lesions caused by *H. ducreyi*.

Most active cases of yaws that were identified at resurveys occurred in local residents who had been absent from initial treatment surveys: 33 of 44 cases (75.0%) at 6 months, and 21 of 34 (61.8%) at 12 months. Some yaws lesions occurred in nontreated visitors or migrants: 2 cases (4.5%) at 6 months, and 4 (11.8%) at 12 months. A total of 9 cases of ulcers (20.5%) at 6 months and 9 (26.5%) at 12 months occurred in previously treated long-term residents of Lihir Island. Of these 18 cases, 11 could be traced directly to contact with infectious visitors or untreated local residents (i.e., probable reinfection), but no source of reinfection was found in 7 cases that could have been due to a relapse of an inadequately treated latent infection.

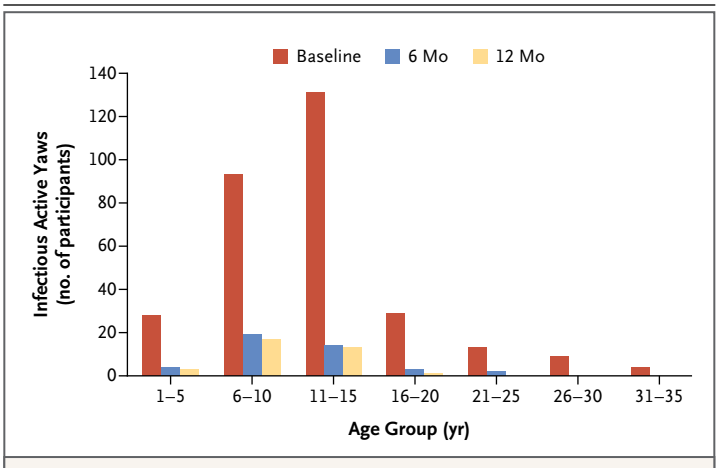

Figure 1. Prevalence of Active Disease over Time in Various Age Groups.

CHANGES IN THE PREVALENCE OF LATENT YAWS

Table 2 shows cross-sectional surveys for latent yaws in asymptomatic children from randomly selected villages. At baseline, we obtained blood samples from 991 children; 874 children were tested at 6 months, and 910 were tested at 12 months. The mean (±SD) ages of the children were 10.4±3.6 years, 10.4±3.2 years, and 10.0±3.7 years at the baseline, 6-month, and 12-month surveys, respectively. No significant differences were seen in the ratio of boys to girls at the three time points.

The prevalence of high-titer latent yaws decreased from 18.3% at baseline to 6.5% at 12 months (difference, 11.8 percentage points; 95% CI, 8.9 to 14.7; P<0.001) (Table 2), with major declines in titer from 6 to 12 months. This result suggests that decreases in titer require a prolonged time after treatment. We also noted a significant reduction in the prevalence of all seropositive results, from 32.8% at baseline to 16.4% at 12 months (difference, 16.4 percentage points; 95% CI, 12.6 to 20.2; P<0.001).

In subgroup analyses, the prevalence of high-titer seropositivity in the group of children 1 to 5 years of age fell significantly, from 13.7% at

Table 2. Prevalence of Latent Yaws.

Time Point	No. of Children Tested	All Cases of Latent Yaws*		High-Titer Latent Yaws†	
		No. of Children (%)	Prevalence Ratio (95% CI)‡	No. of Children (%)	Prevalence Ratio (95% CI)‡
Baseline	991	325 (32.8)	1.00	181 (18.3)	1.00
6 mo	874	261 (29.9)	0.91 (0.80–1.04)	123 (14.1)	0.77 (0.62–0.95)
12 mo	910	149 (16.4)	0.50 (0.42–0.59)	59 (6.5)	0.36 (0.27–0.47)

* The analysis included all seropositive children with a reactive result on the *Treponema pallidum* hemagglutination assay (TPHA) and with a rapid plasma reagin (RPR) titer of at least 1:2.
† The analysis included children with a reactive result on the TPHA and with an RPR titer of at least 1:16.
‡ The prevalence ratio was calculated with the use of a log-binomial regression model. The baseline prevalence is the reference value. P<0.001 for the comparison with baseline.

Table 3. Subgroup Analyses of the Prevalence of Latent Yaws.

Time Point	Children 1–5 Yr of Age					Children 6–15 Yr of Age				
	No. of Children Tested	All Cases of Latent Yaws*		High-Titer Latent Yaws†		No. of Children Tested	All Cases of Latent Yaws*		High-Titer Latent Yaws†	
		no. of children (%)	*prevalence ratio (95% CI)‡§*	*no. of children (%)*	*prevalence ratio (95% CI)‡¶*		*no. of children (%)*	*prevalence ratio (95% CI)‡‖*	*no. of children (%)*	*prevalence ratio (95% CI)‡‖*
Baseline	117	26 (22.2)	1.00	16 (13.7)	1.00	874	299 (34.2)	1.00	165 (18.9)	1.00
6 mo	77	10 (13.0)	0.58 (0.30–1.14)	6 (7.8)	0.57 (0.23–1.39)	797	251 (31.5)	0.92 (0.80–1.06)	117 (14.7)	0.78 (0.63–0.97)
12 mo	114	6 (5.3)	0.24 (0.10–0.55)	1 (0.9)	0.06 (0.01–0.48)	796	143 (18.0)	0.53 (0.44–0.63)	58 (7.3)	0.39 (0.29–0.51)

* The analysis included all seropositive children with a reactive TPHA and RPR titer of at least 1:2.
† The analysis included children with a reactive TPHA and RPR titer of at least 1:16.
‡ The prevalence ratio was calculated with the use of a log-binomial regression model. The baseline prevalence is the reference value.
§ P=0.003 for the comparison with baseline.
¶ P=0.02 for the comparison with baseline.
‖ P<0.001 for the comparison with baseline.

baseline to 0.9% at 12 months (difference, 12.8 percentage points; 95% CI, 6.3 to 19.3; P=0.02). The change in prevalence in the group of children 6 to 15 years of age was also significant (difference, 11.6 percentage points; 95% CI, 8.4 to 14.8; P<0.001) (Table 3).

PROPORTION OF PCR-CONFIRMED ULCERS DUE TO YAWS

PCR analyses of lesion swabs to detect *T. pallidum* subspecies *pertenue* and *H. ducreyi* DNA were available for 90 participants at baseline, for 84 at 6 months, and for 114 at 12 months. A bacterial cause was identified in 73 participants (81.1%) at baseline, in 73 (86.9%) at 6 months, and in 72 (63.2%) at 12 months. Overall, 70 of 288 people (24.3%) who were tested in the three rounds had a negative result on all molecular tests.

At baseline, *T. pallidum* subspecies *pertenue* alone was identified in 19 of 90 participants (21.1%), *H. ducreyi* alone in 42 (46.7%), and coinfection with both organisms in 12 (13.3%), as reported previously.[16] Although the prevalence of active lesions due to any cause was greatly reduced 6 months after treatment, the proportion of patients with lesions due to yaws did not decrease significantly, as compared with baseline, and the proportion of patients with dual infection increased (Table 4). However, at 12 months, there was a significant reduction in the proportion of ulcers containing either *T. pallidum* subspecies *pertenue* alone (risk difference, 10.6 percentage points; 95% CI, 0.4 to 20.7; P=0.04) or coinfection (risk difference, 7.2 percentage points; 95% CI, –1.1 to 15.5; P=0.08), whereas the proportion of ulcers containing *H. ducreyi* alone

Table 4. Results of Polymerase-Chain-Reaction Assay of Lesion Swabs.*

Time Point	Participants Tested	*Treponema pallidum* Subspecies *pertenue* Only Detected	Dual Infection Detected	*Haemophilus ducreyi* Only Detected	Negative in All Tests
	no.	*no. of participants (%)*			
Baseline	90	19 (21.1)	12 (13.3)	42 (46.7)	17 (18.9)
6 mo	84	14 (16.7)	27 (32.1)	32 (38.1)	11 (13.1)
12 mo	114	12 (10.5)	7 (6.1)	53 (46.5)	42 (36.8)

* P<0.001 by the chi-square test for the between-group comparison within each type of infection.

remained at a level similar to the baseline level (risk difference, 0.1 percentage points; 95% CI, –13.6 to 14.0; P=0.98). At all the time points, clusters of *T. pallidum* subspecies *pertenue* were identified among family members.

All 91 confirmed specimens for yaws in the three surveys were positive for several different *T. pallidum* gene targets and had a *tprL* molecular signature that identified them as subspecies *pertenue*. All *T. pallidum* samples obtained before and after mass treatment had wild-type 23S ribosomal DNA findings at positions 2058 and 2059, a finding that is consistent with susceptibility to azithromycin.

DISCUSSION

Our study showed that one round of mass treatment with azithromycin greatly reduced the transmission and endemicity of yaws in Papua New Guinean villages that had high baseline rates of infection. Implementation of the WHO strategy reduced clinical manifestations (ulcers and papillomas) by 90%, thus reducing the likelihood of transmission of infection to susceptible (uninfected) persons. This hypothesis is supported by the near-absence of high-titer seroreactivity among children 1 to 5 years of age (with seroreactivity in these young children indicating relatively recent infection) and by reductions in the proportion of skin ulcers attributable to yaws (confirmed by means of species-specific PCR assay). The intervention also reduced the proportion of seropositive persons, who may be at risk for clinical reactivation, and there was no evidence of resistance to azithromycin after mass treatment. These results support the use of the Morges strategy for the elimination of yaws.

However, our findings suggest that 80% population coverage in mass treatment is not sufficient to extinguish local transmission, findings that highlight the importance of WHO recommendations of nearly 100% coverage during initial mass treatment and implementation of subsequent resurveys to detect and treat residual cases. The number and frequency of resurveys that are necessary to achieve elimination is unknown. Monitoring will be needed until no more cases of active yaws are found and serologic tests among children 1 to 5 years of age prove negative.

Our study has several limitations. First, there was no untreated control group. Although a cluster-randomized trial design would have provided stronger evidence of effect, we can reasonably assume that the decrease in transmission and endemicity of yaws is attributable to mass treatment with an antibiotic agent. Second, the effect of rainfall on the prevalence of active yaws has been well documented, and this effect may have biased our results.[21] However, both the baseline survey and the 12-month survey were conducted during the wet season, and there was a decline in active yaws cases between these two surveys. Finally, elimination of disease is generally easier to accomplish on islands than in contiguous communities, which raises questions regarding the generalizability of our findings. Records show more than 1000 visitors per month between the mainland and Lihir Island, but the risk of local transmission from imported cases is low because staff at rural health facilities have been carefully trained to recognize yaws lesions. Periodic resurveys must be maintained, however, to consolidate the achievements of mass treatment and to ensure the elimination of yaws.

In summary, we observed a sustained quantitative reduction in the prevalence of yaws that was most likely due to mass treatment with azithromycin. In addition, macrolide resistance in *T. pallidum* subspecies *pertenue* was monitored, and no emergence of common resistance mutations was seen; however, close monitoring is required both for the emergence of resistance mutations in yaws and for the effect of macrolide resistance on other colonizing flora. Although the reintroduction of infection is a potential risk, the magnitude of this risk depends on the adequacy of surveillance. Our findings provide evidence of the effectiveness of the WHO strategy regarding yaws. If this strategy is similarly effective in other communities, if a high level of awareness among health workers and the populations is maintained, and if political and financial commitments are forthcoming, the control and potential eradication of yaws may be attainable.

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

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