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MAJOR ARTICLE

A Cluster-Randomized Trial to Assess the Efficacy of Targeting Trachoma Treatment to Children

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Background. The World Health Organization recommends annual treatment of entire trachoma-endemic communities, although children typically have a higher load, longer duration, and greater likelihood of infection.

Methods. Forty-eight communities in Matameye, Niger, were randomized to annual oral azithromycin treatment of the entire community or biannual treatment of children aged 0–12 years only. Both children and adults were monitored for ocular chlamydial infection by polymerase chain reaction.

Results. The prevalence of childhood infection was reduced in the annually treated arm from 21.2% (95% confidence interval [CI], 15.2%–28.0%) at baseline to 5.8% (95% CI, 3.2%–9.0%) at 36 months ($P < .001$) and in the biannual arm from 20.2% (95% CI, 15.5%–25.3%) to 3.8% (95% CI, 2.2%–6.0%; $P < .001$). Adult infection in the annual arm was reduced from 1.7% (95% CI, .9%–2.7%) to 0.3% (95% CI, .0%–.7%) and in the biannual arm from 1.2% (95% CI, .5%–2.2%) to 0.0% (95% CI, .0%–.7%; $P = .005$). The effect of biannual treatment of children compared with annual treatment of the entire community in both children (95% CI, –.04% to .02%) and adults (95% CI, .9%–2.7%) excluded the prespecified noninferiority threshold of 6% ($P = .003$ and $P < .001$, respectively).

Conclusions. Periodic distribution of antibiotics to children in trachoma-endemic communities reduces chlamydial infection in both children and untreated adults, suggesting a form of herd protection. Biannual treatment of children was comparable to (specifically, noninferior to) annual treatment of the entire community, and may offer lower antibiotic use and other logistical advantages.

Clinical Trials Registration. NCT00792922.

Keywords. trachoma; chlamydia; mass drug administration; cluster-randomized trial.

Trachoma-control programs distribute oral azithromycin to treat the ocular strains of chlamydia that cause the blinding disease [1]. As it is difficult, or even impossible, to precisely determine which individuals are infected, the World Health Organization (WHO) recommends treating the entire community when >10% of children have clinical signs of trachoma. In most settings, the prevalence is highest in children, and the majority of adults do not harbor chlamydia [2]. Mathematical models suggest that children could form a core group for the transmission of infection—that is, infection would not persist indefinitely in the community if children were effectively removed from transmission by vaccination or periodic antibiotics [3–5]. Recent empirical studies have shown that periodic mass treatment of children can reduce the prevalence of infection in adults who were not treated, at least over the course of a year [6]. If children do form a core group for transmission, then programs of longer duration might progressively reduce and eliminate infection, even in untreated adults.

Antibiotic distributions can cause adverse events, select for antibiotic resistance, and consume valuable resources. Gastrointestinal side effects are common, but typically mild. No azithromycin-resistant chlamydia has yet been documented in trachoma programs [7–10], although mass azithromycin distributions do select for macrolide-resistant strains of pneumococcus. Mathematical models have estimated that in moderately affected areas, treating children twice per year could eliminate infection, and empirical studies have suggested this may reduce costs [11]. Reducing the proportion of the community that receives treatment could be justified if similar control of trachoma could be obtained. Here, we assess whether the prevalence of ocular chlamydial infection in adults decreases when children alone are periodically treated with oral azithromycin, and compare this to the current WHO

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recommendation of annual treatment of the entire community for 3 years. As trachoma programs target the community rather than the individual, we randomize intervention at the community level.

METHODS

Study Setting and Design

The Partnership for the Rapid Elimination of Trachoma (PRET) was a set of cluster-randomized clinical trials in Tanzania, The Gambia, and Niger (ClinicalTrials.gov identifier NCT00792922) [12–14]. From May 2010 to August 2013, the Niger trial enrolled participants in the Matameye District, Zinder Region, Niger. Forty-eight grappes (smallest government health unit) from 6 Centres de Santé Intégrées (CSIs) were included; in this manuscript each grappe is termed a community.

Community Randomization

Communities were eligible for the study if they had a population between 250 and 600 at the most recent government census (72 of 235 communities in the Zinder Region). Prior to mass antibiotic treatment, a door-to-door census was conducted in 8 communities per CSI. A random sample of 100 children aged 0–60 months was drawn from the census and assessed for active trachoma according to the WHO simplified grading system (trachomatous inflammation–follicular [TF] and/or trachomatous inflammation–intense [TI]) [15, 16]. Communities with <10% prevalence of active trachoma among sampled children were excluded, in which case another community from the CSI was censused and monitored for trachoma until each CSI had 8 enrolled communities [16]. To account for community-level predictors in study arms, we utilized stratified blocked randomization of communities within each CSI by high or low clinical trachoma prevalence in children. Communities within a CSI were ranked by clinical trachoma among children; those above the median were designated high prevalence and those below, low prevalence. Communities were randomized in a 2 × 2 factorial design to assess the effects of (1) standard (~80%) and enhanced (>90%) coverage, and (2) annual treatment of all ages vs biannual treatment of individuals aged ≤12 years. Individuals were randomly selected for trachoma monitoring [15]. One author (T. C. P.) used the statistical package R (version 2.12; R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org) to generate the random allocation sequence of communities [15].

Communities randomized to annual treatment received 3 rounds of mass azithromycin treatment, whereas those randomized to biannual treatment received 6 rounds. In annually treated communities, study participants aged ≥6 months received a directly observed dose of oral azithromycin (20 mg/kg up to a maximum dose of 1 g in adults). In biannually treated communities, only study participants aged 6 months to 12 years were offered treatment. In all communities, children <6 months of age were offered topical tetracycline ointment (1%) to be applied to both eyes twice a day for 6 weeks. Pregnant women (annual arm) and those allergic to macrolides (both arms) were also offered topical tetracycline.

Clinical and Laboratory Assessments

Communities were censused annually. From the most recent PRET study census for trachoma monitoring, we randomly selected 100 children aged 0–5 years (or all children if <100) and 40 individuals aged ≥15 years. Children were examined according to the WHO simplified grading system as previously described [15, 16]. The right and left upper tarsal conjunctiva was everted and the right conjunctiva was swabbed for the presence of chlamydial DNA. In both arms, childhood examinations and swabs were biannual, while adult swabs were at baseline, 6, 12, and 36 months by design. Swabs were collected without media and transported to the University of California, San Francisco (UCSF) and stored at −80°. Swabs were pooled within a community and age group into pools of 5 plus a remainder pool. The pool was processed for chlamydia with Amplicor polymerase chain reaction (PCR) testing (F. Hoffmann-La Roche AG, Basel), and the prevalence of infection estimated from the pooled results as described previously [17]. In communities where >80% of pools were positive, all samples were then processed individually for a more accurate community prevalence.

Statistical Methods

Both arms showed very few events (infections) for adults at all time points and children posttreatment. Our prespecified analytic plan mandated adjusting for baseline prevalence, and using the square root transformed prevalence (due to the relatively heavy tail expected, with many communities having low or no infection and occasional communities having considerably more infection). A noninferiority margin of 6% was prespecified; we fail to find evidence of noninferiority if the confidence interval (CI) includes values ≥6% in difference. Given the binary outcome variable, we used a Monte Carlo version of the shift-alternative procedure. In this procedure, we add additional cases to the treatment arm with a specified probability, and conduct the hypothesis test on this augmented data set [18]. As more and more cases are added to the treatment arm, rejection of the null hypothesis becomes more and more likely. Similarly, we added additional cases to the control arm and repeated the procedure. We approximated the shift in each direction needed to reject the null hypothesis with an expected P value of .025 (for a total α of .05). The analysis

was conducted at the community level using the square root of the prevalence, including as covariates baseline prevalence, an indicator for enhanced vs standard coverage, and an indicator for frequency and targeting (children every 6 months vs community every year).

We estimated that 48 communities (24 communities per arm) would provide >80% power to detect an absolute difference of 6% in the prevalence of infection in children, assuming a standard deviation in the community-level prevalence of 5%. The primary analysis was a comparison of the prevalence of chlamydia in children between the 2 arms. Other prespecified outcomes include comparison of the prevalence of infection in adults between the 2 arms and between baseline and 36-month visits.

Data and Safety Monitoring Committee

Although no formal efficacy or futility stopping rules were prespecified in this trial, a data and safety monitoring committee met annually to review results and serious adverse events.

Ethics Statement

We acquired ethical approval from the UCSF Committee for Human Research and the Comité d'Ethique du Niger (Ethical Committee of Niger). This study was registered at ClinicalTrials.gov (NCT00792922) and implemented in accordance with the Declaration of Helsinki. Given the high rates of illiteracy in the study area, both institutional review boards approved the obtaining of verbal consent from each local community chief before randomization and verbal consent of each individual's or guardian's consent prior to the examination.

RESULTS

The 24 annually treated communities had a mean number of 136 children (range, 59–485) aged 0–12 years and the 24 biannually treated communities had a mean of 146 children (range, 44–580) (Figure 1). Age and sex of children examined were similar between arms at baseline, as were the prevalence of clinical activity and infection (Table 1). The antibiotic coverage obtained at each visit is displayed for children aged 0–12 years and adults >12 years (Table 2).

Childhood infection was reduced in the annually treated arm from 21.2% (95% confidence interval [CI], 15.2%–28.0%) at baseline to 5.8% (95% CI, 3.2%–9.0%) at 36 months ($P < .001$), and in the biannually treated arm from 20.2% (95% CI, 15.5%–25.3%) to 3.8% (95% CI, 2.2%–6.0%; $P < .001$) (Figure 2A and 2B). Note that the majority of any impact on infection occurred after the first treatment. After adjusting for infection at baseline, ocular chlamydial infection at 36 months was 0.2% higher in the biannually treated group than the annually treated group (95% CI, 4.0% lower to 2.0% higher); the 6% noninferiority threshold could be excluded ($P = .003$). Adult infection in the annually treated arm was reduced from 1.7% (95% CI, .9%–2.7%) to 0.3% (95% CI, .0%–.7%; $P < .001$) and in the biannually treated arm from 1.2% (95% CI, .5%–2.2%) to 0.0% (95% CI, .0%–.7%; $P = .005$) (Figure 3A and 3B). The difference between the arms was not significant (95% CI, –.02% to .03%), and the 6% noninferiority threshold could be excluded ($P < .001$).

Childhood clinical activity (TF) was reduced in the annually treated arm from 27.7% (22.0%–34.1%) at baseline to 8.0% (5.0%–11.6%) at 36 months ($P < .001$), and in the biannually treated arm from 24.3% (20.0%–29.7%) to 7.8% (5.3%–11.4%; $P < .001$) (Figure 4A and 4B). No significant difference was found between the 2 arms at 36 months ($P = .67$).

DISCUSSION

Biannual treatment of children aged ≤12 years achieved similar results to the WHO-recommended annual treatment of all individuals in the community. The prevalence of infection in children was reduced >4-fold over 36 months in both biannually and annually treated communities. At 36 months, we were unable to identify infection in adults in the biannually treated communities, even though the adults themselves were not treated. The low baseline prevalence of infection identified in adults (1.2%) and the significantly lower prevalence (0.0%) at 36 months suggests that excellent results are possible even without treating adults, at least in areas with a similar baseline prevalence of trachoma. Treating children can often be logistically easier than treating adults, as children are typically at home or in school during distribution hours. Thus, targeting children may be an attractive alternative to programs wishing to conserve resources while achieving similar results [11].

Mathematical models have suggested that complete elimination can be achieved with periodic antibiotic treatment, even with an imperfect antibiotic and incomplete coverage of the community with an imperfect antibiotic [3]. Previous empirical studies conducted in severely affected communities have confirmed this [19, 20]. In 2 different studies, infants aged <1 year had a significant decrease in ocular chlamydial infection, though they themselves had not received treatment [21, 22]. In several other communities, elimination of infection was achieved with imperfect coverage [19, 20, 23]. Taken together, these lines of evidence suggest that targeting treatment to a relatively small core group most likely to be infected is an effective strategy for reducing ocular chlamydial infection in the entire community.

This study demonstrated a reduction in ocular chlamydia among untreated individuals of the biannually treated group, supporting the hypothesis that repeated mass azithromycin

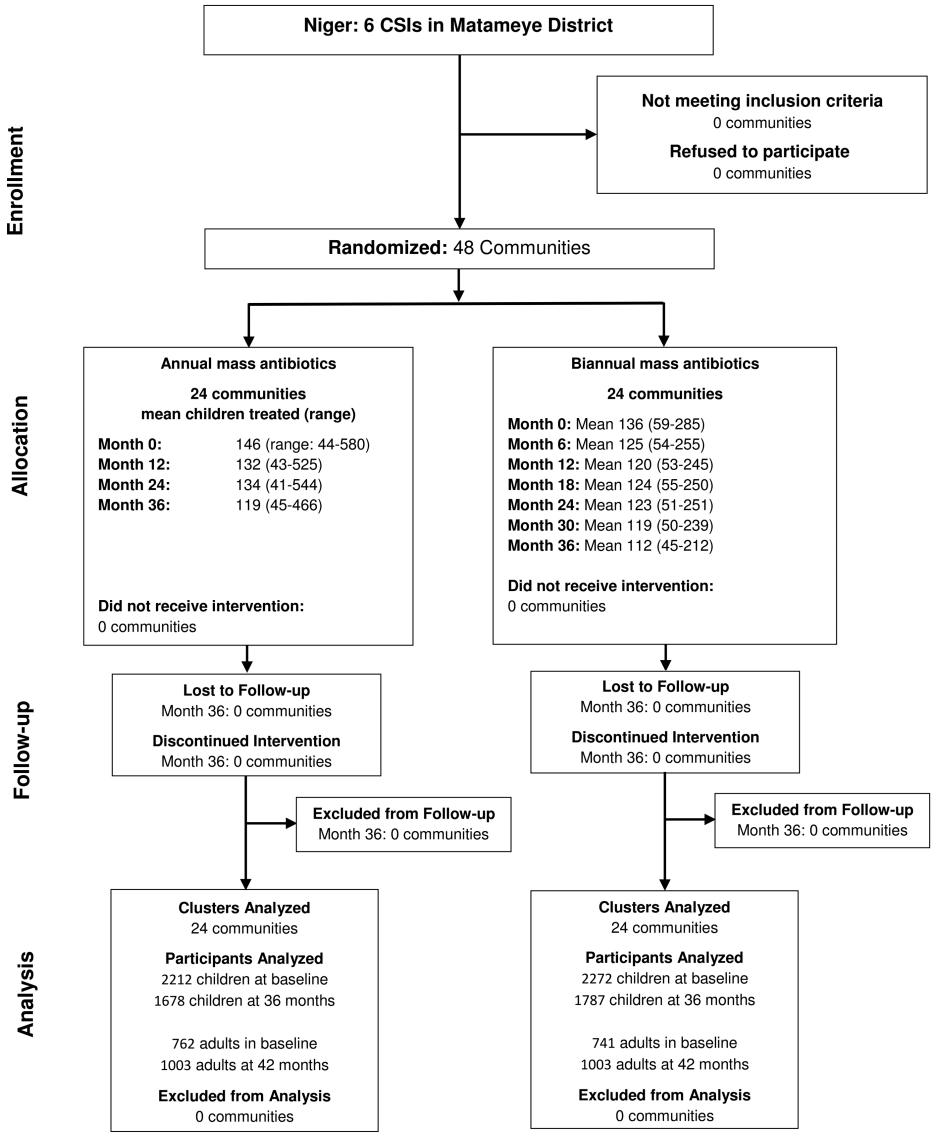

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram. Forty-eight communities were randomized to either annual mass treatment of the entire community or biannual treatment targeted to children aged ≤12 years. No communities were lost to follow-up, and none discontinued the intervention. All communities were included in the analyses at 36 months. Abbreviation: CSI, Centre de Santé Intégrées.

distributions offer a form of herd protection to those not receiving antibiotics. Children typically have a higher prevalence of clinically active trachoma than adults, as well as a higher prevalence of chlamydial infection [2]. Where monitored, the duration of infection is longer and the load of chlamydia is higher in children than adults [24–27]. Mathematical models have suggested that children may form a core group of trachoma transmission [3]; that is, if transmission were to be curtailed in children, then infection would not persist in the rest of the community. These models hypothesized that that elimination would depend on a trade-off between frequency of treatment and ages covered, and would need to be tailored to endemicity. Specifically, models suggested that biannual treatment of children aged <12 years should eventually eliminate infection in moderately infected areas such as

Table 1. Baseline Characteristics of Children and Adults in 48 Communities

Characteristic	Mean (95% CI)	
	Annually Treated (24 Communities)	Biannually Treated (24 Communities)
Children per community (aged 0–5 y)	156 (108–204)	144 (117–171)
Age of children, y	2.6 (2.6–2.7)	2.7 (2.6–2.7)
Proportion female, %	51.2 (49.6–52.8)	49.4 (47.4–51.3)
Prevalence of trachoma (TF), %	27.7 (21.2–34.2)	24.3 (19.1–29.5)
Prevalence of trachoma (TI), %	8.3 (5.2–11.5)	7.6 (5.1–10.1)
Adults per community (aged ≥15 y)	249 (173–325)	228 (183–274)
Age of adults, y	34.5 (33.7–35.2)	33.7 (32.9–34.4)
Proportion female, %	53.7 (52.6–54.9)	51.9 (50.8–52.9)
Prevalence of trachoma (TF), %	0.4 (.1–.9)	1.3 (.4–2.8)
Prevalence of trachoma (TI), %	0.1 (.0–.3)	0.2 (.0–.7)

Abbreviations: CI, confidence interval; TF, trachomatous inflammation–follicular; TI, trachomatous inflammation–intense per the World Health Organization Simplified Grading System [16].

Table 2. Antibiotic Coverage in Children and Adults[a]

Study Arm	0 mo	6 mo	12 mo	18 mo	24 mo	30 mo	36 mo
Annual–children	92.3% (90.2%–94.1%)		89.0% (86.8%–91.2%)		89.8% (87.8%–91.7%)		84.9% (81.6%–88.1%)
Annual–adults	76.8% (72.0%–81.2%)		70.4% (66.7%–74.6%)		71.0% (65.7%–76.2%)		76.5% (69.8%–82.5%)
Biannual–children	87.5% (84.0%–90.8%)	85.4% (82.0%–88.7%)	87.4% (84.3%–90.1%)	87.5% (83.6%–90.7%)	87.8% (85.1%–89.9%)	84.7% (81.1%–87.9%)	83.5% (79.6%–87.1%)
Biannual–adults	0.4% (0.2%–0.8%)		0.1% (0.0%–0.3%)		0.2% (0.1%–0.3%)		2.4% (0.0%–8.0%)

The values in parentheses are mean (95% CI).

[a]Children: aged 0–12 y; adults: aged ≥15 y.

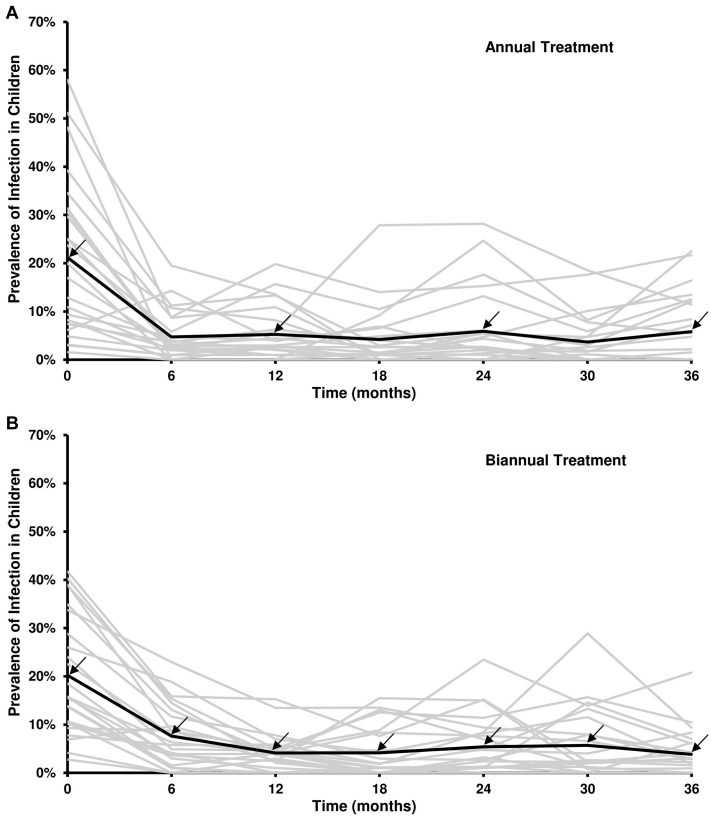

Figure 2. Estimated prevalence of ocular chlamydial infection in children aged ≤5 years over time. Each of 24 communities was monitored biannually (gray curves), with the mean (black curve). Annual treatments (arrows) were offered to all members of the community (*A*); biannual treatment (arrows) was offered only to children aged ≤12 years (*B*).

Niger [3]. A cluster-randomized trial in Nepal found annual mass treatment of children aged <10 years to be as successful as treatment targeted to all clinically active children and their households [28]. In higher-prevalence Nepali communities, mass treatment of children was more cost-effective [11]. A previous cluster-randomized trial in Ethiopia found that quarterly treatment of children under the age of 10 years approximately halved the prevalence of infection in untreated adults at 1 year, suggesting a short-term form of herd protection [29]. Here, we distributed antibiotics biannually to children aged ≤12 years. Thus results would not necessarily apply were treatment given less frequently or to a smaller age group [3].

This cluster-randomized trial had several limitations. The primary outcome was a sample of children and adults. While this sample allows us to make inferences about the entire adult population, an estimated 0% prevalence does not ensure that infection was in fact eliminated in that age group. A newer generation of PCR-based chlamydia tests may be more sensitive than the Roche-Amplicor test used in

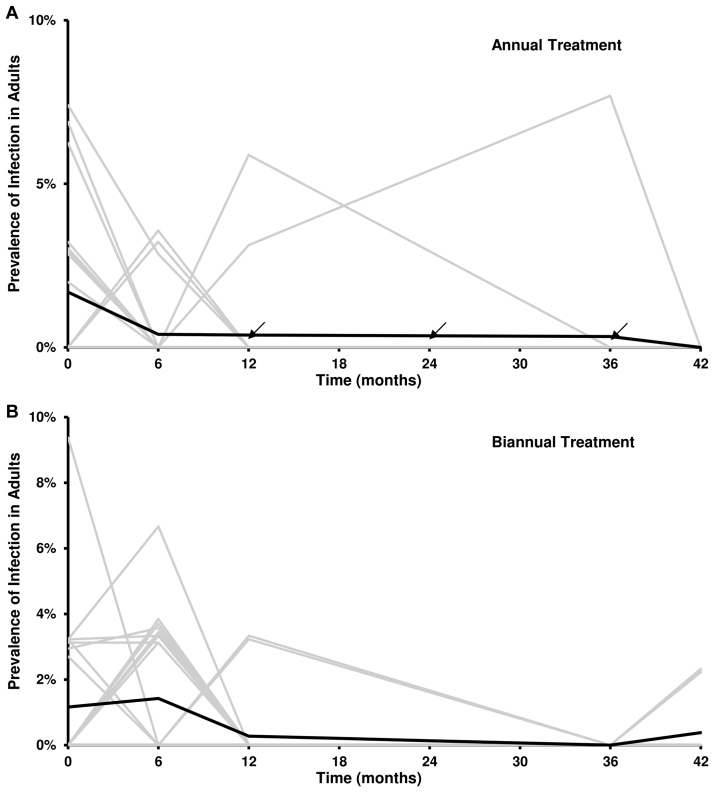

Figure 3. Estimated prevalence of ocular chlamydial infection in adults aged ≥15 years over time. Each of 24 communities was monitored biannually (gray curves), with the mean (black curve). Annual treatments (arrows) were offered to all members of the community (*A*); biannual treatment (arrows) was offered only to children aged ≤12 years (*B*).

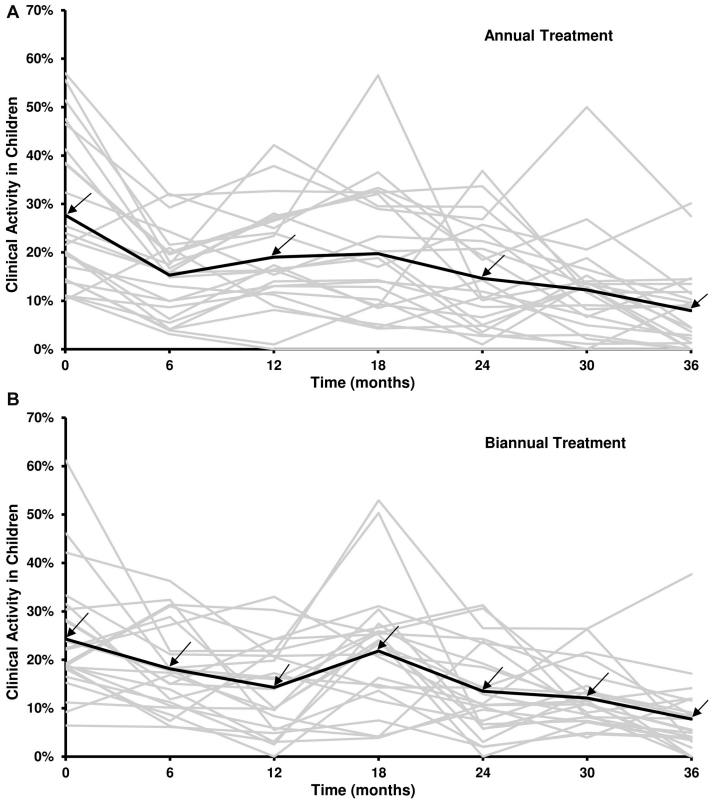

Figure 4. Clinical trachoma activity (follicular trachoma) in children aged ≤5 years over time. Each of 24 communities was monitored biannually (gray curves), with the mean (black curve). Annual treatments (arrows) were offered to all members of the community (*A*); biannual treatment (arrows) was offered only to children aged ≤12 years (*B*).

this study [30]. Migration into these communities did occur, likely from regions that had not just received antibiotics—ideally, neighboring areas would be enrolled in similar mass treatment programs. Only longer-term and more complete follow-up would be able to ensure that complete elimination could be achieved with either of these distribution strategies. We have not demonstrated here that treating children biannually would be more cost-effective than treating all ages annually.

Trachoma control programs have demonstrated remarkable success in reducing the trachoma burden worldwide, in large part due to mass oral azithromycin distributions. More than 50 million doses of oral azithromycin per year are now distributed to trachoma-endemic areas. However, distributions are expensive and attaining high treatment coverage in adults is difficult. In this community-randomized trial in Niger, the prevalence of infection in adults was low at baseline, and even lower after repeated treatment of children alone. In similar settings, treatment of adults may not be necessary, as comparable results can be obtained by focusing on treatment of only children.

Notes

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Author contributions. A. A.: study design, data collection, approval of manuscript; B. K.: study design, data collection, approval of manuscript; B. N.: study design, data collection, approval of manuscript; S. Y. C.: data collection, approval of manuscript; N. E. S.: data collection, approval of manuscript; Z. Z.: data collection, data analysis, figures, approval of manuscript; R. L. B.: study design, approval of manuscript; D. C. M.: study design, approval of manuscript; T. C. P.: study design, data analysis, data interpretation, approval of manuscript; J. D. K.: study design, data collection, data interpretation, writing; B. D. G.: study design, data collection, approval of manuscript; S. K. W.: study design, obtained funding, approval of manuscript; T. M. L.: literature search, study design, data collection, data interpretation, writing.

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