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Targeted Mass Azithromycin Distribution for Trachoma: A Community-Randomized Trial (TANA II)

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Background. Current guidelines recommend annual community-wide mass administration of azithromycin for trachoma. Targeting treatments to those most likely to be infected could reduce the amount of unnecessary antibiotics distributed.

Methods. In a cluster-randomized trial conducted from 1 November 2010 through 8 November 2013, 48 Ethiopian communities previously treated with annual mass azithromycin distributions for trachoma were randomized in equal numbers to (1) annual azithromycin distributions targeted to children aged 0–5 years, (2) annual azithromycin distributions targeted to households with a child aged 0–5 years found to have clinically active trachoma, (3) continued annual mass azithromycin distributions to the entire community, or (4) cessation of treatment. The primary outcome was the community prevalence of ocular chlamydia infection among children aged 0–9 years at month 36. Laboratory personnel were masked to treatment allocation.

Results. The prevalence of ocular chlamydia infection among children aged 0–9 years increased from 4.3% (95% confidence interval [CI], .9%–8.6%) at baseline to 8.7% (95% CI, 4.2%–13.9%) at month 36 in the age-targeted arm, and from 2.8% (95% CI, .8%–5.3%) at baseline to 6.3% (95% CI, 2.9%–10.6%) at month 36 in the household-targeted arm. After adjusting for baseline chlamydia prevalence, the 36-month prevalence of ocular chlamydia was 2.4 percentage points greater in the age-targeted group (95% CI, −4.8% to 9.6%; $P = .50$; prespecified primary analysis). No adverse events were reported.

Conclusions. Targeting azithromycin treatment to preschool children was no different than targeting azithromycin to households with a child with clinically active trachoma. Neither approach reduced ocular chlamydia over the 3-year study.

Clinical Trials Registration. NCT01202331.

Keywords. trachoma; chlamydia; mass drug administration; clinical trial.

The World Health Organization (WHO) recommends the "SAFE" strategy for trachoma: Surgery for trachomatous trichiasis, Antibiotics to reduce the burden of the causative agent *Chlamydia trachomatis*, and Facial cleanliness and Environmental improvements to reduce chlamydia transmission [1]. Mass distribution of azithromycin is a key component of this strategy, with even a single community-wide dose significantly reducing the prevalence of ocular chlamydia [2, 3]. WHO currently recommends 3–5 cycles of annual mass distribution of antibiotics in communities that have a prevalence of at least 10% trachomatous inflammation–follicular (TF) among children aged 1–9 years, with continued rounds of community-wide azithromycin until TF prevalence is <5% in children [4].

In the Trachoma Amelioration in Northern Amhara trial (TANA I), repeated annual mass azithromycin distributions administered to communities with hyperendemic trachoma resulted in a rapid and marked reduction in the prevalence of ocular chlamydia in children aged 0–9 years [5, 6]. In contrast, the clinical signs of trachoma reduced much more slowly, keeping the study communities eligible for continued azithromycin. In this scenario, if azithromycin treatments were continued then the vast majority of treated individuals would not actually have been infected with ocular chlamydia. But perpetual mass treatment with azithromycin has several potential disadvantages, including antibiotic resistance, treatment fatigue, and high costs for trachoma programs [7–9]. Targeting antibiotic treatment to those most likely to harbor infection is thus a potentially attractive strategy. In this continuation study (TANA II), communities from the initial TANA I trial that had been treated with 4 annual mass azithromycin distributions were re-randomized to cessation of treatment, continued annual mass azithromycin treatment, or annual targeted treatments to subpopulations likely to transmit ocular chlamydia. The effects of continuing versus discontinuing mass azithromycin treatment have been published elsewhere [10]. Here we compare 2 targeted azithromycin treatment strategies: treatment of all preschool children, or treatment

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of only those households in which a preschool child had clinically active trachoma. The focus on preschool children was justified based on the high prevalence and infectious load of chlamydia infection in this age group, which likely represents a core group responsible for chlamydia transmission in the community [2, 11–15]. The objective of the trial was to determine whether one of the targeted treatment strategies was superior to the other, and also to compare targeted treatment to continued annual treatments as well as cessation of treatments at the community level.

METHODS

Study Design and Participants

TANA II was a parallel-group, cluster-randomized trial done in a subset of study communities that had been enrolled in the TANA I trial in Goncha Siso Enese district of the Amhara region of Ethiopia. TANA I was conducted from 1 June 2006 to 2 December 2009 (ClinicalTrials.gov identifier NCT00322972), and TANA II was conducted from 1 November 2010 to 8 November 2013 (ClinicalTrials.gov identifier NCT01202331). In TANA I, groups of communities that had never received mass antibiotics for trachoma were randomized to 1 of several different mass azithromycin schedules, including annual and biannual mass treatments [5, 6]. In TANA II, 48 state teams (ie, government-defined administrative units consisting of approximately 50 households) that had received 4 rounds of annual mass azithromycin as part of TANA I were randomized to receive 1 of 4 maintenance strategies for trachoma elimination: (1) discontinuation of mass treatment, (2) continued annual mass azithromycin treatment to the entire community, (3) annual azithromycin treatment targeted to children aged 0–5 years (age-targeted), or (4) annual azithromycin treatment targeted to children aged 0–5 years with clinically active trachoma, along with all household members (household-targeted). Cluster randomization was employed because the intervention was administered at the community level, and because trachoma is a transmissible disease. All community members were included in the study; azithromycin was distributed to subsets of participants according to treatment arm and trachoma monitoring was performed on a random sample of community members. Trial protocol and outcomes were prespecified, with no changes to the methods after initiation of the trial. This study was reviewed and approved by the Committee on Human Research at the University of California, San Francisco, the Institutional Review Board at Emory University, and the Ethiopian Science and Technology Commission [8]. Due to the high level of illiteracy in the study area, verbal informed consent was obtained from participants or from guardians of participants for all study procedures.

Randomization and Masking

In TANA I, 72 subkebeles (ie, government-defined administrative units consisting of approximately 4–6 state teams) were randomized in equal numbers to 1 of 6 arms [5, 15, 16]. Two of the arms—the annual (n = 12 subkebeles) and biannual (n = 12 subkebeles) mass azithromycin arms—were included in TANA II, although only communities in the annual treatment arm are included in the present report. Four randomly selected state teams per annually treated subkebele were randomized in a 1:1:1:1 ratio to 1 of the 4 treatment arms (Figure 1). The randomization sequence was generated in R (version 3) by the trial biostatistician (T. C. P.) and the allocated interventions were assigned by the study coordinator (B. A. H.). Allocation was concealed at the cluster-level by performing randomization of all communities at the same time, after all study communities had been enrolled. Participants were not masked to their community's treatment allocation. Field staff were not informed of treatment allocation. Laboratory staff were masked to treatment allocation by using 5-digit random number labels for specimen collection.

Procedures

Each year of the study, a door-to-door enumerative census was performed, followed by conjunctival examination and swabbing on a random sample of children aged 0–9 years in each of the 4 arms and conjunctival examination of all children aged 0–5 years in the 2 targeted treatment arms. Examiners were trained to assess the everted superior tarsal conjunctiva for TF and trachomatous inflammation–intense (TI) according to WHO's simplified grading system, with validation and oversight performed both in the classroom and in the field [17]. Before being allowed to grade trachoma for a given study visit, each examiner was required to reach sufficient agreement (ie, Cohen $\kappa \geq 0.6$) with the consensus grade from a panel of 3 expert graders on a series of conjunctival photographs. Azithromycin treatments took place 2–4 weeks following the trachoma assessments. In the continued mass treatment arm, all community members enumerated on the most recent census were eligible for azithromycin treatment. In the age-targeted treatment arm, all children aged 0–5 years on the most recent census were eligible for azithromycin treatment. The age-targeted treatment strategy focused on preschool children because of the likelihood that this age group was responsible for most of the chlamydia transmission in the community [11–15]. In the household-targeted treatment arm, all household members of a household in which a child aged 0–5 years was found to have TF and/or TI at the preceding clinical examinations were eligible for azithromycin treatment. The household-targeted treatment strategy included both TF and TI since both of these trachoma diagnoses are associated with chlamydia infection—with especially high chlamydia loads among children with TI [2, 11]. In the treatment cessation group, no mass azithromycin distributions were given. No other interventions for trachoma were implemented in any of the study arms, although all study communities continued to receive routine government

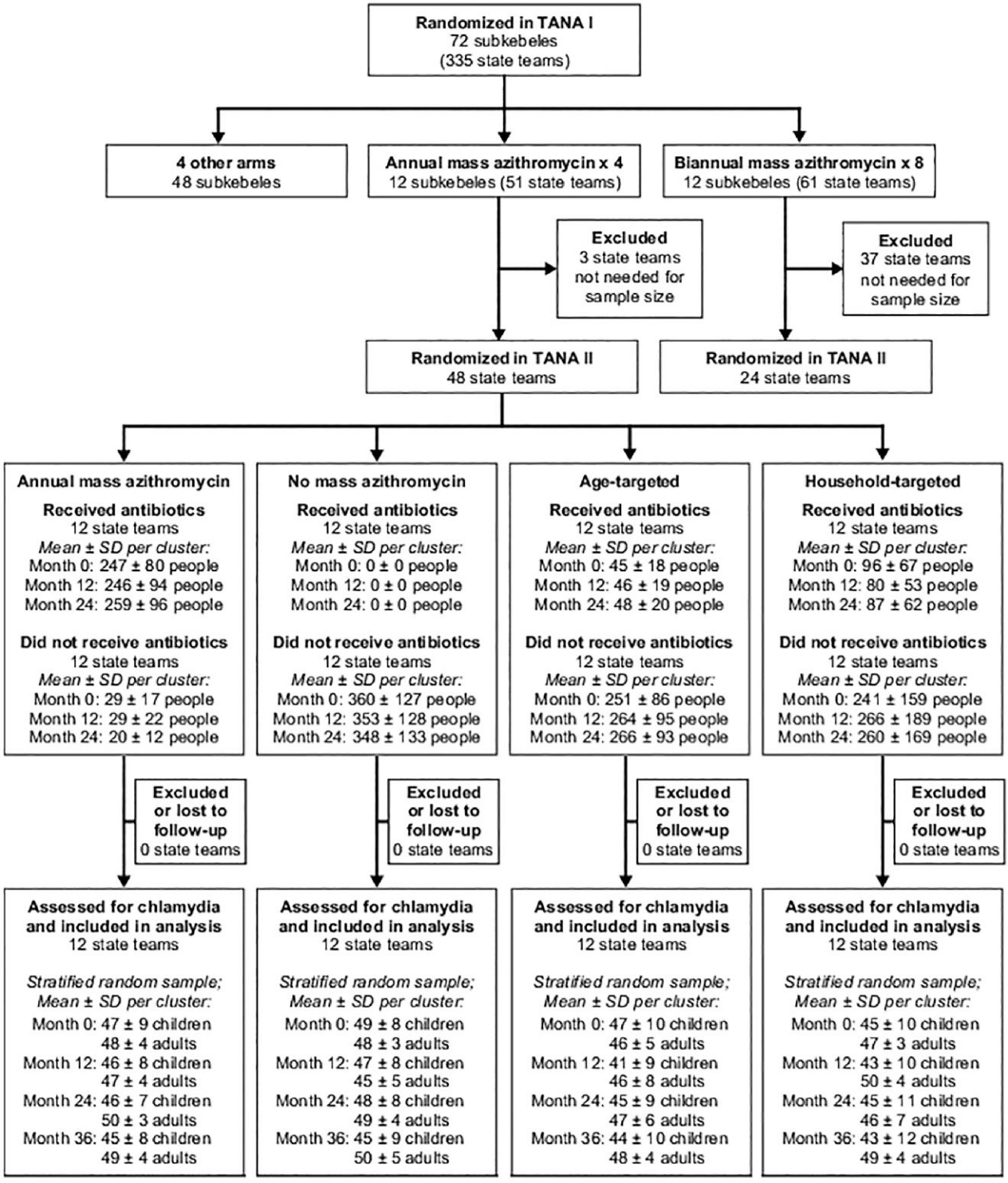

Figure 1. Trial profile. Both the original TANA I randomization and TANA II randomization are shown. Separate cross-sectional stratified random samples were selected for trachoma monitoring in each community, with stratification according to 2 age groups: children (0–9 years) and adults (≥10 years). Abbreviations: SD, standard deviation; TANA, Trachoma Amelioration in Northern Amhara trial.

health promotion services. During each treatment, a single dose of directly observed azithromycin was administered to each eligible participant, using a 20 mg/kg height-based dose for children and 1 g for adults [18]. In accordance with WHO policy, children <6 months of age, pregnant women, and those with allergies to macrolide antibiotics were offered 1% topical tetracycline to be

Table 1. Baseline Characteristics by Study Arm

Characteristic	Age-Targeted (n = 12)	Household-Targeted (n = 12)	Annual MDA (n = 12)	Treatment Cessation (n = 12)
Population, No.				
0–9 y	86 (68–103)	91 (64–137)	81 (63–98)	90 (73–107)
≥10 y	227 (182–268)	265 (198–377)	219 (182–258)	270 (219–325)
Fraction female, %				
0–9 y	47.1% (42.7%–51.0%)	50.8% (45.6%–56.4%)	48.5% (45.7%–51.7%)	51.2% (48.2%–53.9%)
≥10 y	52.0% (50.5%–54.0%)	50.4% (49.6%–51.5%)	51.3% (49.5%–53.0%)	50.2% (48.6%–51.8%)
Fraction with TF, %				
0–9 y	38.1% (29.5%–46.8%)	36.1% (28.5%–43.7%)	40.6% (32.9%–48.4%)	30.5% (21.8%–39.3%)
≥10 y	5.1% (2.0%–8.2%)	6.1% (4.3%–8.0%)	3.8% (.7%–7.0%)	2.3% (.9%–3.7%)
Elevation, m[a]	2524 (2366–2654)	2426 (2246–2588)	2510 (2354–2638)	2586 (2456–2679)

Values indicate the mean community-level estimates and 95% confidence intervals.

Abbreviations: MDA, mass drug administration with azithromycin; TF, trachomatous inflammation–follicular.

[a]Measured with a handheld global positioning system device in a central location of the study community.

applied twice daily to both eyes for 6 weeks, which was not directly observed.

Outcomes

The primary outcome was the community prevalence of ocular chlamydia infection in children aged 0–9 years as measured by polymerase chain reaction. A secondary outcome of interest was TF in children aged 0–9 years old, assessed according to WHO's simplified grading system [17]. Annually, a random sample of 50 children aged 0–9 years and 50 individuals aged ≥10 years per state team was selected for trachoma monitoring. At these monitoring visits, the everted upper right tarsal conjunctiva was assessed for TF by a trained grader using 2.5× loupes and a penlight. A Dacron swab was then passed 3 times across the everted upper tarsal conjunctiva, rotating 120° between passes. Samples were kept on ice in the field and frozen to −20°C within 6 hours, and then transferred at 4°C to the University of California, San Francisco, where they were stored at −80°C until processing. Samples were grouped in pools of 5 by state team and age group, and pools were processed with the Abbott m2000 platform to detect *C. trachomatis* DNA. The community prevalence of ocular chlamydia infection was estimated from the pooled results as previously described [19]. An adverse event notification system allowed individuals to report to the village informant and Ethiopian study coordinator.

Sample Size Determination

Sample size calculations for the primary analysis were based on the community-level results of the TANA I study [5]. Using the formula for an unpaired *t* test, and assuming a 5 percentage point standard deviation in the mean community prevalence of ocular chlamydia and a 2-sided α of .05, then enrolling 12 communities per arm would provide >80% power to detect a 6-percentage point difference in prevalence of ocular chlamydia infection between the 2 arms.

Statistical Analysis

In this report the term baseline refers to TANA II baseline (as opposed to TANA I baseline) and the time points indicate the time since the TANA II baseline visit. Analyses used state team-level prevalence data to account for cluster-randomization. The prespecified primary outcome was the prevalence of ocular chlamydia in the age group 0–9 years at the 36-month time point. The primary analysis compared the 36-month untransformed prevalence values in the age-targeted and household-targeted arms in an analysis of covariance, adjusted for TANA II baseline prevalence. Statistical significance was assessed by Monte Carlo permutation (10 000 replications), with a significance level of .05 for the primary outcome. Similar statistical methods were used for secondary outcomes (ie, TF prevalence) and secondary comparisons (ie, pairwise comparisons of the 4 treatment arms). Square-root transformation of the prevalence outcomes was explored to improve model fit but did not change the results. All analyses were performed as superiority analyses in an intention-to-treat manner. Interim analysis was not indicated. Analyses were conducted in R version 4 software.

RESULTS

A total of 48 communities treated with annual mass drug administration (MDA) during TANA I were randomized to 1 of 4 treatment arms for TANA II. Demographic, geographic, and clinical characteristics assessed in study communities at the TANA II baseline visit were well balanced between the 4 treatment arms (Table 1). Azithromycin was administered to at least 80% of all community members eligible for treatment across the 3 specified annual MDAs (Table 2). As expected, the targeted treatment strategies resulted in a considerable reduction in the overall volume of antibiotics distributed per community, with a mean of 14.9% (95% confidence interval [CI], 14.3%–15.5%) of the total population treated in the age-

Table 2. Antibiotic Coverage per Treatment Arm

Timepoint	Age-Targeted	Household-Targeted	Annual MDA
Of total population			
Month 0	14.9% (13.0%–16.7%)	27.15% (20.4%–32.7%)	89.6% (86.7%–92.3%)
Month 12	14.6% (12.4%–16.7%)	22.9% (16.0%–29.7%)	88.8% (83.5%–93.4%)
Month 24	15.3% (13.5%–17.2%)	24.1% (17.5%–30.0%)	92.6% (90.5%–94.7%)
Of eligible population			
Month 0	91.5% (85.6%–96.5%)	96.1% (92.5%–98.7%)	89.6% (86.7%–92.3%)
Month 12	89.8% (83.5%–94.7%)	93.0% (87.8%–97.2%)	88.8% (83.5%–93.4%)
Month 24	89.1% (84.0%–93.4%)	83.0% (64.2%–94.0%)	92.6% (90.5%–94.7%)

Values indicate the mean community-level coverage (95% confidence interval).

Abbreviation: MDA, mass drug administration with azithromycin.

targeted arm and 24.7% (95% CI, 22.6%–26.7%) of the total population treated in the household-targeted treatment arm. No adverse effects were reported.

Figure 2 shows the prevalence of ocular chlamydia infection among children aged 0–9 years in each community over 36 months in the age-targeted and household-targeted treatment arms (Supplementary Table 1). In the age-targeted arm, the mean prevalence of ocular chlamydia among the 12 communities increased from 4.3% (95% CI, .9%–8.6%) at baseline to 8.7% (95% CI, 4.2%–13.9%) at the 36-month visit ($P = .27$, paired t test). In the household-targeted arm, the mean prevalence of ocular chlamydia increased from 2.8% (95% CI, .8%–5.3%) at baseline to 6.3% (95% CI, 2.9%–10.6%) at 36 months ($P = .05$, paired t test). At 36 months, there was no significant difference in the prevalence of chlamydia between the age-targeted and household-targeted arms when corrected for baseline prevalence (2.4% greater in the age-targeted group [95% CI, −4.8% to 9.6%]; $P = .50$; prespecified primary analysis). Results were similar when using square root–transformed prevalence data ($P = .61$).

The prevalence of ocular chlamydia among 0- to 9-year-olds in the targeted treatment arms was also analyzed in comparison to the annual mass azithromycin arm and treatment cessation arm in prespecified secondary analyses. Both of the targeted treatment arms had lower point estimates for ocular chlamydia infection at 36 months compared with the cessation-of-treatment arm and also the annual mass azithromycin arm (Figure 3), but these differences were not statistically significant when adjusted for baseline prevalence (Table 3).

The prevalence of TF among children aged 0–9 years remained relatively stable across all treatment arms during the study period (Figure 3; Supplementary Table 2). In the age-targeted arm the mean prevalence of TF was 38.1% (95% CI, 30.4%–46.7%) at baseline and 38.0% (95% CI, 28.1%–48.2%) at month 36, and in the household-targeted arm the corresponding figures were 36.1% (95% CI, 28.3%–43.1%) and 36.8% (95% CI, 28.9%–44.4%). There was no significant difference in the prevalence of TF between the age-targeted and household-targeted treatment arms when adjusted for baseline prevalence (0.1% greater in the household-targeted arm [95% CI, −12.0% to 12.2%]; $P = .98$), nor between either of the targeted treatment arms and the continued mass treatment arm or treatment cessation arm (prespecified secondary analyses; Table 3).

The prevalence of ocular chlamydia among individuals aged ≥10 years was much lower than that for children aged 0–9 years (Supplementary Tables 3 and 4). For example, in the age-targeted arm the prevalence among individuals aged ≥10 years increased from 0.4% (95% CI, 0%–1.1%) at baseline to 1.6% (95% CI, .7%–2.7%) at month 36. In the treatment cessation group, the prevalence of ocular chlamydia increased from 0.5% (95% CI, 0%–1.2%) at baseline to 2.1% (95% CI, .9%–3.6%) at month 36. When adjusted for baseline, no statistically significant difference between the age-targeted and treatment cessation arm could be detected, with a mean prevalence 0.4 percentage points lower in the age-targeted arm (95% CI, −2.1% to 1.3%) (prespecified secondary analysis).

DISCUSSION

Ocular chlamydia infection increased over time in both of the targeted treatment arms in this study, with no detectable difference between the age- and household-targeted treatment strategies for either ocular chlamydia or clinical trachoma. Targeted treatments resulted in rates of ocular chlamydia infection that were similar to continued mass antibiotics—although not lower than the treatment-cessation arm. Chlamydia infection increased in all 4 arms over the 3-year study, suggesting that even annual mass treatments were not sufficient to stop transmission in this region of hyperendemic trachoma.

Current trachoma guidelines endorse mass azithromycin distributions to the entire community, but targeting antibiotic treatments could have several potential benefits. Even in the most trachoma-hyperendemic communities, the vast majority of adults will not be infected with ocular chlamydia [7, 8]. Targeting antibiotic treatments to children could therefore limit the risk of adverse drug reactions or side effects in those who are unlikely to benefit directly from the treatment. Reducing

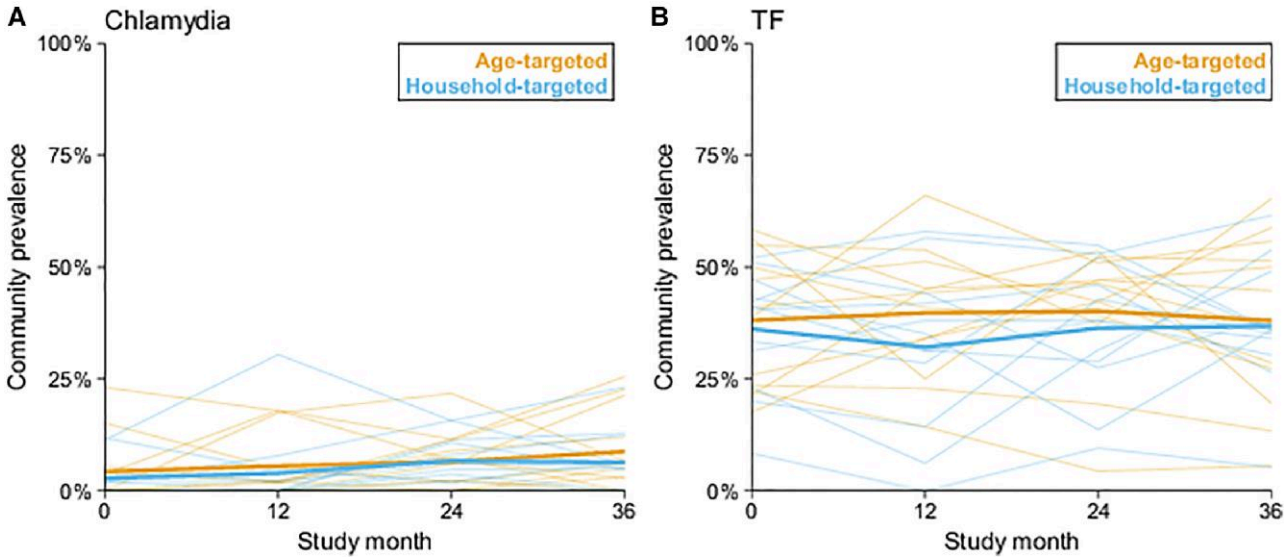

Figure 2. Longitudinal prevalence of ocular chlamydia infection and clinical trachoma in the 2 targeted treatment arms among children aged 0–9 years. Each thin line represents the prevalence of ocular chlamydia (*A*) or trachomatous inflammation–follicular (TF) (*B*) in a specific community over the 4 annual study visits; the thick line is the mean prevalence in the treatment arm.

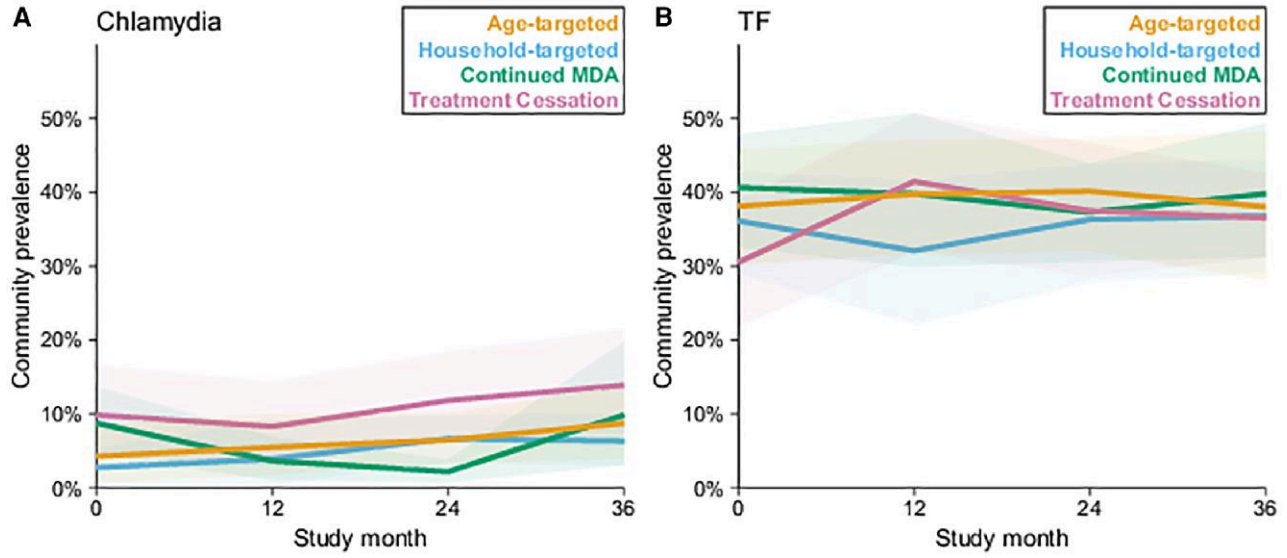

Figure 3. Mean longitudinal prevalence of ocular chlamydia infection and clinical trachoma in 4 treatment arms among children aged 0–9 years. Each line represents the mean prevalence of ocular chlamydia (*A*) or trachomatous inflammation–follicular (*B*) in a treatment arm over the 4 annual study visits, and the bar represents the corresponding 95% confidence interval. Abbreviations: MDA, mass drug administration; TF, trachomatous inflammation–follicular.

the use of antibiotics in the community also has the benefit of limiting antimicrobial resistance. However, targeted treatments also have potential disadvantages. Azithromycin has activity for many infections besides ocular chlamydia infection, and periodic mass azithromycin distributions have been shown to reduce childhood morbidity and mortality in sub-Saharan Africa [20–22]. Targeting treatments would reduce any beneficial off-target impacts of the antibiotic distribution. Moreover, reducing the number of people receiving antibiotics may reduce any indirect effects of mass antibiotic distributions.

Several previous studies have suggested that targeted azithromycin treatments may be beneficial for trachoma. A cluster-randomized trial in a trachoma-mesoendemic area of Nepal found similar reductions in clinically active trachoma and

Table 3. Differences Between Targeted Treatment Arms and the Continued Mass Treatment Arm and Treatment Cessation Arm

	Reference Group			
	Age-Targeted		Household-Targeted	
Comparator Arm	Difference in Prevalence	*P* Value	Difference in Prevalence	*P* Value
Ocular chlamydia				
Age-targeted	…		2.4% (–4.8% to 9.6%)	.50
Household-targeted	–2.4% (–9.6% to 4.8%)	.50	…	
Annual MDA	1.1% (–11.1% to 13.3%)	.89	1.3% (–10.6% to 13.2%)	.58
Treatment cessation	3.8% (–6.3% to 13.8%)	.43	3.8% (–4.9% to 12.6%)	.37
TF				
Age-targeted	…		–0.1% (–12.2% to 12.0%)	.98
Household-targeted	0.1% (–12.0% to 12.2%)	.98	…	
Annual MDA	0.0% (–12.8% to 12.8%)	.99	0.4% (–11.2% to 12.0%)	.95
Treatment cessation	1.8% (–10.7% to 14.3%)	.77	1.4% (–9.0% to 11.8%)	.79

Values represent the mean difference in the 36-month community-level prevalence between pairs of treatment arms after adjusting for baseline prevalence. Positive values indicate a higher prevalence in the comparator arm and negative values a lower prevalence in the comparator arm. Analyses were done both for the prevalence of ocular chlamydia and the prevalence of TF, each of which was assessed in a random sample of children aged 0–9 years.

Abbreviations: MDA, mass drug administration with azithromycin; TF, trachomatous inflammation–follicular.

ocular chlamydia in communities randomized to mass treatment of all 1- to 10-year-olds versus those randomized to a household-targeted strategy [23]. A cluster-randomized trial in a hyperendemic region of Ethiopia found that quarterly mass azithromycin treatment to all children aged 1–10 years decreased the prevalence of ocular chlamydia even in untreated community members, providing evidence of herd protection [15]. Similar conclusions of community herd protection were found from targeting azithromycin treatment biannually to children in a mesoendemic area of Niger [24]. However, other studies performed in areas with either extremely low or extremely high trachoma prevalence—including the present study—were unable to show a benefit of targeted treatments compared with no treatment [14, 25]. These results suggest that targeted treatments may be able to play a role in trachoma elimination, but are likely not going to be effective in all trachoma-endemic settings. Further research is needed not only for the optimal subpopulations to target, but also the optimal setting.

A prespecified secondary outcome of the trial was a comparison of ocular chlamydia among untreated individuals in the age-targeted arm versus treatment cessation arm, given prior research that has shown community-wide antibiotic distributions may be beneficial even for untreated individuals [15]. In this study, the prevalence of ocular chlamydia among individuals aged ≥10 years was slightly—but not significantly—lower in the age-targeted arm compared with the treatment cessation arm, thus failing to provide evidence of any indirect or spillover effects of antibiotics. The low prevalence of ocular chlamydia among the older subgroup made it difficult to detect a difference, especially given the sample size.

Limitations of this study include the sample size of 24 communities, which may not have provided the statistical power needed to detect modest effects. TF is a slowly changing indicator, and thus the 3-year study time frame may have not been long enough to capture changes in clinically active trachoma. The trial was not masked and thus we cannot rule out the possibility of bias from differential cointerventions between the study arms. It is unclear whether our findings can be generalized to meso- or hypoendemic regions.

As trachoma programs approach elimination, the vast majority of people eligible for mass azithromycin treatments will not actually be infected at the time of treatment. Targeted strategies are a feasible option with the benefit of limiting overall antibiotic exposure and community resistance [23–25]. It may be difficult to distinguish a significant difference between various targeted treatment strategies without larger studies, but further research is warranted given the potential societal benefit of reducing antibiotic use.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. The authors: No reported conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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