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Frequency of mass azithromycin distribution for ocular chlamydia in a trachoma endemic region of Ethiopia: a cluster randomized trial

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Abstract

Introduction.—Annual mass azithromycin distribution significantly reduces the prevalence of ocular *Chlamydia trachomatis*, the causative organism of trachoma. However, in some areas a decade or more of treatment has not controlled infection. Here, we compared multiple treatment arms from a community-randomized trial to evaluate whether increasing frequency of azithromycin distribution decreases prevalence in the short term.

Methods.—Seventy-two communities in Goncha Seso Enesie Woreda in the Amhara Region of Northern Ethiopia were randomized to 1 of 6 azithromycin distribution strategies: 1) delayed, 2) annual, 3) biannual, 4) quarterly to children only, 5) biennial, or 6) biennial plus latrine promotion.

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We analyzed data from the 60 communities in the delayed, annual, biannual, quarterly, and biennial distribution arms at the 12-month study visit. Communities in the annual and biennial distribution arm were combined, as they each had a single distribution before any 12-month retreatment. We assessed the effect of increased frequency of azithromycin distribution on ocular chlamydia prevalence.

Results.—Ocular chlamydia prevalence was significantly different across azithromycin distribution frequency in children (P<0.0001) and adults (P<0.0001), with lower prevalence associated with higher frequency. Among children, quarterly azithromycin distribution led to a significantly greater reduction in ocular chlamydia prevalence than the World Health Organization-recommended annual treatment prevalence (mean difference −11.4%, 95% CI - 19.5 to −3.3%, P=0.007).

Conclusions.—Increased frequency of azithromycin distribution leads to decreased ocular chlamydia prevalence over a short-term period. In some regions with high levels of ocular chlamydia prevalence, additional azithromycin distributions may help achieve local elimination of infection.

INTRODUCTION

Trachoma was thought to be the second leading cause of blindness after cataract into the 1990s.[1] Repeated infections with ocular strains of *Chlamydia trachomatis* lead to conjunctival scarring, entropion, trichiasis, vulnerability to corneal ulcers, and eventual corneal blindness.[2] In 1999, the WHO organized an initiative to control infection to a low enough level that resulting blindness would not be a public health concern.[3] The definition of *control* included reducing the district-level prevalence of the follicular signs of trachoma (TF) to less than 5% in children aged 1–9 years.[2–4] The goal of control by 2020 will have been achieved in the majority of previously endemic districts worldwide, but not in all. In fact, progress has stalled in some areas despite more than a decade of intervention.[5] If a more intensive strategy could successfully eliminate infection in these problem areas, then not only would control have been achieved, but eradication might prove to be a feasible goal.

Annual azithromycin administration to entire communities is a core component of the World Health Organization (WHO)'s trachoma control program, in combination with environmental improvements (e.g., latrinization and improved water access) and facial cleanliness.[2,6,7] Annual distribution of azithromycin is highly effective at reducing the prevalence of chlamydia. However, in some communities, multiple years of azithromycin distribution have not been sufficient to achieve control of trachoma.[8–14] Additional strategies have been proposed in these recalcitrant areas. One approach is to enhance environmental changes and facial hygiene programs. No trial has yet shown any non-antibiotic measure to have an effect on the prevalence of chlamydia,[15–18] although a large study is now assessing improved water access, latrine construction, and hygiene education in Ethiopia (SWIFT UG1EY023939).

Another possible strategy to target problem areas is to increase the frequency of mass distributions.[19] The Trachoma Amelioration in Northern Amhara (TANA U10 EY016214) study was a series of 3 community randomized controlled trials evaluating the frequency of

mass azithromycin distributions in hyperendemic communities in Amhara, Ethiopia.[18,20,21] Three primary pre-specified comparisons considered pairs of arms at several pre-specified primary endpoints, and have been published: quarterly distribution to children versus delayed distribution at 12 months[20], annual versus biannual distribution at 42 months[21], and biennial distribution (once every 2 years) compared to biennial distribution plus latrines at 24 months and 48 months.[18] The overall trial was designed to allow additional comparisons, because communities in all 6 arms of the trial were randomly selected from the same pool of communities. Here, we present 12-month results of 4 azithromycin distribution frequencies (none, biennial, biannual, and quarterly) on the prevalence of ocular chlamydia in children aged 1 to 9 years old. We hypothesized that increasing frequency of azithromycin distribution would lead to greater reductions in the prevalence of ocular chlamydia in both children and adults.

METHODS

Study setting and design.

TANA (Trachoma Amelioration in Northern Amhara) was a community-randomized trial in Goncha Seso Enesie woreda in the Amhara Region of Northern Ethiopia (clinicaltrials.gov NCT00322972). Azithromycin distributions and ocular chlamydia evaluations in the present report took place between May 2006 and May 2007. Seventy-two subkebeles (government-defined units consisting of approximately 4 to 5 state teams or communities and a population of 1,400 individuals) were randomized to 1 of 6 study arms:

1. delayed azithromycin distribution (only monitored at 12 months)
2. annual mass azithromycin distribution to the entire community
3. biannual mass azithromycin distribution to the entire community
4. quarterly azithromycin distribution targeted only to children aged 1–10 years (adults not treated)
5. biennial mass azithromycin distribution
6. biennial mass azithromycin distribution plus latrine promotion

Randomization and Masking.

The 72 subkebeles were randomly assigned in a 1:1:1:1:1:1 fashion to 1 of the 6 study arms in Excel (version 2003, performed by Kathryn J Ray, implemented by BA, concealed until assignment). Communities in the latrine promotion arm were excluded from this analysis. Census workers and laboratory personnel were masked to each community's treatment assignment. Because they received the same antibiotic intervention over the 12-month period, we combined communities randomized to annual mass azithromycin distribution and biennial mass azithromycin distribution.

One sentinel community was randomly selected from each subkebele for monitoring (a simple random sample). All communities within each state team were treated according to the subkebele's randomization arm, to reduce contamination (termed a "fried egg" design).

Because of differences in timing of outcome assessment across the 6 study arms after the 12-month visit, all analyses in this report are limited to the 12-month study visit.

Interventions.

An enumerative census was conducted to generate a list of all households in each study community. In the delayed intervention arm, communities received no azithromycin distribution for the 12-month period of the study. In the annual and single azithromycin distribution arms, a single mass azithromycin distribution was administered to all participants over 1 year of age. In the biannual distribution arm, 2 mass azithromycin distributions were administered to all individuals over 1 year of age. In the quarterly distribution arm, all children aged 1–10 years received 4 azithromycin distributions over the 12-month period. For azithromycin distributions, individuals aged 1 year and older received an oral, directly observed 20 mg/kg dose of azithromycin (up to 1 g in adults). Consistent with WHO policy at the time, children under 1 year of age and pregnant women were offered topical 1% tetracycline for 6 weeks, applied twice daily to both eyes and not directly observed. Ten-year old children received oral azithromycin in the quarterly arm, although only children 9 years and under were monitored for infection (0–9 years) and clinical activity (1–9 years, as follicles do not predictably appear before the age of 1 year). We pooled communities from the biennial distribution arm and the annual distribution arm for analyses in this report, as the intervention was identical over the 12-month period of the study.

Outcome Assessment.

In each sentinel community, we randomly selected for outcome assessment 60 children aged 0–9 and 60 individuals aged 11 years and older. The right upper tarsal conjunctiva of each individual was swabbed by passing a dacron swab firmly across 3 times, rotating 120 degrees between every pass. Samples were kept on ice in the field and frozen at −20°C within 6 hours. The swabs were shipped at 4°C to the University of California, San Francisco for processing with the Amplicor DNA test to detect *C. trachomatis* DNA. Samples were pooled into groups of 5 by age group, and the community prevalence of ocular chlamydia was estimated by maximum likelihood estimation.[22]

Sample Size Determination.

The sample size calculations for the study were based on the primary pre-specified analysis plans of the pairwise comparisons.[18,20,21] We estimated that the inclusion of 12 subkebeles per arm would provide 80% power to detect a 6% difference in prevalence of infection assuming a standard deviation of 5.0%, a correlation between baseline and 12 months of 0.5, and a 2-tailed alpha of 0.05.

Statistical Analysis.

All analyses were conducted at the level of the sentinel unit of the randomization cluster (i.e. the community). We first compared the prevalence of ocular chlamydia in children across all 4 arms at 12 months using an analysis of variance (ANOVA) model, with *P*-values calculated via Monte Carlo permutation with 10,000 replications. Pairwise comparisons

were only conducted if the overall ANOVA was significant at $P<0.01$. We assessed if increased azithromycin distribution frequency reduced prevalence of ocular chlamydia with a test for trend in a linear regression model. We used a similar analytic strategy for the prevalence of ocular chlamydia in adults. At both baseline and 24 months, the prevalence of ocular chlamydia in children (but not adults) was available in arms A, B, and F. We similarly performed an ANOVA at 24 months, allowing pairwise comparisons (which could now correct for baseline) if the ANOVA was significant. Analyses were conducted in R version 3.5.1 (The R Foundation for Statistical Computing, Vienna, Austria) and STATA 13.1 (Statacorp, College Station, TX).

Ethics.

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. Verbal consent was obtained from adults and verbal consent for children to participate was obtained from guardians, a procedure that was reviewed and approved by all ethical oversight committees. Delay of treatment for one year in one arm was deemed acceptable by both US and Ethiopian committees, in part because trachoma is disappearing in many areas even in the absence of an active trachoma program. The study was undertaken in accordance with the Declaration of Helsinki.

RESULTS

Of 72 subkebeles enrolled in the trial, 60 subkebeles consisting of 278 state teams were included in this analysis (Figure 1). In sentinel communities, approximately half of children were female and one-third were aged 0–9 years (Table 1). Antibiotic coverage exceeded 80% at most time points in all study arms in the sentinel communities, with the exception of baseline and Month 3 in the quarterly treatment communities, which had approximately 75% coverage (Table 2).

At the 12-month timepoint, ocular chlamydia prevalence in children was significantly different across delayed, annual, biannual, and quarterly arms in children ($P=0.0001$). In particular, a test for trend in a linear regression model found a significant difference as azithromycin distribution frequency increased ($P<0.0001$; Figure 2a).

Compared to the delayed arm, there was a significant decrease in ocular chlamydia prevalence in children in communities receiving annual (−30.6%, 95% CI −38.7 to −22.5%, $P<0.0001$), biannual (mean difference −36.5%, 95% CI −45.8 to −27.1%, $P<0.0001$), and quarterly (mean difference −42.0%, 95% CI −51.3 to −32.7%, $P<0.0001$). Compared to annual distribution, quarterly distribution led to significantly lower ocular chlamydia prevalence (mean difference −11.4%, 95% CI −19.5 to −3.3%, $P=0.007$), but there was no difference between annual and biannual distribution (mean difference −5.9%, 95% CI −14.0 to 2.2%, $P=0.15$).

Among adults after 12 months, ocular chlamydia prevalence was significantly different across delayed, annual, and biannual arms ($P=0.0001$). A test for trend indicated that ocular

chlamydia decreased as distribution frequency increased (P<0.0001; Figure 2b). Compared to delayed distribution, adult ocular chlamydia prevalence was significantly lower with annual (mean difference −6.6%, 95% CI −10.4 to −2.7%, P=0.001) and biannual (mean difference −11.1%, 95% CI −14.9 to −7.2%, P<0.0001) azithromycin distribution. Biannual distribution led to lower ocular chlamydia prevalence compared to annual azithromycin in adults (mean difference −4.5%, 95% CI −8.3% to −0.6%, P=0.02).

At 24 months, the prevalence of ocular chlamydia in children was available in the annual, biannual, and biennial arms. Prevalences were clearly different overall (P=0.005, Figure 3). Annual distributions had significantly more infection than biannual distribution (3.3%, 95% CI .5 to 6.1%, P=0.2) and less than biennial distributions (−2.3%, 95% CI −4.0 to −.7%, P=.008). Biannual distributions had significantly less infection than biennial distribution ((−4.0%, 95% CI −6.3 to −1.7%, P=.002).

DISCUSSION

The TANA study (Trachoma Amelioration in Northern Amhara) randomized a common pool of 72 sentinel communities from 72 subkebeles to 1 of 6 trachoma treatment strategies. While the communities were paired into 3 primary analyses,[18,20,21] the randomization from a common pool allows secondary comparisons between any of the arms. In particular, we can assess whether increasing frequency of mass distribution of azithromycin results in lower chlamydia prevalence.

After 1 year of distributions, we found evidence of greater reduction in ocular chlamydia prevalence in children and adults in communities with hyperendemic trachoma with increasing numbers of antibiotic distributions. As expected all antibiotic distribution frequencies were superior to delayed treatment. After 2 years, infection was significantly less with biannual treatment than annual treatment, and with annual treatment than biennial treatment. Previous work has demonstrated that a single mass azithromycin distribution significantly decreases the prevalence of ocular chlamydia in children and adults.[6,9,23,24] However, in some hyperendemic districts in Ethiopia, even multiple years of mass azithromycin distribution has not reliably led to control of trachoma in all communities.[12,13] Increasing frequency of azithromycin is one potential strategy to reduce ocular chlamydia prevalence in communities with persistent trachoma.

Although increased antibiotic distribution frequency was significantly associated with reduced ocular chlamydia prevalence, the benefit of annual compared to biannual treatment was not significant until year 2.[21] Biannual azithromycin distribution in a different region of Ethiopia had previously been shown to be superior to annual distribution at 36 months.[25] Here, quarterly treatment of children was superior to a single treatment of all members of the community over a 12-month period, and biannual treatment superior to annual or biennial over a 24-month period. Trachoma prevalence increases with decreasing age, and younger children are more likely to be infected with ocular chlamydia than their older peers.[26–29] Children may form a core group for ocular chlamydia, and treatment of only children may be sufficient to eliminate transmission in communities.[19,20,30] Previous work has shown that biannual treatment of children only is non-inferior to annual treatment

of entire communities.[31] While in the present study quarterly treatment of children was superior to annual treatment of the entire community, quarterly treatment of all children may be an ambitious goal for trachoma programs. Identification of alternative, smaller core groups that can be treated more often may be a more realistic alternative if proven to be effective.

As expected, ocular chlamydia prevalence in adults was substantially lower than in children. As in children, increasing antibiotic distribution frequency resulted in lower ocular chlamydia prevalence in adults. In adults after 1 year, biannual (2 treatments) was superior to a single treatment for reducing prevalence. However, infection prevalence could have been lower in biannually-treated communities at 12 months because they had been treated more recently (6 months prior) than annually-treated communities (12 months prior). Analysis of ocular chlamydia prevalence when all communities had been treated 6 months previously showed no difference in ocular chlamydia prevalence in adults.[21] In the present analysis, we did not have data 3 months after the last antibiotic distribution for all study arms, and thus are unable to assess whether the differences herein are due to increased distribution frequency or are due to time since last antibiotic distribution.

Increasing frequency of antibiotic distributions may lead to increased selection for macrolide resistance.[32] Previous cluster randomized trials have demonstrated that mass azithromycin distribution selects for macrolide resistance in *Streptococcus pneumoniae*.[33] Although the prevalence of macrolide resistance in pneumococcus has been shown to decline following cessation of azithromycin distribution[34], it is possible that increased antibiotic distribution would slow the decline of pneumococcal resistance after cessation of distribution. Any program considering increasing frequency of mass azithromycin distribution would need to do so in consideration of the potential for increased resistance selection.

The results of this study must be considered in the context of several limitations. First, a 12-month, or even a 24-month period of evaluation was short. Trachoma programs treat for 3 to 5 years and then re-evaluate continued indication for treatment. Longer-term evaluation of increased distribution frequency may yield important insights for consideration of increased frequency. This study was conducted in a hyperendemic region of Ethiopia, with very high baseline prevalence of ocular chlamydia. As trachoma prevalence is declining globally[35,36], the results of this study are unlikely to be generalizable to lower-prevalence settings. However, some districts in Ethiopia continue to have high levels of ocular chlamydia, despite multiple years of annual mass azithromycin distribution.[12,13] Alternative strategies including increased frequency of antibiotics could be considered in districts with refractory trachoma that remain hyperendemic despite many years of annual azithromycin treatment. Secondary analyses such as these are prone to alpha error. Here, we required omnibus ANOVA analyses of multiple arms to be significant at the level of $P<0.01$, before we allowed pairwise comparisons to be performed. However, given the multiple comparisons we are still at risk for Type I error.

We demonstrated that increased frequency of azithromycin distribution over one and two years led to a significant decrease in the prevalence of ocular chlamydia in both children and adults in a hyperendemic area of Ethiopia. In regions with persistently high levels of ocular

chlamydia, increasing distribution of azithromycin may be an alternative strategy to achieve elimination of trachoma.

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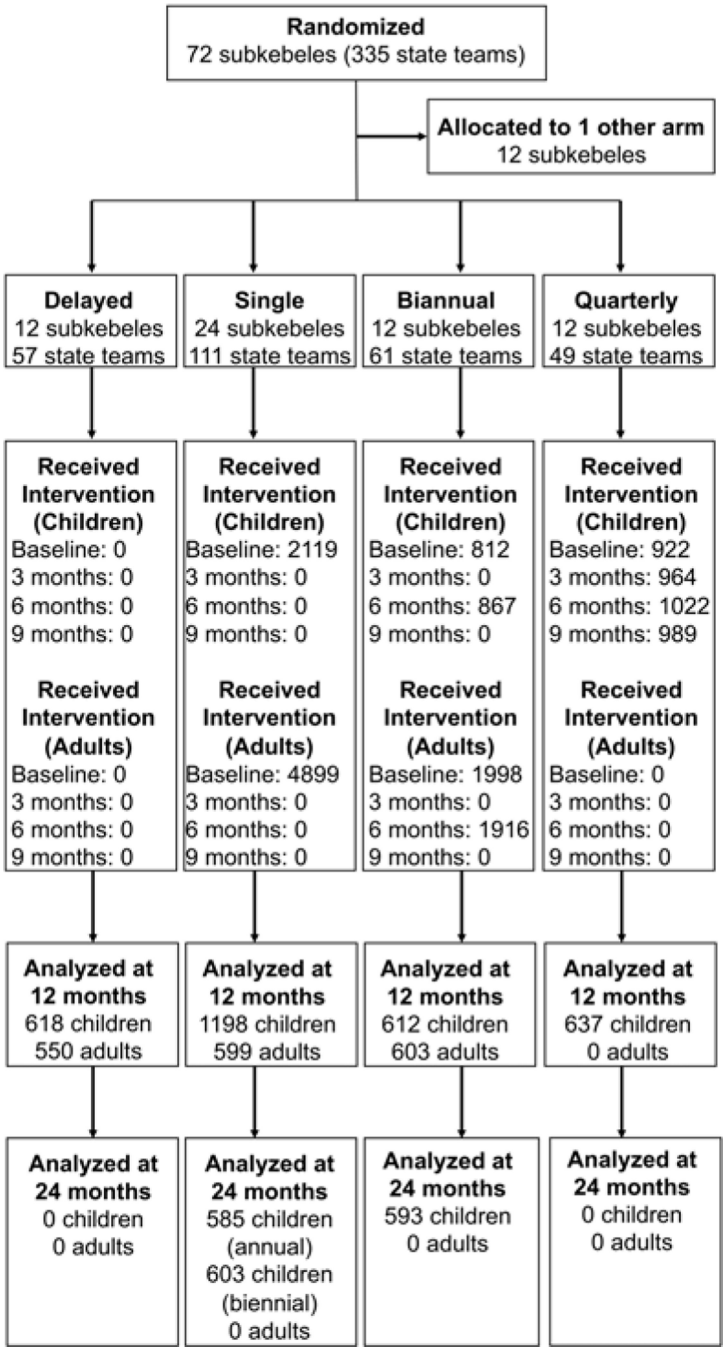

Figure 1.

CONSORT diagram for the trial. Number of children and adults receiving the intervention refers to the number of children and adults in sentinel communities included in the analysis.

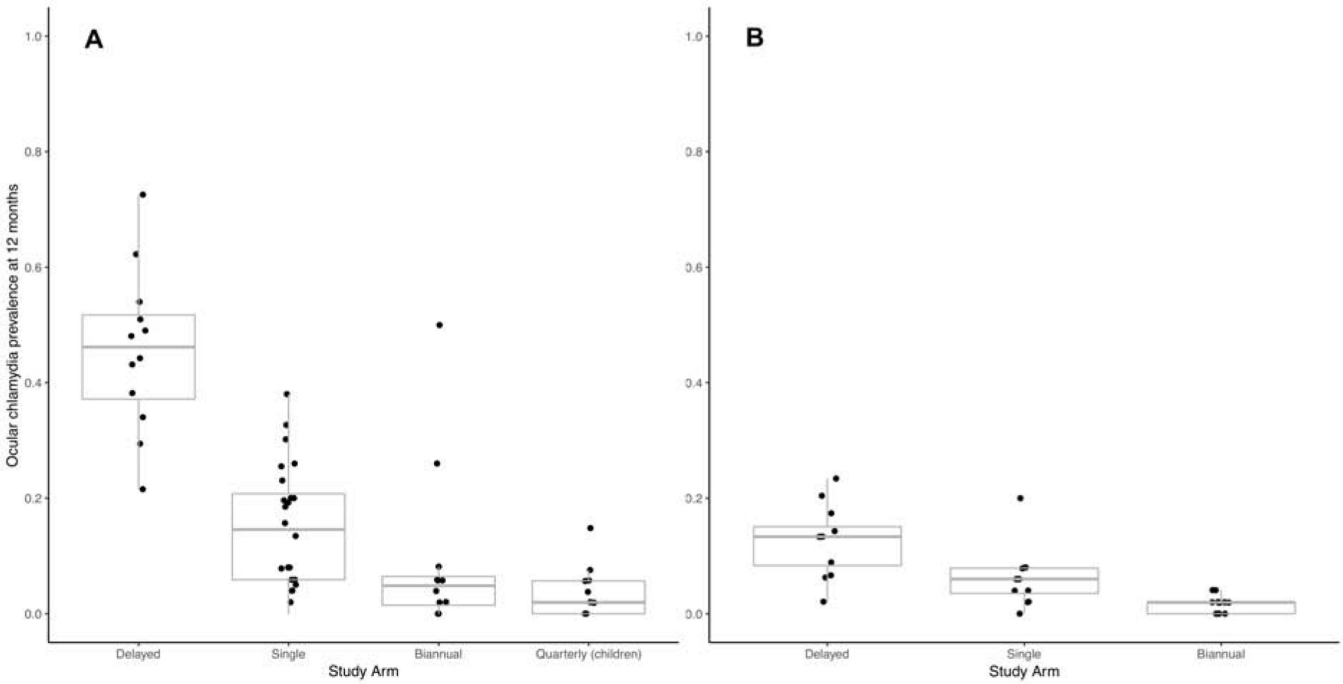

Figure 2.

a. 12-month ocular chlamydia prevalence in children aged 0–9 years by azithromycin distribution frequency. Box plots indicate medians and interquartile ranges. Individual points indicate individual community prevalence. The prevalence was significantly different across arms (P=0.0001), decreasing as distribution frequency increased (P<0.0001).

b. 12-month ocular chlamydia prevalence in adults and older children aged 11 and above by azithromycin distribution frequency. Box plots indicate medians and interquartile ranges. Individual points indicate individual community prevalence. The prevalence was significantly different across arms (P=0.0001), decreasing as distribution frequency increased (P<0.0001).

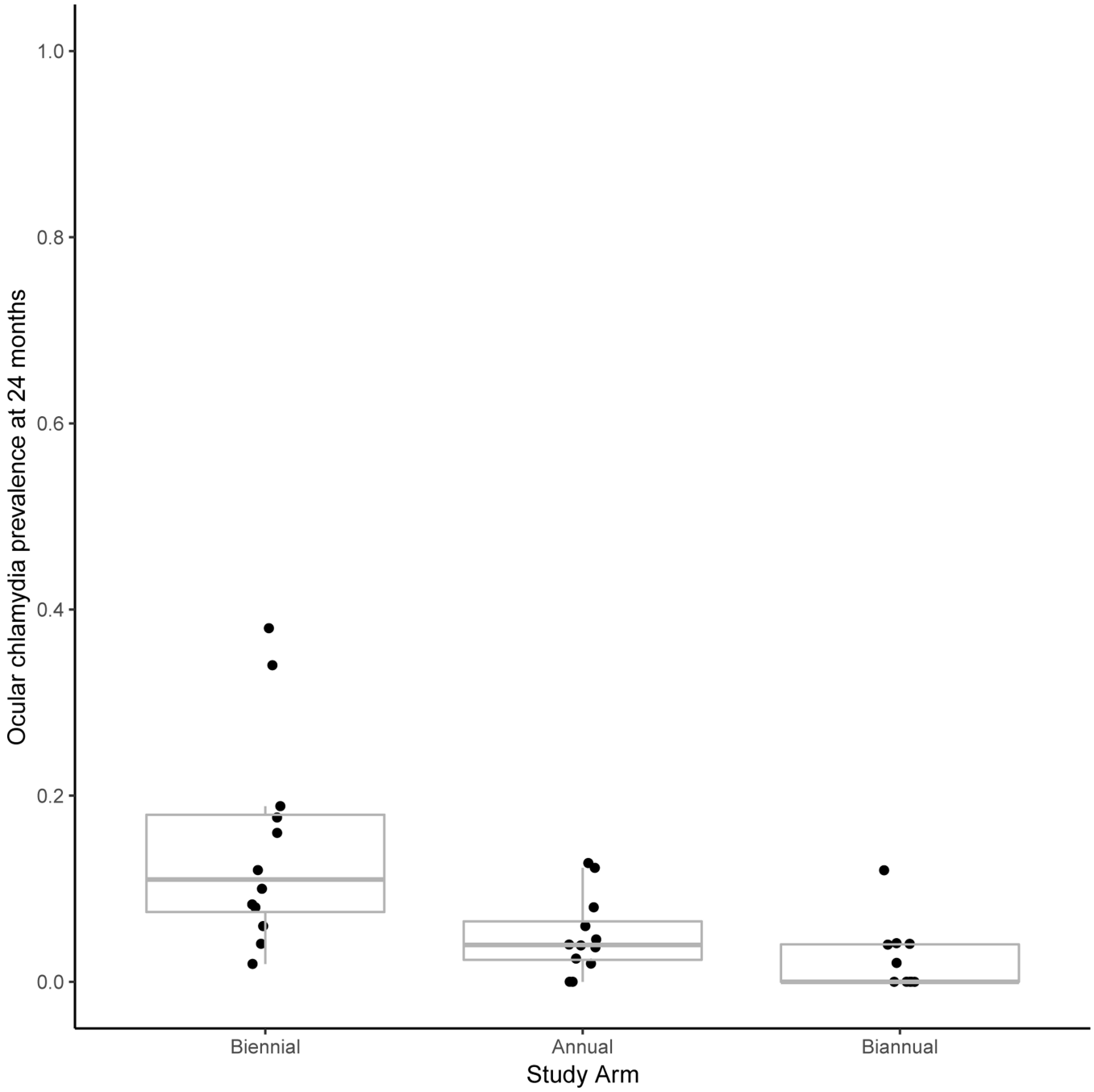

Figure 3.

24-month ocular chlamydia prevalence in children aged 0–9 years by azithromycin distribution frequency. Box plots indicate medians and interquartile ranges. Individual points indicate individual community prevalence. The prevalence was significantly different across arms (P=0.005).

Table 1.

Baseline characteristics by study arm

	Delayed(*n*=12 communities)	**Biennial(*n*=12 communities)**	**Annual((*n*=12 communities)**	**Biannual(*n*=12 communities)**	**Quarterly(*n*=12 communities)**
Children aged 0–9 years, mean (SD)	114(48)	114 (48)	102 (43)	90(24)	107 (33)
Total population, mean (SD)	350(137)	356 (138)	320 (135)	286(77)	312 (85)
Children aged 0–9 years, proportion (SD)	32.0% (3.5%)	31.9% (5.6%)	31.9% (4.5%)	31.7% (3.9%)	34.2% (4.3%)
Female, proportion (SD)	49.8% (1.2%)	49.7% (3.1%)	50.1% (2.8%)	50.3% (3.4%)	51.3% (2.6%)
TF, prevalence (SD)[1]	N/A	57.2% (28.0%)	61.0% (24.1%)	73.1% (20.2%)	54.3% (24.7%)

Results are presented as means of community-level estimates.

[1]Exams were not performed at baseline in the delayed azithromycin arm, and therefore baseline TF (follicular trachoma) estimates are not available.

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Table 2.

Mean community antibiotic coverage in children aged 1–9 years over the 24-month study period by arm

	Delayed	Biennial	Annual	Biannual	Quarterly
Month 0, mean (SD)	--	92.3% (5.7%)	80.9% (13.3%)	82.8% (5.7%)	74.3% (7.5%)
Month 3, mean (SD)	--	--	--	--	77.8% (6.9%)
Month 6, mean (SD)	--	--	--	84.2% (4.0%)	82.9% (5.4%)
Month 9, mean (SD)	--	--	--	--	83.0% (4.7%)
Month 12, mean (SD)	N/A	--	92.1% (5.0%)	92.8% (5.0%)	N/A
Month 18, mean (SD)	N/A	--		87.7% (7.7%)	N/A