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Authors

Mosenia, Arman
Haile, Berhan A
Shiferaw, Ayalew
et al.

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When the Neighboring Village is Not Treated: Role of Geographic Proximity to Communities Not Receiving Mass Antibiotics for Trachoma

Arman Mosenia,[1,2] Berhan A. Haile,[3] Ayalew Shiferaw,[3] Sintayehu Gebresillasie,[3] Teshome Gebre,[3,4] Mulat Zerihun,[3] Zerihun Tadesse,[3] Paul M. Emerson,[5] E. Kelly Callahan,[5] Zhaoxia Zhou,[1] Thomas M. Lietman,[1,6,7,8] and Jeremy D. Keenan[1,6]

[1]Francis I. Proctor Foundation, University of California, San Francisco, California, USA; [2]School of Medicine, University of California, San Francisco, California, USA; [3]The Carter Center Ethiopia, Addis Ababa, Ethiopia; [4]International Trachoma Initiative, The Taskforce for Global Health, Addis Ababa, Ethiopia; [5]The Carter Center, Atlanta, Georgia, USA; [6]Department of Ophthalmology, University of California, San Francisco, California, USA; [7]Department of Epidemiology & Biostatistics, University of California, San Francisco, California, USA; and [8]Institute for Global Health Sciences, University of California, San Francisco, California, USA

Background. Mass administration of azithromycin is an established strategy for decreasing the prevalence of trachoma in endemic areas. However, nearby untreated communities could serve as a reservoir that may increase the chances of chlamydia reinfection in treated communities.

Methods. As part of a cluster-randomized trial in Ethiopia, 60 communities were randomized to receive mass azithromycin distributions and 12 communities were randomized to no treatments until after the first year. Ocular chlamydia was assessed from a random sample of children per community at baseline and month 12. Distances between treated and untreated communities were assessed from global positioning system coordinates collected for the study.

Results. The pretreatment prevalence of ocular chlamydia among 0 to 9 year olds was 43% (95% confidence interval [CI], 39%-47%), which decreased to 11% (95% CI, 9%-14%) at the 12-month visit. The posttreatment prevalence of chlamydia was significantly higher in communities that were closer to an untreated community after adjusting for baseline prevalence and the number of mass treatments during the year (odds ratio, 1.12 [95% CI, 1.03-1.22] for each 1 km closer to an untreated community).

Conclusions. Mass azithromycin distributions to wide, contiguous geographic areas may reduce the likelihood of continued ocular chlamydia infection in the setting of mass antibiotic treatments.

Keywords. trachoma; ocular chlamydia; geographic information systems; mass drug administration; azithromycin.

Trachoma, caused by ocular chlamydia infection, affects more than 136 million people globally and remains the world's leading infectious cause of blindness. Mass administration of a single dose of azithromycin to entire communities has been shown to reduce the prevalence of ocular chlamydia infection. However, contrary to mathematical models, periodic repeated treatments have not resulted in complete regional elimination of ocular chlamydia [1]. A major obstacle is reinfection [2]. The source of reinfections is not entirely clear, but transmission from nearby untreated communities could be a contributing factor [2–4]. Prior studies have found ocular chlamydia infections to exhibit spatial autocorrelation, but evidence documenting the importance of reinfection from geographic proximity to untreated communities is limited [5–7].

The TANA trial was a cluster-randomized trial comparing different mass azithromycin distribution strategies [8]. Some study communities in TANA were randomized to delayed treatment for the first 12 months of the trial, providing an opportunity to assess the importance of geographic proximity to untreated communities. We hypothesized that transmission of ocular chlamydia would be greater in communities located closer to the untreated communities.

METHODS

This is an ancillary geospatial analysis of the TANA trial, the primary outcomes of which have been reported elsewhere [8–11]. The TANA trial was a cluster-randomized trial conducted from May 2006 to November 2009 in the Goncha Siso Enesie *woreda* of the Amhara region of Ethiopia. The study area had not received any mass azithromycin distributions for trachoma. Regions of Ethiopia are subdivided by the government into zones, which are further subdivided into woredas, and then kebeles. For trial purposes, each kebele was further divided into 3 subkebeles, and the subkebele was used as the unit of randomization for the trial. Seventy-two contiguous subkebeles in the TANA study area were randomized in an equal ratio to 1 of

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Correspondence: J. D. Keenan, Francis I. Proctor Foundation, University of California, 490 Illinois St, Box 0944, San Francisco, CA 94158 (jeremy.keenan@ucsf.edu).

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6 treatment arms: annual mass azithromycin distributions, biannual (twice-yearly) mass azithromycin distributions, quarterly mass azithromycin distributions to children aged 1 to 10 years, biennial mass azithromycin distributions, biennial mass azithromycin distributions + latrine promotion, and a delayed treatment arm that was not treated with azithromycin until after the month 12 study visit. Each subkebele consisted of 4 to 6 smaller communities known at the time as state teams. All state teams within the subkebele were treated identically. The present study includes the first 12 months of TANA, resulting in 4 groups of identically treated subkebeles: a single mass azithromycin treatment of the entire community at month 0 (n = 36 subkebeles), biannual mass azithromycin treatment at months 0 and 6 (n = 12 subkebeles), quarterly mass azithromycin treatment of children 1 to 10 years at months 0, 3, 6, and 9 (n = 12 subkebeles), and an untreated arm (n = 12).

Each community received an annual door-to-door census to enumerate the population eligible for treatment and monitoring. During the mass azithromycin distributions, each eligible person in the community was offered a single dose of oral azithromycin (20 mg/kg for children using height-based approximation and 1 g for adults). Children younger than 1 year, pregnant women, and those allergic to macrolide antibiotics who were otherwise eligible for treatment were instead offered 2 tubes of ophthalmic 1% tetracycline ointment to be used twice daily for 6 weeks. Antibiotic coverage was assessed for the present study as the proportion of children aged 1 to 9 years on the most recent census who received antibiotics; this age group was chosen because the majority of infections occur in children younger than 10 years of age [8, 12, 13].

One state team per subkebele was randomly selected as a sentinel state team for monitoring purposes. Because it was selected randomly, the sentinel state team provided a valid estimate of trial outcomes for the entire subkebele. A random sample of 40 children aged 0 to 9 years per sentinel state team was selected for ocular chlamydia monitoring, with the frequency of monitoring depending on treatment arm. For the present analysis, the 60 communities that received treatment at baseline were monitored at month 0, and all 72 communities were monitored at month 12. Monitoring was not performed in the delayed treatment arm at month 0 because of ethical concerns about performing trachoma assessments that would not be immediately followed by an antibiotic distribution. Separate cross-sectional random samples were chosen at each monitoring visit, drawn from the most recent study census. Monitoring visits were performed 2 to 4 weeks before a scheduled antibiotic distribution. A swab was collected from the everted right upper tarsal conjunctiva and processed for *Chlamydia trachomatis* using the AMPLICOR polymerase chain reaction assay (Roche Diagnostics USA, Indianapolis, Indiana) as reported previously [9]. Swabs from each state team were pooled into groups of 5 to increase efficiency, and community-level prevalence was estimated from the results of the pooled polymerase chain reaction using maximum likelihood estimation [14, 15].

Because all state teams in a subkebele were treated identically, the distance to the nearest untreated community was estimated as the distance between a sentinel state team (ie, the location from which the ocular chlamydia data was collected for the study) and the nearest border of an untreated subkebele. Subkebele borders were created manually in Google Earth using state team-level global positioning system data collected specifically for the study in combination with kebele borders from Environmental Systems Research Institute. Study global positioning system coordinates were obtained for all state teams (ie, both sentinel and nonsentinel state teams) of each subkebele in the study area, with a single set of coordinates captured in a central place in each state team. The distance between each of the sentinel state teams and the closest border of an untreated subkebele was calculated in R using the *sf* package.

The relationship between ocular chlamydia and proximity to an untreated subkebele was assessed in a multivariable generalized additive model to account for possible nonlinearity in the relationship (mgcv package in R). The outcome of interest was the prevalence of ocular chlamydia at month 12 from sentinel state teams in the 60 subkebeles that were treated during the first year of the study. State team–level proportions were modeled as a binomial outcome with a logit link, weighted by the number of observations per state team. The exposure variables included a smooth function for baseline ocular chlamydia prevalence, a smooth function for the distance to the nearest untreated subkebele, and a term for treatment frequency (1, 2, or 4 treatments, modeled as a factor). Smoothing was done using thin-plate regression splines, with optimal smoothing parameters selected by restricted maximum likelihood. Because the smoothed terms are nonlinear, their association with the 12-month chlamydia outcome could not be summarized as a single coefficient. Therefore, the relationship between 12-month ocular chlamydia prevalence and each of the smoothed terms from the generalized additive model was depicted visually as a partial residual plot. Partial residual plots are analogous to a scatter plot, but depict the relationship between the outcome variable and smoothed term after adjusting for other covariates in the model. Statistical significance was assessed from the approximate Wald *P* value of the smooth function. A similarly parameterized linear model was run as a sensitivity analysis.

RESULTS

At baseline, a randomly chosen sentinel state team from 60 of 72 study subkebeles was monitored for ocular chlamydia, with monitoring deferred in the 12 subkebeles randomized to delayed treatment. The geospatial distribution of state teams within subkebeles is shown in Figure 1. Overall, the mean baseline prevalence of ocular chlamydia among children aged 0 to 9

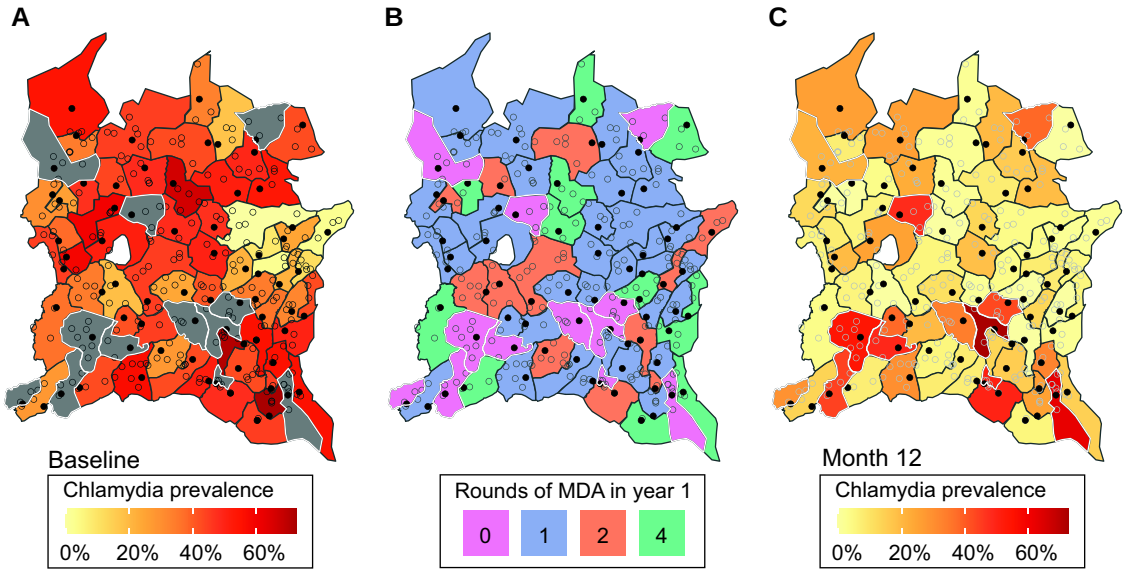

Figure 1. Ocular chlamydia prevalence. Polygons represent the 72 study subkebeles. *A,* Baseline ocular chlamydia prevalence among children aged 0 to 9 y, assessed in a randomly selected sentinel state team per subkebele. Baseline monitoring was not performed in the 12 subkebeles randomized to delayed treatment (shaded gray with white borders). *B,* Randomization allocation for the trial, represented as the number of mass azithromycin distributions in the first 12 mo of the study. The black dots represent the location of the sentinel communities; the empty gray circles represent the location of nonsentinel communities. *B,* ocular chlamydia prevalence at month 12. Abbreviation: MDA, mass drug administration with azithromycin.

years was 43% (95% confidence interval [CI], 39%-47%; range, 6%-74%); Figure 1*A* and Table 1.

During the first year of the trial, 36 subkebeles were treated with a single mass azithromycin distribution, 12 were treated with 2 biannual mass azithromycin distributions, 12 were treated with 4 quarterly mass azithromycin distributions, and 12 received no mass azithromycin distributions (Figure 1*B*). Antibiotic coverage was high in all treatment arms, with an overall mean coverage of 80% or greater among 1 to 9 year olds across all treatments scheduled during the first year of the study (Table 2). At the month 12 monitoring visit, the prevalence of ocular chlamydia decreased in each of the 60 subkebeles randomized to azithromycin treatment—as assessed in the sentinel state team of each subkebele (Figure 1*C* and Table 1)—to a mean of 11% (95% CI, 9%-14%). In contrast, the prevalence of ocular chlamydia in the 12 subkebeles not treated with azithromycin was 46% (38%-54%) at month 12, which was similar to the baseline prevalence in the other subkebeles before initiating treatment (Table 1).

The distance between the sentinel state team of the 60 treated subkebeles and the closest untreated subkebele was on average 2.2 km (95% CI, 1.8-2.6 km). After adjusting for baseline ocular chlamydia and the number of mass azithromycin distributions during the year, the prevalence of ocular chlamydia at month 12 was significantly greater in treated sentinel state teams located closer to an untreated subkebele, regardless of whether the

Table 1. Results of Trachoma Monitoring, Stratified by Treatment Group

	Prevalence (95% confidence interval)			
Outcome	0 MDAs	1 MDA	2 MDAs	4 MDAs
TF and/or TI	…	…	…	…
Month 0	—	67% (60%–74%)	84% (76%–90%)	69% (60%–78%)
Month 12	70% (64%–77%)	55% (51%–58%)	48% (40%–57%)	41% (33%–49%)
Chlamydia trachomatis	…	…	…	…
Month 0	—	43% (38%–49%)	38% (31%–45%)	48% (44%–53%)
Month 12	46% (38%–53%)	14% (11%–18%)	9% (3%–18%)	4% (2%–6%)

The mean prevalence of trachomatous inflammation-follicular (TF) and/or trachomatous inflammation-intense (TI), and the mean prevalence of ocular chlamydia infection are shown for each of the 4 treatment groups, each assessed in a random sample of children aged 0 to 9 years. TF and TI were assessed by conjunctival examination using the World Health Organization grading system and conjunctival swabs were processed for Chlamydia trachomatis using the AMLICOR assay.

Abbreviation: MDA, mass drug administration with azithromycin.

Table 2. Antibiotic Coverage, Stratified by Treatment Group

	Antibiotic coverage (95% confidence interval)			
Time Point	0 MDAs	1 MDA	2 MDAs	4 MDAs
Month 0	—	86% (82%–89%)	83% (80%–86%)	74% (70%–78%)
Month 3	—	—	—	78% (74%–82%)
Month 6	—	—	84% (82%–87%)	83% (80%–86%)
Month 9	—	—	—	83% (80%–85%)

The mean antibiotic coverage among children aged 1 to 9 years is shown in each of the 4 treatment groups.
Abbreviation: MDA, mass drug administration with azithromycin.

data were modeled in nonlinear models (Figure 2; approximate *P* value for smooth distance term < .001) or linear models (odds ratio, 1.12 [95% CI, 1.03-1.22] for each 1 km closer to an untreated subkebele).

DISCUSSION

It has been speculated that reemergence of trachoma in communities treated with mass azithromycin distributions may be partially attributable to the proximity to untreated areas [2, 3, 16]. However, few studies have tested this hypothesis. In the present study, we found that the prevalence of ocular chlamydia infection 12 months after starting mass azithromycin distributions was significantly higher in communities located closer to an untreated community, even after adjusting for baseline prevalence of ocular chlamydia and the number of mass azithromycin treatments. This study is consistent with the theory that at least some of the reinfections observed in communities treated with mass azithromycin distributions may be due to neighboring communities not receiving azithromycin.

Previous studies have suggested that outside areas not receiving mass azithromycin distributions may be an important source of reinfections for mass antibiotic programs. For example, 1 study of mass azithromycin distributions in the Gambia observed a cluster of infections in several communities close to the border of Senegal, where no mass antibiotics had been administered for trachoma [5, 6]. A different study in the Gambia found more reemergent infections in villages in which almost all residents had made a pilgrimage to an untreated area of Senegal [17]. A study in Tanzania found more ocular chlamydia infections among migrants from outside the community [18]. Other studies have speculated about the possibility that nearby untreated communities may have been the source of reinfections during a period of mass azithromycin distributions [2]. The present study is consistent with these prior reports and provides additional evidence that proximity to untreated areas may indeed be important for continued ocular chlamydia infections following mass azithromycin distributions.

We speculate that routine travel to untreated areas may present opportunities for infections to be reintroduced to treated

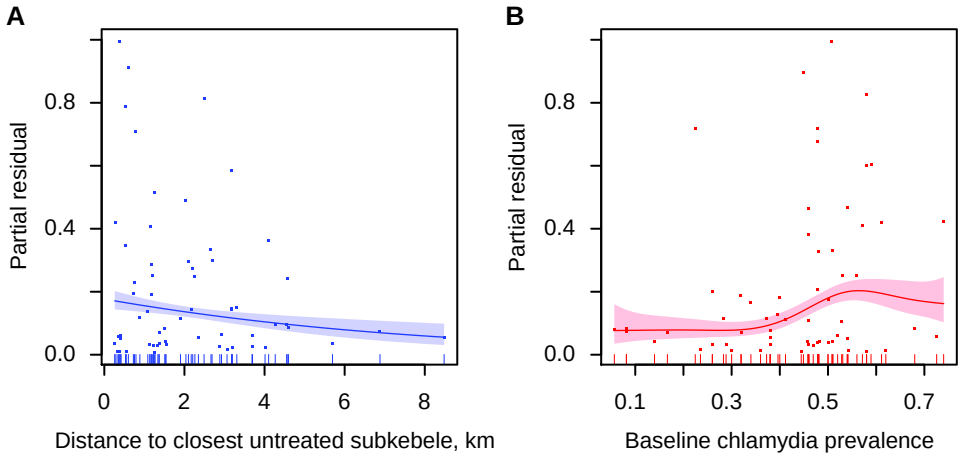

Figure 2. Relationship between ocular chlamydia and distance to closest untreated subkebele. Partial residual plots are shown for a generalized additive model that modeled the prevalence of ocular chlamydia at month 12 as a function of nonlinear terms for distance to the closest untreated subkebele (*A*) and baseline ocular chlamydia prevalence (*B*). Partial residual plots depict the relationship between an outcome (eg, ocular chlamydia prevalence at month 12) and exposure variable (eg, distance to the closest untreated subkebele, baseline ocular chlamydia) after adjusting for the other covariates in the model. The dots represent the partial residuals for each nonlinear term, the lines represent the fitted splines of the smoothing functions, and bars indicate 95% confidence intervals. The frequency of observed explanatory variables are shown in a rug plot along the x-axis.

communities. For example, a previous study from a different area of Ethiopia found travel outside the community to be relatively common, and for a variety of reasons (eg, market, school, work, religious services, family events) [19]. Nomadic populations residing near international borders may be especially at risk for traveling between treated and untreated communities, especially in the absence of any cross-border collaborations [20].

This study has several strengths, including randomization of the untreated communities, which reduced the chances of confounding, and assessment of ocular chlamydia infection in the untreated communities at month 12, which provides increased plausibility that the high prevalence of infections in untreated communities could have been responsible for continued transmission in the treated communities. Moreover, population-based sampling was used at standardized time points. The study also has limitations. We did not collect information on individual-level travel patterns. Communities were randomized to different frequencies of azithromycin distributions, with differing age groups targeted for treatment. Some communities had received a mass azithromycin distribution as little as 3 or 6 months before the month 12 monitoring visit, which likely reduced the overall prevalence of ocular chlamydia, and hence, the statistical power of the study. The study was performed in an area of Ethiopia with hyperendemic trachoma. It is not clear if the findings can be generalized to areas with less prevalent trachoma.

In summary, this study showed that the prevalence of ocular chlamydia 1 year after starting mass azithromycin treatments was significantly higher in communities that were closer to an untreated community. The study supports the World Health Organization recommendation to use districts as the unit of trachoma treatment because administering mass azithromycin distributions over wide contiguous areas should reduce the impact of untreated areas as reservoirs for ocular chlamydia infections. Cross-border collaboration may be important for trachoma elimination in trachoma-endemic areas that span international borders.

Notes

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