Comparison of Annual and Biannual Mass Antibiotic Administration for Elimination of Infectious Trachoma

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Context Treatment recommendations assume that repeated mass antibiotic distributions can control, but not eradicate or even locally eliminate, the ocular strains of chlamydia that cause trachoma. Elimination may be an important end point because of concern that infection will return to communities that have lost immunity to chlamydia after antibiotics are discontinued.

Objective To determine whether biannual treatment can eliminate ocular chlamydial infection from preschool children and to compare results with the World Health Organization–recommended annual treatment.

Design, Setting, and Participants A cluster-randomized clinical trial of biannual vs annual mass azithromycin administrations to all residents of 16 rural villages in the Gurage Zone, Ethiopia, from March 2003 to April 2005.

Interventions At scheduled treatments, all individuals aged 1 year or older were offered a single dose of oral azithromycin either annually or biannually.

Main Outcome Measure Village prevalence of ocular chlamydial infection and presence of elimination at 24 months in preschool children determined by polymerase chain reaction, correcting for baseline prevalence. Antibiotic treatments were performed after sample collections.

Results Overall, 14 897 of 16 403 eligible individuals (90.8%) received their scheduled treatment. In the villages in which residents were treated annually, the prevalence of infection in preschool children was reduced from a mean of 42.6% (range, 14.7%-56.4%) to 6.8% (range, 0.0%-22.0%) at 24 months. In the villages in which residents were treated biannually, infection was reduced from 31.6% pretreatment (range, 6.1%-48.6%) to 0.9% (range, 0.0%-4.8%) at 24 months. Biannual treatment was associated with a lower prevalence at 24 months ($P=.03$, adjusting for baseline prevalence). At 24 months, no infection could be identified in 6 of 8 of those treated biannually and in 1 of 8 of those treated annually ($P=.049$, adjusting for baseline prevalence).

Conclusion Local elimination of ocular chlamydial infection appears feasible even in the most severely affected areas, although it may require biannual mass antibiotic distributions at a high coverage level.

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TRACHOMA IS THE LEADING infectious cause of blindness worldwide.[1] Although it has been eliminated from Western Europe and the United States, it is still endemic in poor, arid areas such as rural sub-Saharan Africa.[2,3] The World Health Organization (WHO) has launched a program to control trachoma, relying in large part on annual repeated mass azithromycin administrations.[2] Program administrators anticipate that the treatments will reduce the prevalence of the ocular strains of chlamydia that cause trachoma to a level low enough that resulting blindness will no longer be a major public health concern. However, local elimination of ocular chlamydia may be obtainable.[4-8] Elimination has become a particularly important end point because of a growing concern that infection may return into communities that have lost some of their immunity to chlamydia after antibiotics are discontinued.[9,10] Mathematical models suggest that elimination is possible, but may require relatively frequent treatments

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in hyperendemic regions where more than 30% of children have evidence of infection.[11-14] These models predict that in a severely affected area of Ethiopia, biannual coverage of 80% of the population may eliminate infection while annual treatments may not.[12] In this study, we tested this hypothesis by comparing mass treatments given annually and biannually in an area hyperendemic for trachoma.

METHODS

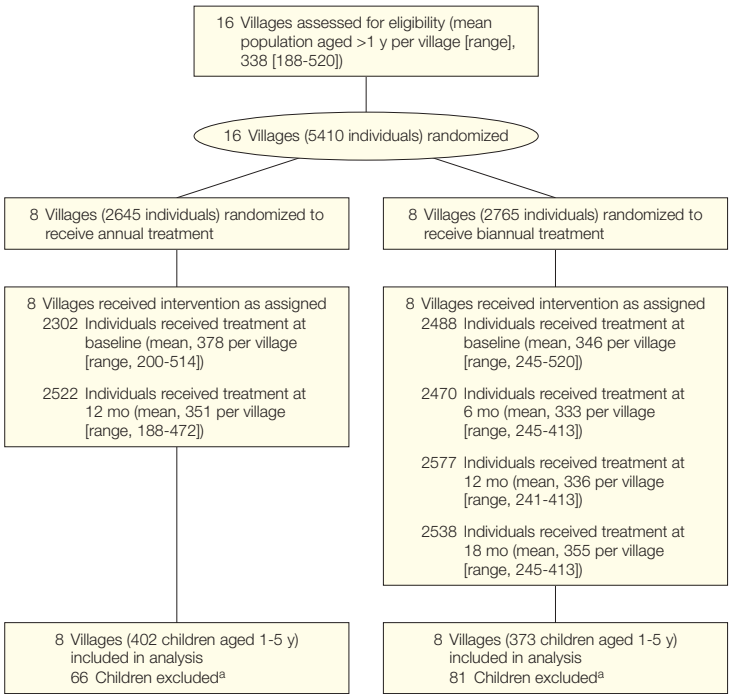
Sixteen adjacent villages from 3 Kebele (government units which, in this area, typically contain 5 to 6 villages) in the Goro district of the Gurage Zone of southern Ethiopia were censused in February 2003. Eight villages were randomly assigned to receive annual treatments and 8 to receive biannual treatments (generation by the RAND command in Excel by T.M.L., implementation including enrollment and assignment of participants by M.M., FIGURE 1). Censuses were performed by individuals masked to study group assignment and to infection prevalence. At scheduled treatments, those aged 1 year and older were offered a single dose of oral azithromycin (1g for adults or 20 mg/kg for children). Consumption of doses was directly observed. Pregnant women and those allergic to macrolides were offered a 6-week course of topical 1% tetracycline ointment (applied twice daily to both eyes and not directly observed). Those younger than 1 year were not treated because oral azithromycin had not yet been approved for use in this age group. Antibiotics were distributed after swabbing was completed, within 2 weeks of the swabbing.

Children aged 1 to 5 years in treated villages were assessed for the presence of ocular chlamydial infection, at baseline (pretreatment) and at 2, 6, 12, 18, and 24 months after treatment. A Dacron swab was passed firmly across the right upper tarsal conjunctiva 3 times, rotating approximately 120° between each pass. Two types of field controls were obtained immediately after the initial study swab: a duplicate control (2 swabs of the same child) in 5 randomly selected children in each village and a negative field control passed within an inch of, but not touching, the conjunctiva of 5 different children who were also randomly selected in each village. Examiners then changed gloves before obtaining swabs from the next child.

In addition to the preschool survey, we used the census from each village to select a simple random sample of 25 individuals older than 5 years to assess the prevalence of ocular chlamydial infection in the whole community at 18 and 24 months. All samples were kept at 4°C in the field and frozen at −20°C within 6 hours. The swabs were shipped at 4°C to San Francisco, California, where they were stored at −70°C until processed. The Amplicor polymerase chain reaction (PCR) test (Roche Diagnostics, Branchburg, New Jersey) was used to detect chlamydial DNA.

Pretreatment samples were tested individually. Posttreatment samples from the same village were randomized and pooled into groups of 5, with a possible remainder pool of 1 to 4 samples. Each pool was then tested according to the Amplicor protocol. If two-thirds or more of the pools tested positive for chlamydia, the individual samples were repooled randomly into groups of 2 and reprocessed to allow for a more accurate estimation.[15] If PCR of any pool was equivocal, then all samples from the pool were individually retested. The prevalence of ocular chlamydial infection in each village was obtained by maximum likelihood estimation.[12] The number of positive individual samples most likely to have resulted in the observed pooled PCR results was chosen as the estimate for that village (Mathematica 5.0, Wolfram Research Inc, Champaign, Illinois). This procedure can accurately estimate the prevalence in the village as long as it is relatively low (ie, $< 10\%$), as is typically found after treatment.[15] However, it does not identify in-

Figure 1. Flow of Participants Through Each Stage of the Cluster-Randomized Trial



[a] The 3 most common reasons for exclusion were absence from village, moved to another village, and death.

Table 1. Baseline Characteristics

	Annually Treated (95% Confidence Interval)	Biannually Treated (95% Confidence Interval)	*P* Value
No. of villages	8	8	
Children aged 1-5 years			
Mean No. per village	56.8 (38.5-75.0)	49.0 (38.7-59.3)	.50
Average age, y	3.23 (3.12-3.34)	3.15 (3.03-3.27)	.42
Girls, %	52.2 (47.7-56.7)	50.8 (46.1-55.4)	.69
Mean PCR prevalence, %	42.6 (31.1-54.0)	31.6 (19.1-44.1)	.15
Mean clinical activity using WHO simplified grading scale, %[a]	82.5 (75.6-89.3)	74.9 (65.4-84.4)	.15

Abbreviations: PCR, polymerase chain reaction; WHO, World Health Organization.
[a] Children were considered clinically active if they had 5 or more follicles in the upper tarsal conjunctiva or pronounced inflammatory thickening of the tarsal conjunctiva obscuring more than half of the normal underlying tarsal vessels.

dividuals with positive results without further testing.[15,16] Fieldworkers who performed antibiotic distributions and clinical assessments were aware of treatment schedules. Laboratory personnel were masked to individual, village, and treatment group identifications. *Elimination* was defined as no children aged 1 to 5 years living in a participating village with positive PCR test results for chlamydia at month 24. It should be noted that this does not prevent subsequent reintroduction from neighboring areas.[17]

Analyses were performed at the village level for several reasons. Analysis at the individual level, after correcting for the relatively high intravillage correlation, offers little additional power.[18,19] Village level–analysis allowed us to use the pooled results in a cost-effective manner.[12,15,16,20] Finally, the level of intervention in trachoma control is the community, so results expressed directly in terms of the community may be more relevant to those implementing programs. We estimated that the inclusion of 8 villages per group would provide 80% power of detecting an 8% difference in the prevalence of infection in preschool children at 24 months, assuming a standard deviation of 5.0%, a correlation between baseline and 24 months of 0.5, and a 2-tailed α of .05. This would also provide 90% power to detect a difference in the proportion of villages in each group with elimination of infection in children at 2 years (2-tailed $\alpha = .05$, assuming 60% elimination in biannually treated village residents and 5% in annually treated village residents).

We used logistic regression to test the hypothesis that study group was associated with local elimination, controlling for baseline prevalence. Due to the small number of villages, we conducted a permutation test for the significance of the coefficients that was designed for small data sets.[21] Robust regression (STATA command rreg, v. 10, STATACorp, College Station, Texas) was used to compare prevalence at 24 months, using treatment group and baseline prevalence rank as covariates[22] (because of the presence of outliers, standard regression models could give misleading results). Baseline characteristics in TABLE 1 were compared using the χ^2 test for sex and the *t* test for other characteristics. Ninety-five percent confidence intervals (CIs) were constructed from the village means, using the t distribution. If the lower confidence limit was negative, we computed a 95% bootstrap percentile interval. All statistical calculations were performed in STATA 10.0 (StataCorp), except for the permutation test, which was conducted in R 2.6.0 (http://www.r-project.org).

Predictions in FIGURE 2 were produced using a standard Susceptible-Infected-Susceptible (SIS) model. In this model, susceptible individuals are infected with chlamydia and recover to again become susceptible either naturally or through treatment, as previously described.[11,12] Briefly, mass treatments were simulated by reducing infection at the appropriate time points by the effective coverage level. Return of infection between treatments was estimated using the differential equation:

$$dy/dt = \beta\, y(1\text{-}y) - \gamma\, y,$$

where y is the prevalence of infection in the community, γ is a recovery parameter, and β is a transmission parameter previously estimated from 24 separate but nearby Ethiopian villages.[12-14]

Oral consent was obtained from adults and from guardians of minors. Ethical approval for this study was obtained from the Committee for Human Research of the University of California, San Francisco, and the Ethiopian Science and Technology Commission. The study was carried out in accordance with the Declaration of Helsinki.

RESULTS

At baseline, 821 children aged 1 to 5 years were monitored for infection in the 16 communities. The mean age and the sex of children in the 2 groups were similar (Table 1). At baseline, the annually treated group had more infection than the biannually treated group, although the difference was not statistically significant ($P = .15$). Because of this difference, the 24-month outcomes were adjusted for the baseline prevalence. The mean antibiotic coverage for villages in both groups was estimated to be 91.2% relative to the census (range, 78%-100%; TABLE 2). An analysis of variance revealed that there was no statistically significant difference in coverage between study groups ($P = .12$), although there was a difference in coverage at different visits ($P = .03$). The 3 most common reasons for missing a scheduled treatment or examination were that the individual was absent from the village, the family had moved, or the individual had died since the previous visit. No village dropped out of the study. There were no serious adverse advents due to the study medicine reported. In village 1 and village 6 at the 12-month visit, the proportion of pools (of 5) that had positive test results exceeded two-thirds, so samples were rerandomized into pools of 2. A single negative field

control tested positive by PCR (1/336) and 3 duplicate controls were discordant (3/328).

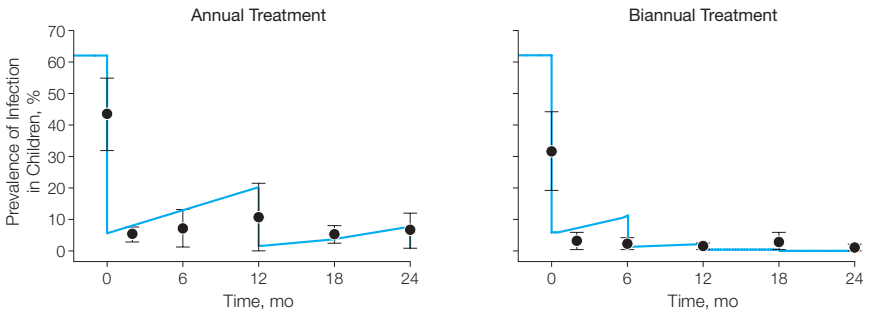
The prevalence of infection in preschool children by village over time is shown in TABLE 3. The mean prevalence of the 16 villages was dramatically reduced after the first treatment ($P<.001$, Wilcoxon signed-rank test). Two annual treatments (baseline and 12 months) reduced infection in 8 villages 6-fold to 6.8% (range, 0%-22%) by 24 months. Four biannual treatments (baseline, 6, 12, and 18 months) reduced infection in the other 8 villages 35-fold to 0.9% (range, 0.0%-5.0%) by 24 months. The prevalence of infection at 24 months was significantly lower in the biannually treated villages (0.9%; 95% CI, 0.0%-2.1%) than in the annually treated villages (6.8%; 95% CI, 1.2%-12.4%), adjusting for baseline prevalence ($P=.03$, robust regression).

At 24 months, no infection could be identified in preschool children in 6 of 8 of the residents receiving biannual treatment and 1 of 8 of the residents receiving annual treatments. Having no infection identified at 24 months was associated with being in the biannual treatment group ($P=.049$, Potter test, 10^7 replicates).[21] Having no infection at 24 months was not significantly associated with baseline prevalence ($P=.06$, Potter test, 10^4 replicates).[21] In the sample of individuals outside the preschool age group, a single infection was found at 18 months (0.74%; 95% CI, 0.02% to 4.03%; with the single infection in village 6) and at 24 months (0.88%; 95% CI, 0.02% to 4.79%, with the single infection in village 10). Both villages 6 and 10 had infection identified in the preschool group as well at these visits. Thus, if no infection was found in preschool children, then none was found in the sample of the rest of that community either. The mean prevalence of the annually and the biannually treated groups from this study can be compared with the predictions of the mathematical model with hypothetical coverage of 91.2%, the mean level achieved in these villages (Figure 2).

COMMENT

The long-term rationale for mass antibiotic distributions for trachoma continues to be the subject of debate.[4,7-9,23] The WHO recommends that annual mass treatments be administered to control infection until the prevalence of clinical activity using the WHO Simplified Grading Scale falls below 10% in children.[24,25] WHO expects that minimal blindness will result if infection is kept at a low enough level, but they do not anticipate global eradication or even local elimination of infection from an area. The WHO plan relies on interventions, such as hygiene education or latrine construction, to prevent infection from returning. Although there are reasons to be optimistic, these interventions have yet to be proven to have an effect on ocular chlamydial infection.[26-29] As an alternative rationale, some have suggested that a single treatment may have a lasting effect, and even

Figure 2. Treatment Frequency and Infection Prevalence in 16 Ethiopian Villages



Annual treatment shows the estimated mean prevalence of infection in children observed in 8 participating villages (black points with 95% confidence intervals) superimposed on a prediction of a previous mathematical model, assuming the 91.2% coverage achieved in the villages (blue curve).[11-14] Biannual treatment shows the estimated mean prevalence in another 8 participating villages (black points with 95% confidence intervals) superimposed on the model with 91.2% coverage (blue curve).

Table 2. Antibiotic Coverage

Village	% (No./Total) of Treated Patients			
	Baseline	6 Months	12 Months	18 Months
		Annual		
1	100.0 (220/220)		99.1 (223/225)	
2	86.0 (172/200)		90.0 (180/200)	
3	78.4 (287/366)		83.6 (315/377)	
4	91.4 (372/407)		91.4 (372/407)	
5	88.1 (453/514)		78.3 (367/469)	
6	84.7 (400/472)		91.7 (433/472)	
7	85.4 (398/466)		96.6 (450/466)	
8	NA		96.8 (182/188)	
Mean (95% CI), %	87.7 (81.5-93.9)		90.9 (85.0-96.8)	
		Biannual		
9	89.8 (255/284)	95.2 (296/311)	98.0 (287/293)	94.2 (306/325)
10	89.5 (331/370)	87.8 (325/370)	94.2 (358/380)	88.1 (376/427)
11	92.3 (350/379)	95.3 (361/379)	96.2 (376/391)	96.0 (404/421)
12	92.2 (226/245)	98.8 (242/245)	99.6 (240/241)	82.9 (203/245)
13	93.3 (485/520)	91.8 (379/413)	93.2 (385/413)	79.0 (328/415)
14	87.1 (330/379)	90.0 (306/340)	99.5 (377/379)	96.1 (366/381)
15	85.8 (235/274)	96.5 (274/284)	97.1 (266/274)	85.1 (245/288)
16	87.9 (276/314)	90.0 (287/319)	90.3 (288/319)	92.3 (310/336)
Mean (95% CI), %	89.7 (87.5-92.0)	93.2 (90.0-96.3)	96.0 (93.3-98.7)	89.2 (83.8-94.6)

Abbreviations: CI, confidence interval; NA, not available.

be sufficient to prevent infection from returning.[6-8,30,31] Unfortunately, this appears not to be the case, at least in settings where a high percentage of children are infected before treatment.[7,12,32] In a neighboring district where the baseline prevalence of infection was more than 50%, infection gradually returned from very low levels within 6 to 24 months after a single treatment.[12,33] In the 8 villages whose residents received annual treatment, the average prevalence of infection rose between 2 and 12 months, further demonstrating that a single treatment alone is not sufficient for elimination in this setting (Figure 2). A third rationale for mass antibiotics is that infection may be locally eliminated with repeated distributions, as long as the frequency and coverage of antibiotics are sufficient.[4,5,7,11,12,34] Repeated treatments reduced the prevalence of infection in a single village in Nepal from 27% of children to a single case, and in a single village in Tanzania from 16% to a single case.[5,6] However, no previous study has documented that repeated mass treatments have eliminated infection from a hyperendemic area (where more than 30% of children may be infected).

Previously, we used a mathematical model of trachoma transmission to estimate the necessary frequency of antibiotic administration to eliminate infection.[11-14] Essentially, infection must be reduced more from each distribution than it returns between distributions. The rate of return found in 24 villages from a neighboring area of Ethiopia implies that with 80% coverage, treating more frequently than annually would eventually eliminate infection, but treating less frequently than annually would not.[12] At the higher coverage obtained in this study, the model predicts that infection would decrease with either annual or biannual treatment (Figure 2). Actual results agree well with the predictions, particularly in those receiving annual treatment. The departure from the predicted values in those receiving biannual treatment may reflect that with a small number of remaining infections, a stochastic model that takes into account the effects of chance may be more appropriate.[14] A previously published stochastic model predicts that it would take twice as long to achieve 75% elimination with annual treatment as with biannual treatment, which is consistent with the observed results herein.[14] In this study, infection decreased dramatically with both treatment frequencies. Although biannual treatment achieved a lower prevalence at 24 months, cost-effectiveness analysis will be necessary to assess whether the extra effort expended for biannual treatments is worthwhile. WHO recommendations must be based not only on what is feasible scientifically but also on what is feasible financially given finite resources. If the goal of treatment is to locally eliminate infection, biannual treatment may be more cost-effective in the long run. In our study, greater effort in distribution resulted in elimination of infection in preschool children in more villages.

There are several limitations to this study. A wide variation exists in the pretreatment prevalence of infection in these 16 neighboring villages. Even with randomization of 8 communities per group, the average pretreatment prevalence of infection was 11% higher in the

Table 3. Estimated Prevalence of Infection in Children Aged 1 to 5 Years

	Prevalence of Infection, % (No./Total)					
Village	Baseline	2 Months	6 Months	12 Months	18 Months	24 Months
			Annual			
1	48.5 (16/33)	6.3 (2/32)	15.6 (5/32)	37.8 (17/45)	7.9 (3/38)	22.0 (9/41)
2	50.0 (16/32)	3.1 (1/32)	0.0 (0/36)	3.6 (1/28)	3.1 (1/32)	9.1 (2/22)
3	56.4 (31/55)	7.1 (4/56)	10.9 (6/55)	11.1 (6/54)	6.3 (4/63)	4.8 (3/63)
4	30.0 (21/70)	0.0 (0/72)	0.0 (0/60)	0.0 (0/67)	3.0 (2/67)	4.7 (3/64)
5	52.2 (47/90)	5.7 (5/88)	3.7 (3/81)	3.4 (3/87)	5.7 (5/87)	4.9 (4/81)
6	45.6 (31/68)	7.6 (5/66)	18.6 (13/70)	22.8 (18/79)	9.9 (8/81)	6.3 (4/63)
7	43.1 (31/72)	7.7 (6/78)	4.2 (3/71)	5.3 (4/75)	1.5 (1/68)	2.5 (1/40)
8	14.7 (5/34)	3.3 (1/30)	3.8 (1/26)	3.6 (1/28)	0.0 (0/27)	0.0 (0/28)
Mean (95% CI), %	42.6 (31.1-54.0)	5.1 (2.8-7.4)	7.1 (1.2-13.0)	10.9 (0.1-21.8)	4.7 (1.9-7.5)	6.8 (1.2-12.4)
			Biannual			
9	25.6 (11/43)	2.4 (1/41)	2.1 (1/48)	1.9 (1/53)	4.1 (2/49)	0.0 (0/46)
10	42.9 (24/56)	10.5 (6/57)	7.1 (4/56)	1.6 (1/61)	12.5 (7/56)	4.8 (3/62)
11	28.9 (13/45)	2.1 (1/48)	0.0 (0/47)	0.0 (0/52)	0.0 (0/54)	0.0 (0/53)
12	6.1 (2/33)	0.0 (0/32)	0.0 (0/33)	0.0 (0/28)	0.0 (0/28)	0.0 (0/31)
13	48.3 (28/58)	1.6 (1/64)	0.0 (0/54)	0.0 (0/65)	0.0 (0/70)	2.1 (1/47)
14	48.6 (35/72)	2.8 (2/72)	2.9 (2/69)	0.0 (0/66)	0.0 (0/66)	0.0 (0/60)
15	34.1 (14/41)	5.0 (2/40)	4.7 (2/43)	2.3 (1/44)	0.0 (0/40)	0.0 (0/37)
16	18.2 (8/44)	0.0 (0/41)	0.0 (0/38)	5.0 (2/40)	4.4 (2/45)	0.0 (0/37)
Mean (95% CI), %	31.6 (19.0-44.1)	3.0 (0.2-5.9)	2.1 (0.5-3.9)	1.3 (0.3-2.6)	2.6 (0.5-5.8)	0.9 (0.0-2.1)

Abbreviation: CI, confidence interval.

annually treated than in the biannually treated groups (although this difference was not statistically significant). Other, unidentifiable factors in the biannually treated groups may have contributed to making the intervention appear more effective. Because this pretreatment prevalence was associated with later elimination in preschool children, we corrected for baseline prevalence in the regression models.

Another limitation is that not all individuals in the communities were sampled. However, monitoring coverage was high in the preschool age group, which is most likely to harbor ocular chlamydial infection both before and after treatment.[6,35] A sample of those aged 6 years and older at 18 and 24 months indicated no infection in the villages where none had been found in preschool children. Nevertheless, a complete survey of all individuals in the community will need to be conducted before complete elimination in a community can be definitively declared. Lastly, reinfection in communities where no infection was identified at a previous visit could come from individuals who had false-negative tests, from older individuals not sampled, or from contact with neighboring communities. To address this, additional follow-up visits will be necessary.

As trachoma programs progress, local elimination may become an important goal in trachoma control, at least in some areas. Complete elimination may not be necessary in hypoendemic regions where trachoma is no longer a major cause of blindness, or in areas with a strong secular trend causing trachoma to disappear in the absence of programmatic activity. However in severely affected areas, infection clearly returns after a single mass treatment unless it is locally eliminated.[32,33] It is not clear that antibiotic distributions should be continued indefinitely, due to limited resources and to the threat of emerging antibiotic resistance in chlamydia and other pathogens such as *Streptococcus pneumoniae*.[36-38] In addition, there is concern that communities from which trachoma has been partially eliminated will lose much of their immunity to chlamydia, only to have it return with a vengeance after treatments have been discontinued.[9,10,39] Complete local elimination from a region may be the best way to alleviate these concerns and the quickest path to elimination may be the optimal strategy.

The necessary frequency of mass azithromycin distributions depends on various factors, including the pretreatment prevalence of infection and the attainable coverage.[11,12] It also depends on the goal of treatment. Annual distributions reduce the prevalence of infection to a level in which, if sustained, minimal blindness would be expected. However, there is little evidence that other measures such as hygiene promotion and latrine construction can keep infection from returning once antibiotics have been discontinued.[26-29] Biannual coverage of a large portion of the community may be necessary to eliminate infection from a severely affected community or at least to do so in a timely manner. Although programs may be reluctant to devote their scarce resources to more frequent treatment, this may be more cost-effective in the long term. Local elimination of the ocular strains of chlamydia from villages is a feasible goal but may require biannual distributions in hyperendemic areas. The results of this study confirm models that suggest treatments will need to be given for more than the 2 years to predictably achieve elimination in more than 95% of villages.[14] Whether elimination from a larger area is possible will depend on the frequency of community-to-community transmission.[31]

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Study concept and design: Melese, Alemayehu, Lakew, Yi, Chidambaram, Gaynor, Whitcher, Lietman.
Acquisition of data: Melese, Alemayehu, Lakew, Yi, House, Chidambaram, Zhou, Cevallos, Ray, Hong, Phan, Zaidi, Gaynor, Lietman.
Analysis and interpretation of data: Ray, Porco, Lietman.
Drafting of the manuscript: House, Zhou, Cevallos, Hong, Porco, Gaynor, Whitcher.
Critical revision of the manuscript for important intellectual content: Melese, Alemayehu, Lakew, Yi, Chidambaram, Ray, Phan, Zaidi, Lietman.
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Statistical Review: Travis Porco, PhD, MD, Department of Epidemiology and Biostatistics, University of California, San Francisco performed the statistical analysis for the study.

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Standing for right when it is unpopular is a true test of moral character.
—Margaret Chase Smith (1897-1995)

