Can We Stop Mass Drug Administration Prior to 3 Annual Rounds in Communities With Low Prevalence of Trachoma?

PRET Ziada Trial Results

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Importance: The World Health Organization recommends at least 3 annual mass drug administrations (MDAs) of azithromycin in places where the prevalence of follicular trachoma (FT) is greater than 10%. However, stopping MDA prior to 3 rounds, if monitoring indicates an absence of infection with *Chlamydia trachomatis* even if FT persists, may be more cost-effective.

Objective: To determine the prevalence of infection in communities randomized to 3 rounds of annual MDAs with azithromycin compared with communities randomized to a stopping rule, where MDA could cease if the infection rate was low.

Design: A 1:1 community randomized trial comparing usual care with a cessation rule. The Partnership for the Rapid Elimination of Trachoma–Ziada Trial was conducted from February 1, 2010, through September 1, 2011.

Setting: Sixteen communities in Tanzania with trachoma prevalence rates between 10% and 20%.

Participants: A total of 100 children aged 5 years or younger randomly drawn from each community. Children had to reside in an eligible community, have no ocular condition that prevented trachoma grading or ocular specimen collection, and have a guardian who could provide consent for participation.

Interventions: Cessation of MDA with azithromycin if the community had no infection in their sample at 6 months or 18 months.

Main Outcome Measure: The prevalence of *C trachomatis* at 18 months.

Results: None of the intervention communities met criteria to stop MDA based on the 6-month or 18-month survey; all, as well as the usual care communities, were scheduled for a third MDA round. There was no difference in infection (2.9% vs 4.7%; $P = .25$) between the usual care and cessation rule communities at 18 months.

Conclusions and Relevance: In this setting, communities with low (10%-20%) initial prevalence of active trachoma did not have MDA stopped before 3 annual rounds on the basis of monitoring for infection. Infection with *C trachomatis* in communities with average trachoma rates at 12% to 13% cannot be eliminated before 3 rounds of MDA with azithromycin.

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TRACHOMA IS THE LEADING infectious cause of blindness in the world.[1] It is the result of repeated infection with *Chlamydia trachomatis*, which result in inflammation, scarring of the conjunctiva, entropion, and trichiasis, with the blinding sequelae of corneal opacification and visual impairment.[2] Trachoma disproportionately affects the poorest parts of the world and contributes to an ongoing cycle of disability and economic deprivation.

The World Health Organization (WHO) has recommended a 4-pronged approach to trachoma elimination called SAFE (Surgery to repair inturned eyelashes, mass administration of Antibiotics to reduce the pool of *C trachomatis*, Facial cleanliness to reduce transmission from mucosal secretions and Environmental improvements to interrupt transmission and prevent reemergence of infection). In communities where clinical trachoma (follicular trachoma [FT]) prevalence is greater than 10% in children aged

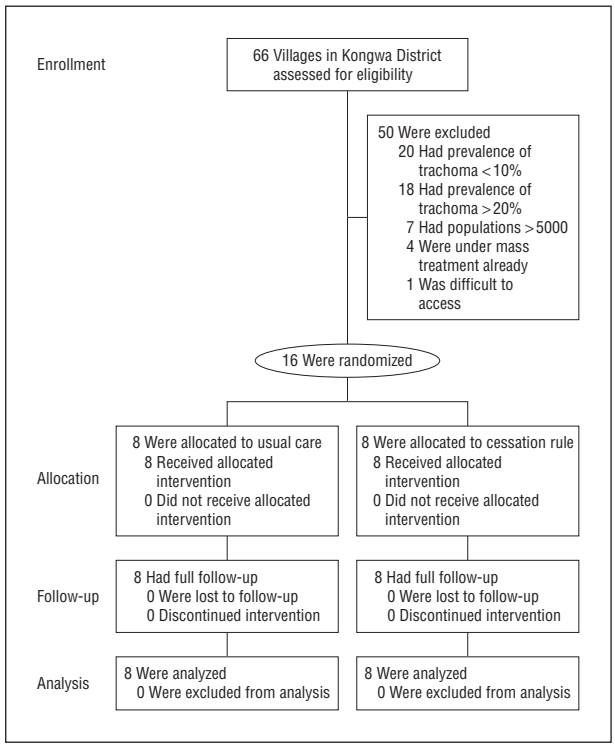

Figure 1. Consort diagram of the design and characteristics of the Partnership for the Rapid Elimination of Trachoma–Ziada Trial. The usual care arm received 3 rounds of MDAs, while the cessation rule group received MDA at baseline and thereafter only if infection prevalence was greater than 0% at the 6-month or 18-month follow-up visit.

1 to 9 years, the WHO recommends annual community-wide mass drug administrations (MDAs) for at least 3 years, with coverage of at least 80% of the population, followed by an impact survey.[3] If the survey indicates a prevalence of active trachoma of less than 5%, then antibiotic administration can be discontinued. The most widely used antibiotic is azithromycin, a single oral dose at 20 mg/kg up to 1 g. Topical tetracycline ointment has also been used, applied twice a day for 4 to 6 weeks.

However, several studies have shown that clinical signs of trachoma can persist, even if there is no infection.[4-7] Relying on clinical signs of trachoma for treatment decisions may result in unnecessary treatment of communities where infection is virtually eliminated and only residual signs are present in the sample surveyed. Yet, in some communities, even low rates of active trachoma are associated with the presence of *C trachomatis* infection.[8] Therefore, using a test for infection might have merit in deciding whether MDA can be stopped. It is still unclear how many rounds of annual MDA are needed to achieve the goal of less than 5% trachoma prevalence or even sustained low prevalence of infection. Studies of communities in Tanzania with prevalence rates of trachoma of more than 50% pretreatment suggest that multiple rounds (more than 7 years) of mass annual treatment may be necessary.[9,10] However, in one Tanzanian community with 20% prevalence of trachoma, as measured in all residents in a district with very little trachoma, a single round of MDA with high coverage (>95%) plus treating cases with topical tetracycline was enough to virtually eliminate infection.[11] Finally, in Gambian communities with an average of 8% trachoma prevalence (range, 3%-24%), trachoma elimination was feasible with 1 round of treatment.[5,12]

Such data suggest that in low prevalence communities (between 10% and 20%) and with delivery of MDA at high coverage, 3 annual rounds of MDA may be unnecessary. However, these data also suggest that the expectation that 1 round of MDA may eliminate trachoma in all low-prevalence settings might be unrealistic. The results from Gambian communities where trachoma prevalence was greater than 10%[12] but in districts at the tail end of elimination may not be the same as results from other communities with a prevalence close to 10% that are at the vanguard of elimination efforts in higher trachoma prevalence districts.

We hypothesized that, in communities where the starting prevalence of trachoma was estimated between 10% and 20%, less than 3 rounds of MDA would be needed to achieve an infection rate of less than 5% in children aged 5 years or younger. Furthermore, where communities achieved an estimated prevalence of infection of less than 5% (regardless of the status of clinical signs), we hypothesized that the community could cease mass treatment without reemergence of infection.

METHODS

OVERVIEW

To test these hypotheses, we conducted a community-randomized trial in Kongwa, Tanzania, where 16 communities were randomized in a 1:1 design to 2 different annual MDA strategies: yearly mass treatment for 3 years (usual care) vs yearly mass treatment each year if warranted by *C trachomatis* infection prevalence greater than 5%; otherwise, the MDA would cease for communities in this arm and the community would be monitored for reemergent infection (cessation rule). This cutoff was chosen based on a previous study that showed that when infection averaged greater than 5% after treatment, infection was likely to return.[13]

The trial was conducted between February 2010 and September 2011. Communities in Kongwa district were eligible for the study if they met the following criteria (**Figure 1**):

1. Had an estimated prevalence of FT between 10% and 20% among children aged 5 years or younger based on preliminary surveys carried out prior to the baseline survey.
2. Had not been treated in the previous 3 years.
3. Had fewer than 5000 persons.
4. Had leadership approval for participation.

Sixteen communities met the eligibility criteria, and all were randomized. Prior to participation, community leaders provided consent to overall community involvement in the study. To participate in the study as a sentinel child, the following criteria had to be met:

1. Be aged 5 years or younger at the time of census.
2. Resided in an eligible community.
3. Had no ocular condition that prevented trachoma grading or ocular specimen collection.
4. Had an identifiable guardian who could provide consent to participate.

Individual written consent was obtained before all surveys. All procedures and protocols were approved by the Johns Hop-

kins Medical Institutions institutional review board and the Tanzania National Institute for Medical Research.

INTERVENTION

The intervention was the planned cessation of MDA after 1 or 2 rounds, if the prevalence of infection declined to less than 5% in the community as estimated at the 6-month and 18-month surveys. The working definition of less than 5% was conservative, based on the random sample of 100 sentinel children. If no children in the sample had infection, then the upper confidence limit of the estimate of infection was less than 5%. Azithromycin, 20 mg/kg, was provided to all residents older than age 6 months in all communities, and topical tetracycline was offered to all children 6 months of age and younger. Treatment was provided by trained community residents supervised by our research staff at several community locations (for details about MDA and antibiotic coverage monitoring, see the eAppendix, http://www.jamaophth.com).

OUTCOME MEASURES

The outcome measure was the prevalence of infection with *C trachomatis* in the communities. The comparison was the infection rates in the communities in the cessation rule arm, presuming they had stopped MDA, with infection in the communities in the usual care arm, which had ongoing MDA. However, no communities in the cessation rule arm met the criteria at either the 6-month or 18-month survey points, and the communities randomized to the usual care arm would receive 3 rounds of MDA in any case, thus all communities in both arms proceeded to 3 rounds of MDA. After viewing the 18-month data, the data and safety monitoring committee ended the trial on the basis of futility that MDA in the communities in the cessation rule arm would not be stopped and all communities in the trial would receive 3 annual MDAs.

RANDOMIZATION SCHEME

The 16 eligible villages were randomized using a constrained randomization scheme of 1:1 to each arm of the trial. The likelihood of unbalanced randomization was reduced by balancing each arm on baseline trachoma prevalence.[14] In each community, 100 children were randomly selected for the surveys based on the census list and using a simple random number assignment in Access (Microsoft).

SAMPLE SIZE DETERMINATION

We determined sample size by using a sample size formula for a 2-sample *t* test[15]:

$$\Psi_{2n-2}\left(t_{\alpha/2,2n-2}\frac{|\delta|\sqrt{n}}{\sigma\sqrt{2}}\right)=|\beta$$

Here $\Psi_m(x,k)$ is the cumulative distribution function of the *t* distribution, α is the significant level, $1-\beta$ is power, δ is the effect size between groups, n is the number of communities necessary in each group, and σ is the estimated standard deviation. Eight communities in each arm were required to test the null hypothesis that the prevalence of infection at 36 months in the cessation group was not worse than in the control group by more than 8% ($\delta=0.08$), with a 2-sided α of 0.05, power ($1-\beta$) of 0.8, and estimated standard deviation of 4% ($\sigma=0.04$). The 8% margin was based on clinical considerations; reemergence rates were reported elsewhere.[13]

MASKING: STUDY METHODS

Census Prior to Each Treatment Round

The study team performed a complete census and census update of all households in the study community. The methods are described in detail elsewhere[16] and in the eAppendix.

Surveys

At each survey visit, trained graders performed clinical assessment for trachoma by examination of the upper tarsal plate with a 2.5-time magnifying loop and using WHO standards for the presence or absence of FT or intense inflammatory trachoma. To establish infection with *C trachomatis*, samples were obtained using Dacron swabs from the conjunctiva of the right eye, taking detailed precautions to avoid contamination. The swabs were placed in a tube, kept cold, and sent within 30 days to the Johns Hopkins International Chlamydia Laboratory for polymerase chain reaction analysis. The validity of polymerase chain reaction results was confirmed using positive and negative control subjects in every sample run. Details of field methods and polymerase chain reaction testing are described in the eAppendix. Samples were retested if the results were equivocal; samples were called positive if results were positive on retest, or negative if results were negative or equivocal on retest.

Additionally, at each survey visit, sentinel children were assessed for facial cleanliness based on the presence of at least 1 of the following signs[17]: (1) ocular discharge on the eyelashes or lids; (2) nasal discharge on the nares, cheeks, or lips; and (3) flies landed on the face during a 3-second observation.

STATISTICAL ANALYSES

This study was analyzed on an intention to treat basis as of the 18-month survey. The communities were analyzed according to their randomization assignment, regardless of the fact that those in the cessation rule arm had equal numbers of MDAs to the usual care arm.

Baseline characteristics of communities were analyzed by randomization arm using mean values obtained for each arm by averaging the community mean values. *P* values were calculated using the Wilcoxon rank-sum test.

Plots were made showing changes in FT and *C trachomatis* infection over time in each village and for the mean of the villages in each arm. *P* values were calculated using the Wilcoxon rank-sum test to check for significant difference in FT or *C trachomatis* infection between arms at 18 months. We modeled community-level prevalence of trachoma and *C trachomatis* infection on a square-root-transformed scale to stabilize the variance. Multiple linear regression fitted with the ordinal least-squares method was used to model the outcome of the square root of 18-month prevalence, testing for the intervention and adjusting for the baseline prevalence. The statistical analysis was conducted using R version 2.14.0 (The R Foundation for Statistical Computing).

RESULTS

There were no significant differences in baseline characteristics between the 2 randomization arms (**Table 1**).

There was no difference in antibiotic coverage in either arm at baseline or 12 months (Table 1). Average coverage was greater than 80% in both rounds, although lower in the second round. Antibiotic coverage was measured

Table 1. Baseline Characteristics of Communities and Antibiotic Coverage in the 2 Study Groups

Characteristic	Group, Mean (SD)		*P* Value[a]
	Usual Care	Cessation Rule	
Population size, No. (%)	1140 (390)	1121 (255)	.96
Average duration of education of household head, y	4.0 (0.7)	3.9 (0.4)	.51
Houses >30 min from water, %	61.6 (17.9)	58.4 (22.7)	.80
Houses with latrine, %	68.3 (9.5)	67.5 (14.6)	.88
Sentinel children with clean faces, %	57.5 (7.7)	54.8 (14.2)	.40
Prevalence of FT	12.9 (3.3)	11.5 (3.5)	.46
Prevalence of *Chlamydia trachomatis*	5.4 (3.5)	6.4 (2.8)	.46
Baseline antibiotic coverage	89.6 (5.9)	94.2 (5.0)	.13
12-mo antibiotic coverage	82.7 (7.4)	88.9 (5.4)	.13

Abbreviation: FT, follicular trachoma.
[a] *P* values were calculated using the Wilcoxon rank-sum test for nonparametric data.

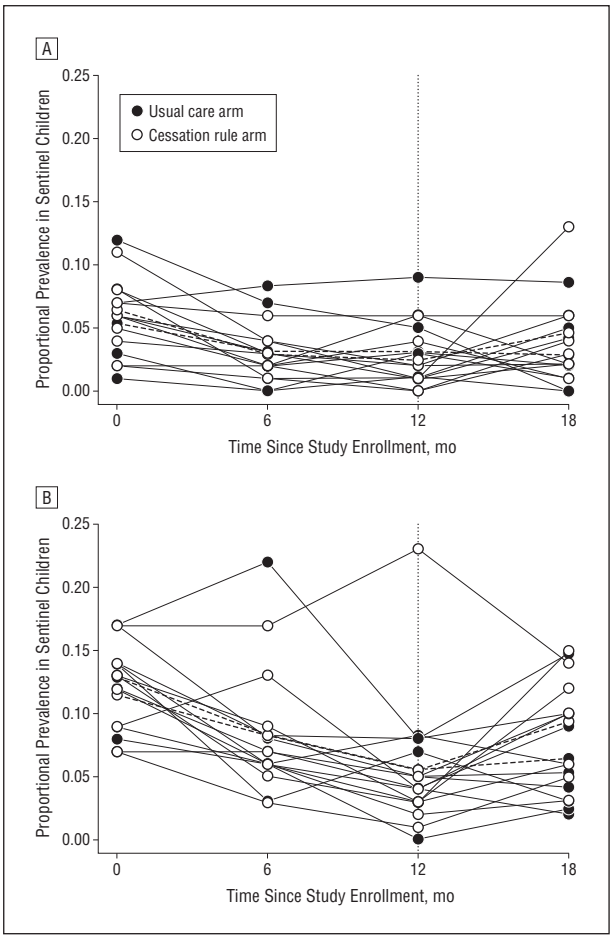

Figure 2. Graphs indicating infection/disease rates in villages over time. A, Graph shows the prevalence of *Chlamydia trachomatis* infection over time in the usual care and cessation rule arms. The dashed lines indicate the mean prevalence in each arm, and the thin lines indicate community-level prevalence. B, Graph shows the prevalence of follicular trachoma over time in the usual care and cessation rule arms. The dashed lines indicate the mean prevalence in each arm, and the thin lines indicate community-level prevalence.

by recording direct observation of ingestion of azithromycin in a census book.

Overall, the prevalence of FT and infection declined during the 18-month study in both groups (**Figure 2**). At baseline, *C trachomatis* infection rates were 5% and 6% in the usual care and cessation arms, respectively. After baseline antibiotic treatment, infection declined to 3% at 6 months in both groups; none of the communities in the cessation rule arm met the rule, so all proceeded to the second round of MDA. By 18 months, infection rates were 3% and 5% in the usual care and cessation groups, respectively. No community in the cessation rule arm met the rule at 18 months, so all proceeded to the third round of MDA. There were no statistically significant differences in infection between the groups at any point.

The prevalence rates of FT at baseline were 12% and 13% in the usual care arm and cessation rule arm, respectively; after antibiotic treatment, they declined to approximately 8% in both groups at 6 months. At 6 months, 13 of the 16 communities had a prevalence of FT less than 10%. By 18 months, the prevalence of FT was 7% in the usual care arm and 9% in the cessation rule arm. There were no significant differences in FT prevalence between the groups at any time during the study.

Table 2 presents the intent to treat model adjusted for baseline prevalence. There were no significant differences at 18 months in either infection or active trachoma. There was no effect of increasing coverage. Neither baseline infection nor trachoma predicted infection or trachoma prevalence in these communities at 18 months (**Table 3**).

COMMENT

The results of this study demonstrate that in Kongwa district, where the overall prevalence of active trachoma in children ages 5 years and younger was estimated at greater than 20% at baseline, communities with a starting prevalence of active trachoma in this age group averaged close to 10% still required at least 3 rounds of MDA, and none could be stopped early based on a stopping rule of infection of less than 5%.

We note that after 1 round of MDA, the average trachoma prevalence in both arms of the trial had fallen to less than 10%. However, all but 2 of the communities still had at least 1% and up to 8% infection at 6 months. At 18 months (6 months after the second round of MDA), 5 of the 16 communities were at greater than 10% preva-

lence of FT in the age group 5 years and younger, even though the average prevalence of FT was less than 10%. Based on the presence of infection, all the communities randomized to the cessation rule proceeded to the third round of MDA.

We believe our data show the importance of the wider geographic construct to be considered when evaluating even subdistricts for potential cessation of antibiotics. Unlike the experience with villages in Gambia,[5,12] 2 rounds of MDA with high coverage were not sufficient to stop MDA based on our cessation rule. The entire Kongwa district, where the trachoma rate is greater than 20%, is being treated along with these communities; thus, it is unlikely that migration from neighboring communities is a major cause of maintaining infection in this setting, although we cannot rule out migration from communities outside the district. There were some communities where, even after a second round of MDA, infection appeared to increase at 18 months. Notably, one village was an outlier, with 13% prevalence of infection at 18 months, where the rest of the 15 villages were at 7% or lower. We have no explanation for this spike, and the nearest neighboring communities enrolled in the trial had 18-month infection rates at 1% and 4%. Antibiotic coverage at 12 months was 80% in this particular village, thus, low coverage is an unlikely explanation.

We do not feel that the antibiotic coverage would explain the disappointing slow decline in infection, as all communities had coverage greater than 80%, specifically in children aged younger than 10 years at baseline, and only 1 community had less than 80% (71%) for the second round. Treatment verification showed high concordance with observed treatment as well. In a model of infection at 18 months, we examined the relationship of infection to average treatment coverage, and it was not significantly related, suggesting there was no difference within the range of coverage we observed. Mean antibiotic coverage was nonsignificantly associated with a lower 18-month infection prevalence, suggesting that coverage may be an important factor in eliminating infection. However, our study was not powered to answer this question. Moreover, while there is evidence that missing MDA does not occur at random,[18] there is no evidence that missing MDA is related to infection status, suggesting that children with infection were not preferentially missed by treatment. We also noted data that suggest it takes more than 6 months for infection to spread outside the household,[19] thus, even if there was any differential coverage, it is unlikely to explain how infection increased in some communities within 6 months after MDA. Our coverage was similar to that of Burton et al[5,12] in the Gambian villages where 1 round was sufficient to stop infection and reemergence did not occur.

We chose a very conservative cessation rule, with a working definition of no infection in the sentinel sample of 100 children. If we had chosen a less-strict guideline, we may have been able to stop MDA earlier. However, there are no data to guide the selection of a stopping rule based on infection or a specific age group, and we reasoned that if the Gambian villages could drop infection to less than 5% and have no reemergence, then our guideline was reasonable. Others have shown that even with almost no infection in communities, once antibiotic pressure is removed, reemergence does occur.[20] We suggest that these data support a viewpoint wider than a community when considering trachoma status and stopping MDA, in line with WHO guidelines on the assessment at district level. In Gambia, when the last few remaining villages are being treated, then possible acceleration to zero infection with 1 round of MDA may be reasonable. However, low-prevalence communities in a district like Kongwa, which on average has a trachoma rate estimated at greater than 20%, cannot be singled out and will need at least the full 3 rounds of MDA even with high coverage.

In conclusion, we found that using a rule for cessation of MDA based on infection status did not change the frequency of treatment, which, based on clinical assessment, was 3 rounds of MDA. Moreover, we found that in our low-prevalence communities (average FT at baseline of 12%), 2 rounds of MDA were not sufficient to reduce infection to zero. The fact that these communities were at the low end of baseline prevalence in a district with overall higher rates of trachoma suggests the wisdom of treating a wide geographic area for at least 3 rounds before impact surveys, and not presuming that subdistricts on their own can be stopped if the wider district-level prevalence supports mass treatment.

Table 2. Multivariate Linear Model of Infection and Follicular Trachoma Prevalence at 18 Months Predicted by Randomization Group and Baseline Infection or Trachoma

Characteristic	β Coefficient (95% CI)	*P* Value
Predicting Infection		
Cessation rule arm	0.06 (−0.03 to 0.16)	.22
Baseline infection, square root	−0.02 (−0.76 to 0.72)	.96
Predicting Follicular Trachoma		
Cessation rule arm	0.07 (−0.01 to .15)	.09
Baseline trachoma, square root	0.66 (−0.13 to 1.45)	.12

Table 3. Multivariate Linear Model of Infection and Follicular Trachoma Prevalence at 18 Months Predicted by 12-Month Antibiotic Coverage and Baseline Infection or Trachoma

Characteristic	β Coefficient (95% CI)	*P* Value
Predicting Infection		
Mean antibiotic coverage	−0.34 (−1.42 to 0.75)	.50
Baseline infection, square root	−0.21 (−0.66 to 1.08)	.64
Predicting Follicular Trachoma		
Mean antibiotic coverage	0.29 (−0.50 to 1.08)	.49
Baseline trachoma, square root	0.46 (−0.40 to 1.31)	.31

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