

Single-Dose Azithromycin Prevents Trichiasis Recurrence Following Surgery

Randomized Trial in Ethiopia

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Background: Trichiasis recurrence following surgery is a serious problem for trachoma programs.

Objective: To determine if postoperative treatment with azithromycin compared with topical tetracycline reduces recurrence up to 1 year, and if azithromycin treatment of household members provides additional benefit compared with treating only the surgical patient.

Design: A randomized, single-masked, clinical trial was conducted in Ethiopia. A total of 1452 patients with trichiasis were randomized 1:1:1 to the following 3 arms: single-dose (1 g) oral azithromycin alone, single-dose azithromycin for household members (20 mg/kg up to 1 g) plus the patient, or topical tetracycline (twice per day for 6 weeks).

Main Outcome Measures: Trichiasis recurrence within 1 year following surgery.

Results: The combined azithromycin groups had significantly fewer recurrences, 6.9 of 100 person-years overall, compared with topical tetracycline, 10.3 of 100 person-years ($P = .047$). There was no additional reduction in the arm that also treated household members, 8.1 of 100 person-years, compared with treating the surgical patients alone, 5.8 of 100 person-years ($P = .19$).

Conclusions: In trachoma-endemic areas, a single dose of azithromycin reduced postoperative trichiasis recurrence rates by one third compared with topical tetracycline.

Application to Clinical Practice: In countries where azithromycin is part of the Trachoma Control Program, patients with trichomatous trichiasis should be treated postoperatively to prevent recurrence.

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TRACHOMA, AN OCULAR DISEASE caused by *Chlamydia trachomatis*, is the leading infectious cause of blindness worldwide.¹ If the scarring from repeated infection over years is sufficiently severe, trichiasis or inturned eyelashes rubbing the globe may result. Until the burden of active trachoma is reduced for a sustained period, surgery for trichiasis will be needed to prevent progression to blindness. In trachoma-endemic areas such as Ethiopia, more than 7% of adults may have trichiasis.²⁻⁴

The World Health Organization (WHO) has endorsed a multifaceted control strategy, which includes surgery to correct trichiasis. However, under the best of circumstances the rate of recurrence following surgery is disappointingly high, estimated in different settings between 16% to 50% at 2 or more years of follow-up.⁵⁻⁹

Reasons for high recurrence rates are not clear, although surgical factors likely play

a role in early recurrence.^{5,10,11} Data also support a role for *C trachomatis* infection post-surgery in recurrence. Persons with both scarring and infection were at greatest risk of developing trichiasis¹² and *C trachomatis* is present in a significant proportion of adults, which may drive progression of trachoma.¹³⁻¹⁵ Follow-up studies of surgical cases have found that postsurgical recurrence was highest in areas with greatest trachoma prevalence.^{5,8} One study reported a higher rate of recurrence in surgical eyes with ocular *C trachomatis* infection compared with eyes without infection.¹⁶

There is no standard for postsurgical care following trichiasis surgery; the WHO manual for trichiasis surgery recommends using topical tetracycline ointment for 7 days following surgery.¹⁷ However, at least 6 weeks of topical tetracycline is recommended for specific treatment of ocular *C trachomatis*. Moreover, patients with trichiasis who have had surgery and return to environments of trachoma-endemic fami-

lies may again be at risk of infection, with the possibility of developing recurrent trichiasis. Therefore, treating all household members of patients with trichiasis who have had surgery may provide significant value, despite the intensive effort involved.

The specific objectives of this randomized, single-masked, clinical trial were as follows: (1) to determine if treating patients with trichiasis with oral azithromycin postsurgery compared with usual care (topical tetracycline) results in a reduction in trichiasis recurrence at 1 year following surgery; (2) to determine if treating all household members with azithromycin provides additional benefit compared with treating only surgical patients with azithromycin.

METHODS

The trial was conducted in Wolayta Zone, Ethiopia, where trachoma was hyperendemic.¹⁸ Community health assistants were previously trained to screen for trichiasis, and as part of the newly offered surgical services in this area, they were screening all individuals and referring them for surgery. Trichiasis surgery was provided by trained integrated eye care workers (IECWs) who have equally successful surgical outcomes compared with ophthalmologists.¹⁹ All IECWs used in our study were certified for surgery by our study team following WHO guidelines to ensure quality.²⁰

All patients with trichiasis who sought surgery between November 8, 2002, through December 30, 2002, March 1 through May 10, 2003, and October 8 through December 30, 2003, were screened for eligibility. Methods and procedures have been published and are summarized here.²¹ Enrollment periods were defined around the rainy season to ensure that follow-up could be carried out when roads were passable. Assuming a 2-sided α of .05, we estimated that we needed a minimum sample size of 1425 patients to be able to detect a 40% reduction in trichiasis recurrence from 17% to 10% with 80% power. We did not adjust the sample size for multiple comparisons because we analyzed the data only for the primary hypotheses. Eligibility criteria included the following: (1) age 18 years or older; (2) presence of trichiasis in at least 1 eye;²² (3) no previous report of trichiasis surgery in the study eye; and (4) no other household members participating in the trial. If multiple, eligible household members had trichiasis, 1 was randomly selected to participate. This criterion was essential, as the household-based treatment arm required all members to be treated with azithromycin (all household members were still eligible for surgery).

The following were exclusion criteria: (1) self-reported pregnancy; (2) documented allergy to tetracycline; and (3) plans to move out of the region within 1 year. If both eyes were eligible for the study, the study eye was assigned according to the study identification number—left eye if odd and right eye if even.

This trial had the following 3 treatment arms: azithromycin treatment following surgery, azithromycin treatment for surgical cases and household members, and usual care with topical tetracycline. Patients in the usual care arm were provided 2 tubes of tetracycline with instructions to apply to the operated-on eye twice daily for 6 weeks following surgery. The first dose was administered by study staff, but further dosing was not observed. In the azithromycin arms, a single dose of azithromycin, 1 g orally, was given. For those randomized to the household-based treatment arm, all individuals residing in the surgical patient's house were also provided with azithromycin, 20 mg/kg up to 1 g. Women who reported being pregnant were treated with topical tetracycline. Azithromycin treatment was observed. No antibiotics were offered by the study at any follow-up visit.

The primary outcome, trichiasis recurrence in the study eye, was assessed at 2 weeks and 1.5, 6, and 12 months following surgery. All assessments were performed clinically using the WHO simplified grading classification of trichiasis, defined as presence of a lash touching the globe or evidence of epilation.²² For the outcome assessment, history of epilation since surgery required evidence of epilation, such as lash stubble. Trichiasis assessment was carried out by a trained trachoma grader, which was standardized to the senior project ophthalmologist (W.A.) prior to each follow-up period. Level of agreement was always greater than $\kappa = .65$. The grader was masked to treatment assignment and baseline assessment data. Severity of recurrence was defined as mild if only 1 lash was touching the globe (and not the cornea), moderate if 2 to 4 lashes were touching the globe (and not the cornea), and severe if 5 or more lashes were touching the globe or at least 1 was touching the cornea. If the recurrent lashes were epilated so that the number of lashes could not be determined, the severity was not coded.

Patients were asked about their age using an events calendar to assist in determining their correct age. Patients were also asked about the duration of trichiasis and whether they had previously had trichiasis surgery on either lid. A complete census of the household members was taken from the patient to guide treatment of household members in the event the patient was randomized to that arm. The census also assured that another person from the same household was not enrolled. This approach was successful; no 2 surgical cases were ever followed-up from the same household.

A standardized protocol, described in detail elsewhere,²¹ and a tumbling E chart equivalent to an Early Treatment Diabetic Retinopathy Study chart were used to assess visual acuity at baseline.

An ocular swab was taken of the study eye using a standard protocol to avoid field contamination. After every 25th swab, a swab of the technician's hands was taken to determine if field contamination had occurred. All swabs were kept frozen at -20°C until they were shipped frozen to the international chlamydia laboratory at Johns Hopkins University, Baltimore, Md. Swabs were processed for presence of *C trachomatis* using the AmpliCor qualitative polymerase chain reaction test kit (Roche Molecular Systems, Indianapolis, Ind). Samples were processed according to manufacturer's specifications, with positive and negative controls in each run. Swab positivity was designated according to manufacturer's specifications. For these analyses, infection was defined as a positive laboratory result.

For this trial, trichiasis severity was assessed by determining the number of lashes touching the globe, the number of lashes touching the cornea, and the degree of entropion or inside deviation of the lid margin.²³

Patients were assigned randomly to treatment groups prior to surgery. Envelopes containing randomly assigned masked treatment packages (tetracycline tubes, pills, or pills plus a slip indicating household treatment) were labeled with sequential study numbers. Treatment assignments were blocked in variable sizes of 6 and 12. Safeguards were in place to assure each sequential patient received the next available study number. Office personnel responsible for randomization were not involved in assessment of trichiasis severity, selecting patients for enrollment, or aware of the blocking scheme. Community health assistants brought patients into the offices for consent and randomization and were not involved in treatment.

Adverse events were defined as death, hospitalization, and specific illnesses or gastrointestinal or ocular symptoms. At the 1.5-month follow-up visit, specific questions were asked of each subject about himself/herself and all his/her family members about these adverse events. The interviewer was either a physician or a medical assistant.

Analyses were conducted following the intention-to-treat principle. Characteristics of participants across treatment arms were

Table 1. Characteristics of 1452 STAR Trial Participants at Baseline by Randomization Group*

Characteristic	Randomization Group			Total (N = 1452)
	Tetracycline (n = 484)	Azithromycin (n = 483)	Azithromycin Household (n = 485)	
Age, mean (SD), y	48.0 (12.8)	48.5 (13.0)	50.0 (12.6)	48.9 (13.0)
Female	390 (80.6)	366 (75.8)	365 (75.3)	1121 (77.2)
Residing in households with children aged <11 y	400 (82.6)	403 (83.4)	404 (83.3)	1207 (83.1)
Previous surgery in fellow eye	4 (0.8)	17 (3.5)	10 (2.1)	31 (2.2)
Trichiasis†				
Unilateral	91 (18.8)	103 (21.3)	84 (17.3)	278 (19.2)
Bilateral	393 (81.2)	380 (78.7)	401 (82.7)	1174 (80.8)
Study eye				
Right eye	240 (49.6)	233 (48.2)	244 (50.3)	717 (49.4)
Ocular <i>Chlamydia trachomatis</i>	84 (17.4)	108 (22.4)	89 (18.4)	281 (19.4)
Entropion				
Mild	257 (53.1)	287 (59.4)	266 (54.9)	810 (55.8)
Moderate	150 (31.0)	130 (26.9)	137 (28.2)	417 (28.7)
Severe	77 (15.9)	66 (13.7)	82 (16.9)	225 (15.5)
No. of lashes touching the globe				
None	112 (23.2)	94 (19.5)	103 (21.2)	309 (21.3)
1-3	103 (21.4)	128 (26.5)	109 (22.5)	340 (23.5)
4-6	97 (20.1)	92 (19.1)	90 (18.6)	279 (19.2)
7-9	45 (9.3)	53 (11.0)	44 (9.1)	142 (9.8)
≥10	125 (25.9)	116 (24.0)	139 (28.7)	380 (26.2)
No. of lashes touching the cornea				
None	147 (30.6)	133 (27.4)	142 (29.3)	422 (29.1)
1-3	158 (32.9)	168 (34.8)	151 (31.2)	477 (32.9)
4-6	86 (17.9)	91 (18.8)	94 (19.4)	271 (18.7)
7-9	19 (4.0)	22 (4.6)	21 (4.3)	62 (4.3)
≥10	71 (14.8)	69 (14.3)	76 (15.7)	216 (14.9)
Visual acuity				
20/40 or better	132 (27.6)	136 (28.5)	116 (24.2)	384 (26.8)
>20/40 to 20/60	95 (19.9)	96 (20.1)	95 (19.8)	286 (19.9)
>20/60 to <20/200	165 (34.5)	136 (28.5)	152 (31.7)	453 (31.6)
20/200 to 20/400	23 (4.8)	29 (6.1)	25 (5.2)	77 (5.4)
<20/400	63 (13.2)	80 (16.8)	92 (19.2)	235 (16.4)
Integrated eye care worker (surgeon) code				
04	248 (51.2)	225 (46.6)	236 (48.7)	709 (48.8)
05	6 (1.2)	3 (0.6)	5 (1.0)	14 (1.0)
08	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
10	164 (33.9)	175 (36.2)	170 (35.0)	509 (35.0)
21	66 (13.6)	79 (16.4)	74 (15.3)	219 (15.1)

Abbreviation: STAR, surgery for trichiasis, antibiotics to prevent recurrence.

*All data are expressed as No. (%) unless otherwise indicated.

†Defined as lashes touching the globe or history of epilation.

compared using χ^2 tests or Fisher exact tests. Confidence intervals for adverse event rates were calculated using Poisson approximation of the binomial. The primary outcome, postsurgical trichiasis recurrence in the study eye, was assessed at 4 time points. To incorporate the period in which recurrence occurred, life table or actuarial estimates of survival (free of trichiasis recurrence) were used. The 2 primary comparisons were recurrence rates (expressed as person-years) in the tetracycline arm compared with the 2 azithromycin arms combined, and recurrence rates between the 2 azithromycin arms. The log-rank test was used to assess differences in survival rates. The Cox proportional hazard model was used to evaluate risk factors and adjust for confounding in predicting recurrence.

All subjects provided signed consent for the study following a detailed description of all study procedures given both in writing and orally in the local language. The consent was witnessed by trained study personnel and a member of the community. All procedures were approved by the institutional re-

view board at Johns Hopkins Medical Institution and the Ethiopian Science and Technology Committee's National Ethical Clearance Committee.

RESULTS

Of 1635 trichiasis cases, 1452 subjects were enrolled in the trial, with 483 to 485 subjects in each arm (**Table 1**). The majority of ineligible subjects (118 of 183 or 64%) had had previous lid surgery on the only eligible eye. The enrolled patients and study eyes in each arm had similar characteristics, which demonstrates successful randomization. In this area of Ethiopia, trichiasis was severe; over half of study eyes had 5 or more lashes touching the cornea, with 53% having visual acuity worse than 20/60. For adults, ocular chlamydia infection rates were high at 19%. The propor-

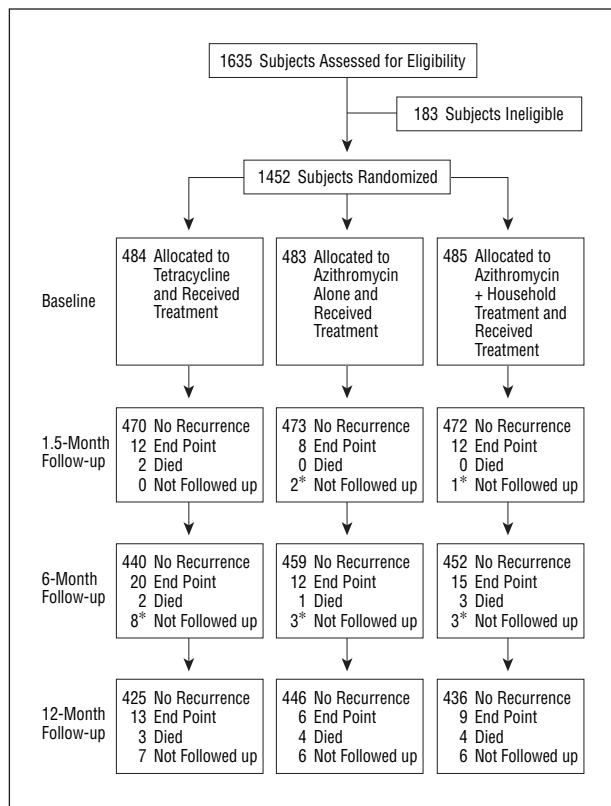


Figure 1. Flow diagram of enrolled subjects at each visit. Asterisk indicates patients who were still eligible for follow-up at subsequent visits.

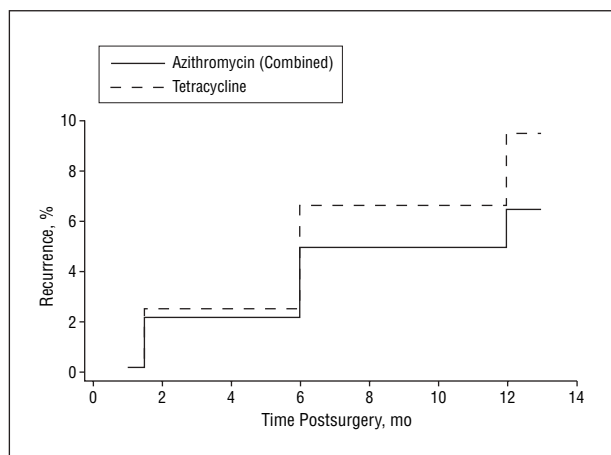


Figure 2. Cumulative incidence of recurrence by treatment group. Log-rank test, P value = .047.

tion of patients operated on by each IECW was similar, with over 80% of all surgeries performed by 2 surgeons.

The trial had excellent subject retention through the 1-year follow-up; over 98% of subjects who had not reached endpoint or died were examined (**Figure 1**). In the household-based treatment arm, 92% of the household members (2158 of 2338) were treated within 1 week following the patient's surgery.

Subjects randomized to receive azithromycin had a significantly longer time to recurrence compared with those randomized to topical tetracycline (**Figure 2**). The in-

Table 2. Chlamydia Infection in Surgical Eye of Patients at 1.5 Months and at Time of Recurrence or 12-Month Follow-up† by Randomization Group

Characteristic	No.	Infected, %	P Value
Infection at 1.5 mo*			
Tetracycline	477	4.4	<.001
Azithromycin	479	0.0	<.001
Azithromycin household	484	1.2	<.001
Infection at end of follow-up†			
Tetracycline	468	6.8	.012
Azithromycin	469	4.5	.012
Azithromycin household	469	2.8	.012

*Twelve subjects were missing laboratory results.

†At visit when trichiasis recurrence was detected or at 12 months if not recurrent, 46 subjects were missing laboratory results at the end of follow-up.

cidence of recurrence was 6.9 of 100 person-years in the azithromycin group compared with 10.3 in the topical tetracycline group ($P = .047$). Treating the household members with azithromycin provided no advantage compared with treating surgical patients alone. The incidence rate in the azithromycin-alone group was 5.8 of 100 person-years, compared with 8.1 of 100 person-years in the household treatment arm ($P = .19$).

Infection with *C trachomatis* declined in all randomization groups from baseline (**Table 2**). Azithromycin appeared to be more effective in clearing infection compared with topical tetracycline, as judged by infection rates at 1.5 months postsurgery. However, *C trachomatis* infection posttreatment was not a risk factor for recurrent trichiasis (**Table 3**).

Predictors of recurrence included male sex (hazard ratio, 1.61; 95% confidence interval [CI], 1.06-2.50) and severity of entropion prior to surgery (hazard ratio, 1.96; 95% CI, 1.25-3.08 for moderate entropion and hazard ratio, 3.01; 95% CI, 1.86-4.87 for severe entropion) (**Table 3**). Adjusting for these factors, azithromycin was protective against recurrence, compared with topical tetracycline (hazard ratio, 0.67; 95% CI, 0.45-0.98). There were no significant differences in recurrence rates by IECWs (data not shown). Recurrent trichiasis, when present, tended to be severe with over 50% of recurrences having 5 or more lashes touching the globe or at least 1 lash touching the cornea in all treatment arms.

The adverse event rate was low among surgical patients and household members in all groups (**Table 4**). There was no significant difference in overall adverse event rates or death rates.

COMMENT

A single dose of postsurgical azithromycin in this region of rural Ethiopia was significantly associated with a 33% reduction in trichiasis recurrence up to 1 year, compared with topical tetracycline prescribed for 6 weeks. This result differs from a smaller clinical trial of azithromycin compared with 2 weeks of topical tetracycline conducted among patients with trichiasis in The Gambia.¹¹ One important difference between our trial and the trial

Table 3. Multivariate Model of Factors Predicting Cumulative Trichiasis Recurrence to 1 Year

Characteristic	Hazard Ratio (95% Confidence Interval)
Age per year	1.01 (0.99-1.03)
Male	1.61 (1.06-2.50)
Treatment with azithromycin (compared with tetracycline)	0.67 (0.45-0.98)
Entropion severity at baseline	
Mild	1.00
Moderate	1.96 (1.25-3.08)
Severe	3.01 (1.86-4.87)

in The Gambia was the absence in the latter trial of standardization of surgeons, resulting in recurrence rates that varied from 0% to 80%, with an average recurrence of 32% by 6 months. Because it is unreasonable to expect that an antibiotic can overcome such profound surgeon effects, it is difficult to interpret the Gambian study findings for effect of azithromycin on recurrence.

Special care was taken to maintain the outcome assessor masked to treatment intervention. The outcome assessment team was composed of different people than the team at the surgical station, and the outcome assessor was never present at the surgical station where treatment was administered. The outcome assessor did not speak the local language spoken by the surgical subjects and the translator was unaware of the treatment status. Thus, we do not feel that bias in outcome assessment was responsible for our finding.

The high proportion of eyes with severe trichiasis at baseline in our population had suggested that recurrence rates may be high because severity is linked to recurrence.^{11,16,24} We also found such association, but despite the severity, 1-year recurrence rates were low compared with other reports.⁵⁻⁹ While we have no supportive data, our observation is that our strict adherence to sterile techniques, coupled with careful IECW training, may well be part of the reason for the low overall rate. Also, the rate may be low because eyes that had previous trichiasis surgery were excluded from the trial. Previous surgery is associated with a higher rate of recurrence, as these eyes have already experienced trichiasis recurrence at least once²⁴ and have scarring owing to prior surgery. A total of 118 persons were excluded based on this criterion, which represents 7% of the total number of patients seeking surgery over our recruitment period. If they had been enrolled and experienced 50% recurrence, then overall recurrence may have increased slightly, from 8 of 100 person-years to an estimated 10 of 100 person-years. In areas with long-standing surgical programs, recurrence rates may be higher owing to higher volume of repeated procedures.⁵ Another reason for low recurrence may be the policy of delaying removal of sutures until 2 weeks postsurgery, as opposed to 1 week, on the advice of our Data and Safety Monitoring Committee. Since the purpose of the sutures is to affect the outward rotation of the distal fragment as it is reattached, a longer period for maintaining the sutures may lead to stronger adhesion between the surgical mar-

Table 4. Rate of Adverse Effects Elicited at 1.5 Months Posttreatment by Randomization Group

	Adverse Effects			Total Rate Per 100 Persons (95% Confidence Interval)
	Death	Illness	Ocular Complaints	
Surgical patients				
Azithromycin	0	2.28	0.62	2.90 (1.93-4.19)
Tetracycline	0.41	1.24	1.44	3.10 (1.73-5.11)
Household members				
Azithromycin	0.17	0.38	0	0.55 (0.29-0.94)
Not treated	0	0.35	0.04	0.39 (0.23-0.62)

gins, thus maintaining the correction. This supposition would need corroboration from a clinical trial. With this trial protocol, the overall recurrence rates were low and the absolute reduction in risk was modest. The absolute reduction may be more pronounced in areas with greater recurrence. Further work on surgery-related factors to reduce recurrence is clearly needed based on what we accomplished in rural Ethiopia.

Contrary to our expectation, infection with *C trachomatis* did not appear to be associated with postsurgery recurrence. The rate of infection posttreatment was low in all treatment arms, and did not reemerge to presurgery levels over time in any of the treatment arms. We expected the infection rate during the course of the study to be low in patients who received azithromycin.^{14,15} However, we expected to see protection from reinfection with treatment of the household members, which was not apparent. Perhaps transmission to these older patients within household units is not strong in this Ethiopian setting (at least within the 1 year of observation). An estimated 82% of the patients lived in households with children, who are the primary reservoir for infection, suggesting the environment for reinfection was present. We have previously reported that transmission within households in rural Tanzania was apparent within 6 months following azithromycin treatment,²⁵ but we did not examine the ages of incident cases of intrafamilial spread to see if they were adults. Interestingly, the subsequent infection rates in the topical tetracycline group also were lower than baseline levels. Patients randomized to tetracycline may have been more compliant than expected and were able to clear their infection as well. While azithromycin treatment in the surgical patients was observed and compliance was 100%, the study team could not observe compliance with the 6 weeks of topical treatment.

We were unable to demonstrate any additional reduction of recurrence by treating household members as well as treating the surgical patient. One reason may be that, with such low recurrence rates, we were underpowered to detect a difference within the azithromycin groups. As noted above, there is also little evidence for spread of infection to these cases from household members, suggesting that in this setting additional benefit would be unlikely.

The mechanism of action for the protective effect of azithromycin does not appear to be by means of lower postsurgical rates of ocular *C trachomatis*. However, we only obtained specimens at 2 time points postsurgery and

may have missed episodes occurring between examination points. Thus, the role of sporadic infections cannot be excluded. We still might expect a higher infection rate in 1 group compared with the other if there was a general trend to more infection in 1 group. It is also difficult to obtain adequate specimens from scarred eyelids. To circumvent this problem, we also swabbed the inferior fornix. However, our ability to collect organisms may be compromised in such eyes.

Azithromycin is a broad-spectrum antibiotic with long-lasting activity against a host of organisms. It is possible that the wider systemic protection afforded by azithromycin prevented other infections from contributing to recurrence.²⁶ In addition, research has described the anti-inflammatory effect of azithromycin, possibly owing to enhancement of the antibacterial effect of neutrophils and suppression of an inflammatory response.²⁷ Such activity may prevent overproduction of scar tissue following surgery, which may lead to recurrence of trichiasis. This mechanism is conjecture without proper studies. The lack of adverse effects from azithromycin suggests excellent safety in administering this drug for prevention of postsurgical recurrence.

Surgery to correct trichiasis is one of the mainstays of the WHO surgery, antibiotics, face washing, and environmental change (SAFE) strategy for trachoma control. High recurrence rates following surgery are destructive to national trachoma control programs because patients refuse surgery and eyes with recurrence are at an even higher risk of subsequent failure. Research to find interventions that will lower recurrence rates has a high priority as it will help improve the surgical component of SAFE. No other nonsurgical intervention has been shown to reduce trichiasis recurrence following surgery. Thus, the findings from this randomized clinical trial, a 33% reduction in the risk of recurrence up to 1 year with a single dose of azithromycin, have significant clinical relevance for surgical programs using similar procedures in other countries.

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Author Contribution: Dr S. West had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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script. The Data Safety and Monitoring Committee includes the following voting members: Maureen Maguire, PhD (chair), Yemane Teklai, PhD, Mohammed A. Yassin, MD, PhD, Gene Howard, MD, Gerald Byrne, PhD, Julius Schachter, PhD. The following are nonvoting members: Don Everett, MS (National Eye Institute), Aminul Islam, MD, Dr S. West (principal investigator, Johns Hopkins University), Drs E. West, Alemayehu, Meinert, Munoz, Quinn, and Gaydos.

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