

Impact of Annual Targeted Treatment on Infectious Trachoma and Susceptibility to Reinfection

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IN 1995, THE WORLD HEALTH ORGANIZATION (WHO) first published data on global blindness and reported that 15% of cases were due to trachoma,¹ making it the second major cause of blindness after cataract.¹ At that time, the WHO estimated that 146 million individuals were in need of treatment for active trachoma to prevent blindness, 10 million were in need of surgery for trachomatous trichiasis (eyelash[es] touching the globe), and 8 million were already blind.¹ In 1996, the WHO designed the SAFE (Surgery for trachomatous trichiasis; Antibiotics for *Chlamydia trachomatis*; Facial cleanliness; and Environmental improvement) strategy with the goal of elimination of blinding trachoma by the year 2020.^{2,3}

For the antibiotic arm of the SAFE strategy, the WHO has recommended antibiotic treatment with either topical tetracycline or oral azithromycin for 3 categories of patients with active trachoma: (1) all children and women with follicular inflammation and/or intense inflammation in areas with a prevalence of greater than 20%; (2) targeted treatment of schoolchildren with follicular inflammation and/or intense inflammation and their households in areas with a prevalence of 10%-20%; and (3) individual treatment for follicular inflam-

Context The World Health Organization developed the SAFE strategy (Surgery for trichiasis; Antibiotics for *Chlamydia trachomatis* infection; Facial cleanliness; and Environmental improvement) to eliminate blinding trachoma globally by the year 2020. Despite a number of studies using various intervals of treatment for different prevalence rates, there has been a lack of sufficient follow-up beyond the final treatment point to determine rates of recurrence of disease and infection and the risk factors that may contribute to each.

Objective To evaluate the impact of 2 annual targeted azithromycin treatments on active trachoma and *C trachomatis* infection rates over 3 years in Vietnam.

Design, Setting, and Participants Three communes were randomly selected for a longitudinal study in Vietnam from November 2000 through November 2003. Individuals (n=3186) were graded for trachoma followed by conjunctival sampling to detect chlamydiae by commercial polymerase chain reaction. Grading and chlamydial detection were repeated every 6 months for 3 years.

Intervention Azithromycin was given to children aged 5 through 15 years with active trachoma and their household members in SAFE and SA communes at baseline and 12 months; these communes were compared with the S-only control commune that did not receive azithromycin targeted treatment.

Main Outcome Measures Prevalence and incidence of active trachoma and *C trachomatis* infection in all communes at baseline, 6, 12, 18, 24, and 36 months. Subgroup analysis evaluated new infection, continuing infection, and reinfection at 6, 12, 18, 24, and 36 months and risk factors for each.

Results Reinfection rates increased significantly between 12 and 36 months for SAFE (from 1.6 to 29.3 per 1000; $P<.001$) and SA (5.1 to 25.3 per 1000; $P=.002$) communes but not for the S-only commune (13.4 to 6.7 per 1000; $P=.55$) after 24 months. Compared with the S-only commune, mixed-effects and generalized estimating equations (GEE) logistic models showed that reinfection risk was significantly higher for SAFE (odds ratio [OR], 4.1; 95% confidence interval [CI], 1.5-9.8; $P=.005$) and SA (OR, 4.2; 95% CI, 1.1-17.3; $P=.04$) communes at 36 months.

Conclusions Increasing reinfection rates suggest that treatment may interrupt the duration of infection required for developing immunity, increasing the number of individuals susceptible to reinfection and adversely affecting disease prevalence over time. Additional research is needed to determine optimal trachoma control strategies, including evaluation of the "F" and "E" components.

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mation and/or intense inflammation in areas with a prevalence of less than 10%.⁴

Oral azithromycin has become the drug of choice for the SAFE programs

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because of the difficulty of administering topical tetracycline eye ointment, the low rates of adherence among affected populations, and the inability of topical therapy to eradicate extraocular sites of *C trachomatis* infection. Using a mathematical model to determine the frequency of mass oral antibiotic treatment, Lietman et al⁵ proposed biannual treatment of active trachoma in areas with prevalence rates of approximately 50% for children younger than 10 years of age, and once a year if the prevalence was less than 35%.⁵ Despite a number of studies using various intervals of treatment for different prevalence rates, there has been a lack of sufficient follow-up beyond the final treatment time point to determine rates of recurrence of disease and infection and the risk factors that may contribute to each.⁶⁻¹⁵

Vietnam is 1 of 16 priority countries in which the SAFE program has been launched.² According to Vietnamese National Survey Data in the 1950s, through intensive health care programs active trachoma and trachomatous trichiasis prevalence rates were reduced from approximately 70% to 10% and 6% to 2%, respectively.^{4,16} Yet trachoma remains the number one cause of blindness in Vietnam.¹⁷⁻¹⁹ Pockets of active trachoma with rates as high as 17% among schoolchildren aged 5 to 15 years persist in some rural regions of the country.

We prospectively evaluated the effect of targeted oral azithromycin treatment of schoolage children and their household members on active trachoma and *C trachomatis* infection rates. SAFE and SA communes received annual azithromycin treatment over 2 consecutive years with follow-up for 2 years beyond the last treatment. Individuals in the SAFE and SA communes with active trachoma who were not index cases or household members of an index case received topical tetracycline. We included a control commune (S-only commune) where individuals with trachomatous trichiasis received surgery and those with active trachoma received topical tetracycline. Inclusion of this latter commune was an important element of the study

design because trachoma rates can fluctuate independent of implementation of SAFE programmatic components.²⁰

METHODS

Design

We conducted a longitudinal community intervention study approved by the institutional review board of Children's Hospital and Research Center at Oakland, Calif, and of the Vietnamese Ministry of Health, National Institute of Ophthalmology. Informed consent was obtained orally from participants and parents of children before entering the study. The study began in November 2000 and ended in November 2003. Three of 8 communes in Thanh Hoa Province were randomly chosen using a random number list. All 8 communes had approximately a 20% prevalence rate of active trachoma based on rapid assessment.²¹ The 8 communes were located in proximity to the Sông Huong River and tributaries and had similar socioeconomic status, but the 3 randomly selected communes were geographically isolated from one another. One commune was designated a SAFE commune and all components of the program were implemented. Another was designated an SA commune (surgery plus antibiotics), and a third commune was designated S-only where trachomatous trichiasis cases were identified and informed of the availability of surgery. The assignment of the communes to the various treatments was performed randomly.

Treatment

All commune residents older than 6 months were included in the study. There were 2 components to the assessment and intervention as outlined in FIGURE 1. The first component involved examination of all schoolchildren aged 5 through 15 years; children who had active trachoma defined as follicular inflammation, intense inflammation, or both were considered index cases. The second component included examination of the remaining individuals either at a central commune or village site. In the SAFE and SA communes at baseline and 12 months, index cases and their house-

hold members were treated with a single oral dose of azithromycin (20 mg/kg for children, 1 g for nonpregnant adults; pregnant women received erythromycin). Non-index cases and nonhousehold members who had active trachoma (follicular inflammation, intense inflammation, or both) in the SAFE and SA communes received topical tetracycline, as did all patients with active trachoma in the S-only commune. Trachoma grading and conjunctival sample collection were performed prior to treatment at baseline and at 6, 12, 18, 24, and 36 months.

Clinical Diagnosis of Active Trachoma

At each time point of the study, all participants were examined by an ophthalmologist and graded for trachoma in a masked fashion using a modified grading scale²²: no evidence for trachoma (T0), follicular inflammation (TF), intense inflammation (TI), trachomatous scarring (TS), trachomatous trichiasis (TT), and corneal opacity (CO). Spot checks of grading and sample collection for every 10th person for each day of field work were also performed during each point of the study, with discrepancies resolved at the time of the spot check.

Detection of *C trachomatis* Infection

Chlamydia trachomatis infection was determined using Amplicor-PCR (polymerase chain reaction) assay (Roche Diagnostics, Branchburg, NJ) of conjunctival samples according to the manufacturer's instructions and as described previously.²³ Conjunctival samples were collected for each time point after grading and before treatment from the individual's right upper tarsal conjunctiva using a cotton swab, as previously described.²³ Briefly, the swab was placed in collection media (M4-RT, Micro Test Inc, Lilburn, Ga) and stored at 4°C for less than 8 hours before transfer to a -20°C freezer. Samples were labeled with date and a unique identification number to maintain confidentiality and to process samples in a masked fashion. Samples were stored at -20°C until arrival at Children's Hospital Oakland Research

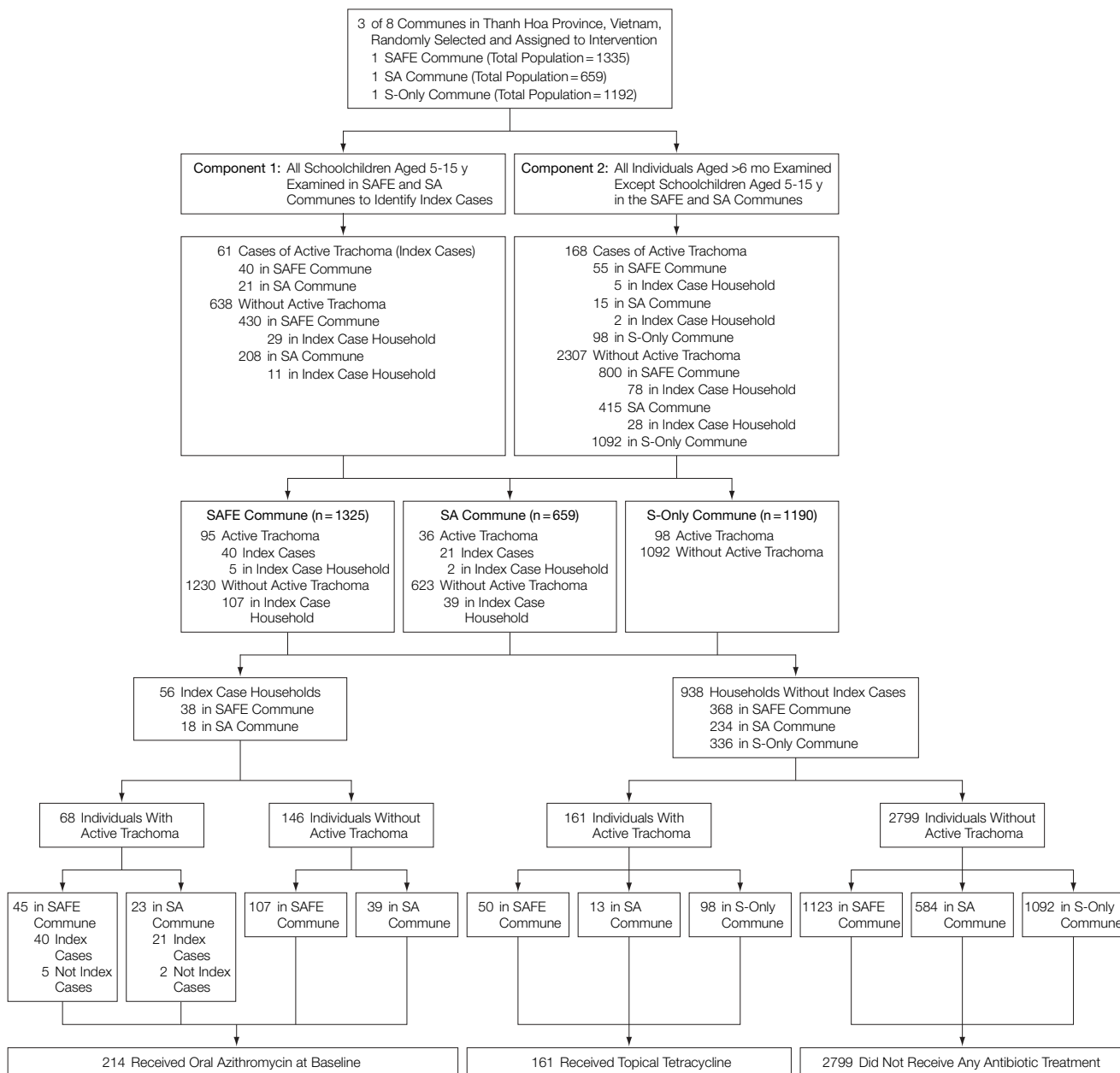
Institute in Oakland, Calif, where they were maintained at -80°C until processed. Technicians who performed PCR were masked to all clinical and demographic data for each time point; field workers were masked to PCR results.

Statistical Analysis

Follicular inflammation, intense inflammation, or both were designated as outcome indicators for active trachoma. A positive PCR result was an outcome indicator for *C trachomatis*

infection. The main outcomes were prevalence and incidence of active trachoma and *C trachomatis* infection in all communes at baseline, 6, 12, 18, 24, and 36 months. For subgroup analysis, the outcomes were new

Figure 1. Two-Component Targeted-Household Treatment Model for Active Trachoma Screening and Antibiotic Treatment



Active trachoma refers to individuals with follicular inflammation, intense inflammation, or both, as defined in the "Clinical Diagnosis" section of the "Methods". Component 1 included SAFE (Surgery for trachomatous trichiasis; Antibiotics for *Chlamydia trachomatis*; Facial cleanliness; and Environmental improvement) and SA communes to identify index cases aged 5 through 15 years. Component 2 was designed to identify household members of index cases in the SAFE and SA communes and to identify active trachoma cases in the SAFE, SA, and S-only communes. Targeted azithromycin treatment was not administered in the S-only commune. Individuals missing a clinical diagnosis of trachoma or age data were excluded from this model.

infection, continuing infection, and reinfection at 6, 12, 18, 24, and 36 months and risk factors for each. New infection was defined as no prior PCR-positive result at any time point; continuing infection as PCR-positive result at the immediate prior time point; and reinfection as PCR-positive result at one time point followed by a PCR-negative result followed by a PCR-positive result. Reinfection may also represent the recrudescence of an established antibiotic-refractory infection. However, determining antibiotic resistance was beyond the scope of this study.

Multiple logistic regression was used to analyze data. Participant's sex, age, commune type, treatment with azithromycin or tetracycline, and having at least 1 person with chlamydial infection in the household were used as explanatory variables in multiple logistic regression. Within the multi-level framework of the study, we used a 2-level model (individuals nested within households) including mixed random-effects models (for individuals) and generalized estimating equations (GEE) logistic model (for population subgroup analyses) for odds ratios (ORs) with 95% confidence intervals (CIs). These models were used for the subgroup analysis for a subset of 1260 individuals who were graded for trachoma and tested by PCR for *C trachomatis* infection at every follow-up during the 3-year study. The referent category for commune was the S-only commune and for age was the age group of 5 through 15 years.

Cluster analysis using the Jacard coefficient was employed to test whether active trachoma or *C trachomatis* infection clustered by household. We also performed a power analysis to ensure that significant results were based on a sufficient sample size for the respective data analysis. We used a 2-sided α -level of .05 to determine significance. Data were analyzed using Stata 9.0 (Stata Corp, College Station, Tex).

RESULTS

Demographic Characteristics at Baseline and Follow-up

A total of 3186 individuals were registered at baseline. Baseline characteristics by intervention type are shown in TABLE 1. There was no difference in demographics and active trachoma rates among the communes at baseline, but the infection rates differed for the SAFE commune compared with SA and S-only communes ($P = .001$). There were no statistically significant differences in the rate of follow-up within the communes over the 3-year study period.

Treatment at Baseline and 12 Months

At baseline, 100% of 40 index cases and household members (38 households) in the SAFE commune and 100% of 21 index cases and household members (18 households) in the SA commune were given oral azithromycin. At 12 months, 100% of 28 index cases and

household members (24 households) in the SAFE commune and 100% of 12 index cases and household members (11 households) in the SA commune were treated similarly (TABLE 2). No one received azithromycin in the S-only commune.

Although all index cases and household members with active trachoma and infection were treated at baseline and at 12 months in the SAFE and SA communes, the overall azithromycin treatment of patients with active trachoma in the 2 commune populations was 47.4% and 63.9% at baseline, and 69.6% and 61.9% at 12 months, respectively (Table 2). In contrast, azithromycin treatment of those with *C trachomatis* infection was only 11% and 4%, and 9.8% and 0%, respectively (Table 2).

Individuals with active trachoma in all 3 communes were treated with topical tetracycline unless they had received azithromycin. While all individuals with active trachoma were

Table 1. Baseline Characteristics of Vietnamese Communes by Intervention Type

	No./Total (%)*		
	SAFE	SA	S-Only
Total population	n = 1335	n = 659	n = 1192
Sex	n = 1330	n = 659	n = 1190
Male	569 (43)	260 (39.5)	537 (45)
Female	761 (57)	399 (60.5)	653 (55)
Active trachoma, by age, y†	n = 1325	n = 659	n = 1190
>15	51/733 (6.9)	14/390 (3.6)	81/765 (10.6)
5-15‡	40/470 (8.5)	21/229 (9.2)	16/341 (4.7)
<5§	4/122 (3.3)	1/40 (2.5)	1/84 (1.2)
<i>C trachomatis</i> infection, by age, y	n = 1308	n = 643	n = 1129
>15	57/720 (7.9)	82/384 (21.4)	123/727 (16.9)
5-15‡	42/466 (9)	38/219 (17.4)	47/323 (14.6)
<5§	9/122 (7.4)	5/40 (12.5)	15/79 (19)
<i>C trachomatis</i> infection by trachoma grade¶	n = 1315	n = 643	n = 1130
Active trachoma	7/94 (7.4)	7/35 (20)	18/95 (18.9)
No trachoma	98/1143 (8.6)	102/546 (18.7)	153/941 (16.3)

Abbreviations: SAFE, SA, and S-only are derived from the abbreviation for Surgery for trachomatous trichiasis; Antibiotics for *Chlamydia trachomatis*; Facial cleanliness; and Environmental improvement.

*Denominators for each variable are shown; they vary from overall population due to missing data.

†Active trachoma was defined as follicular inflammation (TF), intense inflammation (TI), or both. The denominator reflects the total number of individuals in the respective age group graded for trachoma in the respective commune.

‡Children aged 5 through 15 years with active trachoma were index cases.

§Infants younger than 6 months were excluded.

||*Chlamydia trachomatis* infection determined by commercial polymerase chain reaction (PCR) assay. The denominator reflects the total number of individuals in the respective age group tested for *C trachomatis* in the respective commune.

¶For active trachoma, the number of individuals with active trachoma with positive PCR was divided by the number of individuals with active trachoma who were tested by PCR in the respective commune. For no trachoma, the number of individuals with no evidence for trachoma with positive PCR was divided by the number of individuals with no trachoma who were tested by PCR in the respective commune.

Table 2. Targeted Household Treatment With Azithromycin in SAFE and SA Communes

	No./Total (%)			
	Baseline		12 Months	
	SAFE (n = 1335; 406 Households)	SA (n = 659; 252 Households)	SAFE (n = 1060; 380 Households)	SA (n = 522; 224 Households)
No. of index cases	40	21	28	12
No. of households with index case	38	18	24	11
No. of individuals in households with index case*	152	62	95	26
No. of additional individuals with active trachoma in households with index case	5	2	4	1
No. of individuals with active trachoma treated with azithromycin in total population with active trachoma*†	45/95 (47.4)	23/36 (63.9)	32/46 (69.6)	13/21 (61.9)
No. of individuals with <i>C trachomatis</i> infection treated with azithromycin in total population with infection‡	12/108 (11)	5/125 (4)	7/71 (9.8)	0/23 (0)

Abbreviations: SAFE, SA, and S-only are derived from the abbreviation for Surgery for trachomatous trichiasis; Antibiotics for *Chlamydia trachomatis*; Facial cleanliness; and Environmental improvement.

*Including index case.

†The numbers treated with azithromycin in index case households were exactly the same as those treated with azithromycin for the entire commune.

‡The number of infected individuals was determined at a later date after laboratory screening using the polymerase chain reaction assay; these data were not used to identify individuals for treatment.

Table 3. Topical Tetracycline Treatment for *Chlamydia trachomatis* Infection in All Communes for All Time Points*

Time, by Commune	No./Total (%)	
	Individuals With Infection	Treated Individuals With Infection
Baseline		
SAFE	96/1167 (8.2)	4/96 (4.1)
SA	120/581 (20.6)	3/120 (2.5)
S-only	185/1129 (16.4)	18/185 (9.7)
6 mo		
SAFE	213/935 (22.8)	9/213 (4.2)
SA	25/466 (5.4)	0/25 (0)
S-only	88/905 (9.7)	6/86 (7)†
12 mo		
SAFE	64/910 (7)	1/64 (1.6)
SA	23/398 (5.8)	1/23 (4.3)
S-only	68/894 (7.6)	0/68 (0)
18 mo		
SAFE	41/1039 (3.9)	0/41 (0)
SA	8/471 (1.7)	0/8 (0)
S-only	12/912 (1.3)	1/12 (8.3)
24 mo		
SAFE	17/940 (1.8)	0/17 (0)
SA	2/344 (0.6)	0/2 (0)
S-only	25/844 (3)	2/25 (8)

Abbreviations: SAFE, SA, and S-only are derived from the abbreviation for Surgery for trachomatous trichiasis; Antibiotics for *Chlamydia trachomatis*; Facial cleanliness; and Environmental improvement.

*For the SAFE and SA communes, the denominators for individuals with infection, except for baseline and 12 months, includes all the individuals in the communes. At baseline and 12 months, index cases and their household members in the SAFE and SA communes received azithromycin as part of targeted treatment (Table 2). Thus, the denominators for baseline and 12 months for the SAFE and SA communes reflect only individuals who were not in a household with an index case and who had conjunctival samples obtained for commercial polymerase chain reaction (PCR) testing for *C trachomatis* infection. For the S-only commune for all time points, the denominator includes all individuals with conjunctival samples obtained for PCR testing, since none of the S-only individuals received azithromycin treatment.

†There were 2 individuals with infection whose treatment information was missing in the S-only commune at 6 months.

treated with tetracycline at other time points, in all 3 communes low numbers of individuals with *C trachomatis* infection received topical treatment at any time point, as shown in TABLE 3.

Active Trachoma and *C trachomatis* Infection Rates for Each Time Point

Overall, the rates of active trachoma were similar in all communes at each time point during the 3-year study (FIGURE 2). There was a significant decrease in active trachoma rates in all 3 communes at 6 months ($P = .005$ for SAFE and SA; $P = .008$ for S-only). Active trachoma rates decreased again in all communes at 18 months but were only significant for SAFE and SA communes ($P = .003$ and $P = .04$, respectively). The rates reached a nadir at 24 months and increased only slightly at 36 months (P values were not significant for all communes).

Although active trachoma rates tended to be higher in females, the difference was significant only in the S-only commune at 12 months ($P = .01$). Active trachoma rates significantly differed by age group during the first 3 time points (data not shown). There was no clustering of active trachoma by household.

There was a significant decrease in *C trachomatis* infection rates over the course of 3 years for all 3 communes as shown in Figure 2, with a significant increase in infection at 36 months for the SAFE ($P < .001$) and SA communes ($P < .002$). While infection rates decreased at 6 months for the SA and S-only communes ($P < .001$ for both), there was an unexpected increase in infection in the SAFE commune from 8.3% to 23.4% ($P < .001$). Infection rates decreased significantly in this commune at 12 months ($P < .001$), a trend that continued until 36 months. The infection rates did not significantly differ by age or sex over the 3 years in any commune. There was clustering of individual infection by household in the SAFE commune, but only at baseline.

Active trachoma and infection rates differed significantly at baseline for SA

and S-only communes ($P < .001$ for both), and at 6 months for SAFE ($P < .001$), SA ($P < .001$), and S-only ($P = .02$) communes (data not shown). There were no significant differences for the remaining time points.

The estimated power for the above analyses ranged from 81% to 100%, with only 1 estimate at 59%. Because this is a public health program with community intervention, not a clinical trial, we did not perform a sample size calculation to estimate power for outcomes before the study.

Incidence of *C trachomatis* Infection and Risk Factors for Reinfection

FIGURE 3 is a graphical representation of 3 different categories of infection status and the incidence of infection for each time point. The categories include prevalence, new infection (incidence), continuing infection, and reinfection. Since the immune response to *C trachomatis* is usually sustained for only 1 to 4 months,²⁴ we reasoned that individuals with resolved infection (conversion of PCR-positive result to negative at a subsequent time point) would be susceptible to infection at the next time point, 6 months later. The

number of individuals who were susceptible (no prior infection or resolved infection) to infection remained high in all 3 communes, ranging from 85.4% to 97.9% over the 3 years of the study (data not shown).

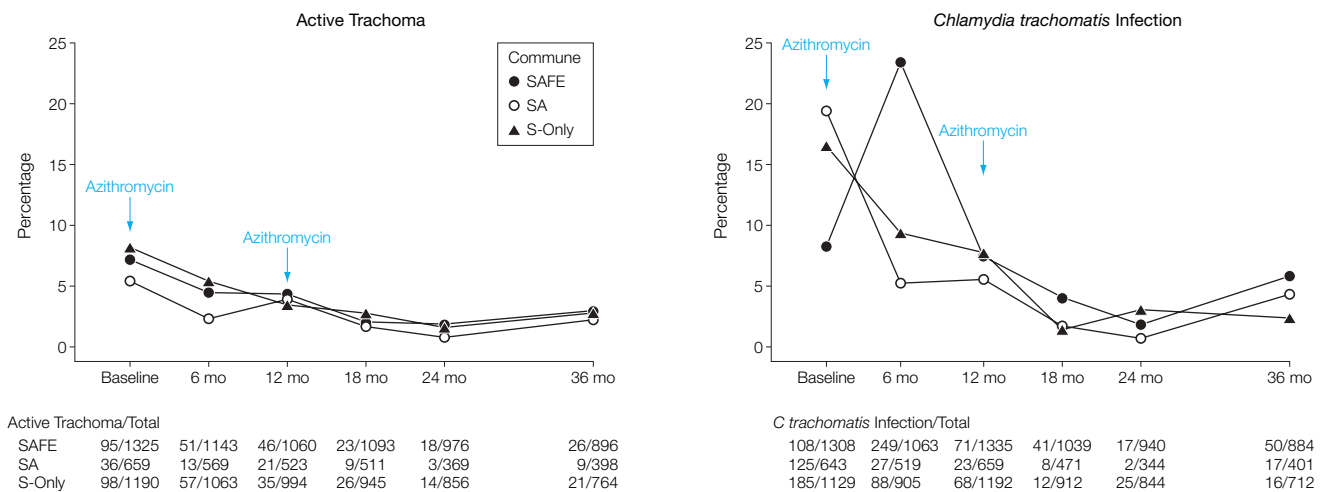
As shown in Figure 3, for all communes most of the infected cases were new incident cases (70%-100%) at each follow-up point. The incidence did not differ significantly by age group, sex, or having at least 1 person with chlamydial infection in the household. New infection rates were significantly higher for the SAFE and SA communes at 6 months ($P < .001$ and $P = .006$), for the S-only commune at 12 months ($P = .006$), for the SAFE commune at 18 months ($P < .001$), and for the S-only commune at 24 and 36 months ($P = .03$ for both). Reinfection rates were low when prevalence rates were decreasing. However, reinfection rates increased significantly at 36 months in the SAFE ($P < .001$) and SA ($P = .01$) communes (Figure 3). Power estimates ranged from 81% to 100%.

FIGURE 4 shows the analyses of a subset of 1260 individuals who were tested by PCR for *C trachomatis* infection at every follow-up during the 3-year study (614 in the SAFE commune, 198 in the

SA commune, and 448 in the S-only commune). Overall, 365 (59.4%) in the SAFE commune, 125 (63.2%) in the SA commune, and 305 (68.1%) in the S-only commune had no infection during the study. Those infected once were 221 (36%) in the SAFE commune, 66 (33.3%) in the SA commune, and 126 (28.1%) in the S-only commune. Those infected twice were 27 (4.4%) in the SAFE commune, 7 (3.5%) in the SA commune, and 17 (3.8%) in the S-only commune. Only 1 individual (0.2%) was infected 3 times in the SAFE commune only. The frequency of reinfection did not differ significantly by sex or age, except for at the 24-month time point.

Reinfection rates for second episodes were similar for the SAFE and SA communes, increasing significantly from 1.6 and 5.1 cases per 1000 population at 12 months to 29.3 and 25.3 cases per 1000 population, respectively, at 36 months in the SAFE ($P < .001$) and SA ($P = .01$) communes (Figure 4). The estimated power for comparison of 12- to 36-month reinfection rates in the SAFE commune ($n = 614$) was 1 and 0.82 in the SA commune ($n = 198$). Results of the mixed-effects and GEE logistic models

Figure 2. Rates of Active Trachoma and *Chlamydia trachomatis* Infection by Commune



Azithromycin treatment was administered just after trachoma grading and collection of the conjunctival sample for commercial polymerase chain reaction (PCR) detection of *Chlamydia trachomatis* infection. Numbers in the chart below the plots represent numerator and denominator values for the respective commune at each time point. SAFE, SA, and S-only are derived from the abbreviation for Surgery for trachomatous trichiasis; Antibiotics for *Chlamydia trachomatis*; Facial cleanliness; and Environmental improvement.

revealed risk factors for *C trachomatis* reinfection as summarized in TABLE 4. Although the Cox proportional hazard ratios with 95% CIs were similar, the mixed-effects and GEE models data

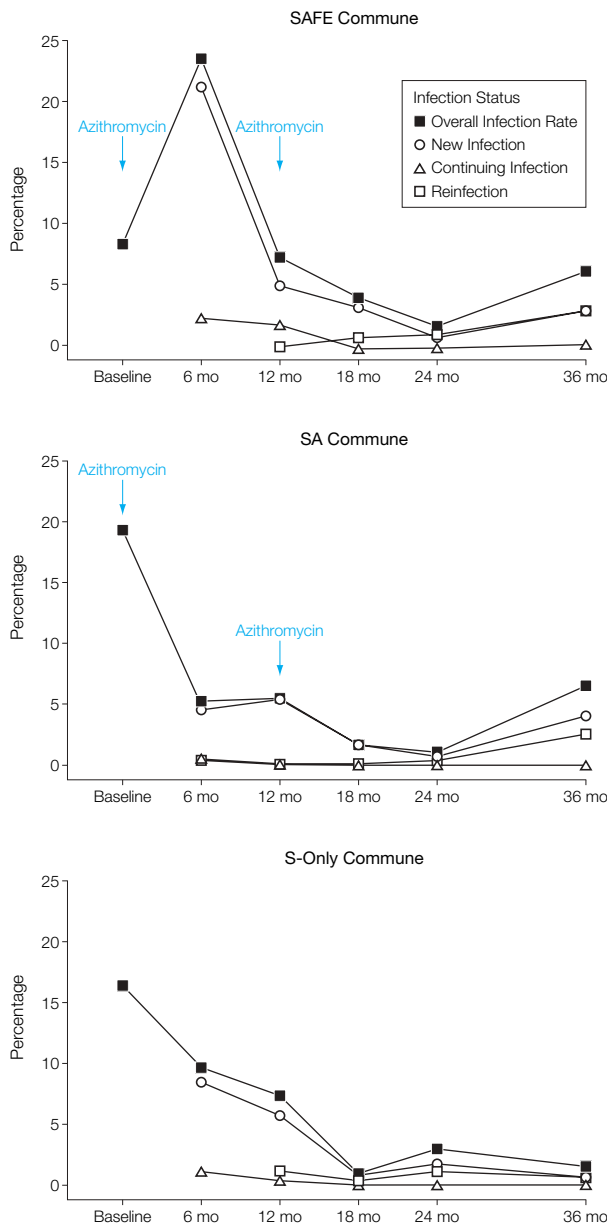
are shown because these data are more robust. The SAFE and SA communes but not the S-only commune were at significantly higher risk for reinfection at 36 months.

COMMENT

This is the first study to evaluate the efficacy of 2 consecutive years of targeted annual azithromycin therapy for the treatment of trachoma, with follow-up every 6 months out to 36 months, 2 years beyond the last treatment. All previous studies were either designed as mass treatment of children or performed for 14 months or less, except for one study that had an end point of 24 months, 1 year after the final treatment.^{6-15,25-28} In our study, the “F” and “E” components had no effect on the outcomes for the SAFE commune. Treatment of index cases and their households did not cover a sufficient number of infectious cases to sustain a decreased rate of infection in the SAFE and SA communes at 36 months (Table 2). Additionally, both the SAFE and SA communes had significantly higher rates of reinfection (Figure 4) and a significantly increased risk for reinfection (Table 4) compared with the S-only commune at 36 months. These findings could not be explained by administration of topical tetracycline treatment because the treatment coverage of *C trachomatis* infection was extremely low for all communes at all time points (Table 3).

Collectively, the data are consistent with the hypothesis that systemic azithromycin treatment may interrupt the duration of infection, interfering with host immune responses and, thereby, increase the number of individuals who are susceptible to *C trachomatis* reinfection. Our data are supported by previous findings in sexually transmitted disease populations in which the relative risk of reinfection increased annually after an initial decrease in infection rates following the introduction of an azithromycin treatment control program in Vancouver, British Columbia.²⁹ Consequently, the strategy of targeting only active trachoma for treatment is likely to be ineffective for long-term trachoma control and may adversely affect disease prevalence over time. While the “F” and “E” components of the SAFE program will need to be evaluated for their efficacy in decreasing rates of active tra-

Figure 3. Total Infection Prevalence and New Infection, Continuing Infection, and Reinfection Rates



Total infection prevalence (baseline) and new infection, continuing infection, and reinfection rates for each commune over 3 years. At each time point, data are shown as percentage of the population in each commune. Targeted-household azithromycin treatment was administered just after trachoma grading and collection of the conjunctival sample for commercial polymerase chain reaction detection of *Chlamydia trachomatis* infection. SAFE, SA, and S-only are derived from the abbreviation for Surgery for trachomatous trichiasis; Antibiotics for *Chlamydia trachomatis*; Facial cleanliness; and Environmental improvement.

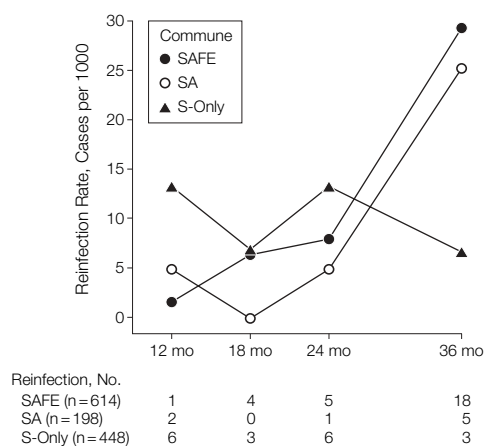
choma and infection, a vaccine will likely be needed for long-term control.

In our study, all index cases and their household members were treated in the SAFE and SA communes. However, 46.9% to 69.6% of the individuals with active trachoma received azithromycin at baseline and at 12 months, while the rest received topical tetracycline (Tables 2 and 3). There are 2 main rationales for the targeted-household treatment strategy. First, other studies have observed that trachoma tends to cluster within households.^{30,31} Thus, the extension of treatment from individual active cases to all household members should result in covering more cases of active trachoma.³² However, similar to research in Taiwan,³³ we did not find any clustering of active trachoma within households. Neither did we find clustering of infection by household, except for the SAFE commune at baseline.

The second rationale for targeted-household treatment is that it can theoretically lower the cost of azithromycin treatment when active trachoma prevalence is between 10% and 20%.⁴ However, in a study comparing the cost-effectiveness of the targeted-household strategy with mass treatment of children where active trachoma prevalence was 8% to 21%, mass treatment was not found to be more expensive than targeted-household treatment.³⁴

In this study, significantly fewer individuals with infection received azithromycin (Table 2). Success of the index case-based targeted-household treatment strategy requires that certain assumptions are true for the particular study community. First, that clinical grading is a good indicator of infection (unless screening for *C trachomatis* infection is in place); second, that children are the main proportion of the population with active trachoma; and third, that most of the children attend school. Previous studies have indicated that clinical grading is a poor indicator of infection compared with detection by PCR.^{8,32,35,36} We also found a discrepancy between the prevalence of active trachoma and in-

Figure 4. Reinfection Rates by Commune



Reinfection rates for infected cases per 1000 of the population for each commune. SAFE, SA, and S-only are derived from the abbreviation for Surgery for trachomatous trichiasis; Antibiotics for *Chlamydia trachomatis*; Facial cleanliness; and Environmental improvement.

fection at baseline and 6 months, although there was excellent correlation between the 2 for all later time points, likely reflecting improved trachoma grading over the course of the first 2 field camps. We found the highest rates of active trachoma among adults aged 45 years and older and children in the 6- to 15-year age group. Targeted-household treatment has the potential to cover this adult group while mass treatment of children would miss these adults who are part of the reservoir of infection, although, as in our study, not all adults with active trachoma would reside in a household with an index case. Finally, school attendance was very good in Vietnam.³⁷ If all of the active cases had been children, the outreach strategy likely would have been more successful.

At 6 months, we observed an unexpected increase in infection rates in the SAFE commune while there was a significant decrease in the other 2 communes. The lower rate of infection (Figure 2), clustering of infection by household, and high number of susceptible individuals in the SAFE commune at baseline may have contributed to the higher infection rates seen at this time point.

Chlamydia trachomatis infection is also dependent on the birth rate and the

Table 4. Risk Factors for Reinfection at Each Time Point Over 36 Months*

Predicting Factor by Time Point†	OR (95% CI)	P Value
18 mo		
SAFE commune	3.2 (1.2-8.6)	.02
Infection at 6 mo	20.1 (4.1-94.8)	<.001
24 mo		
Infection at baseline	3.3 (1.3-8.1)	.007
Infection at 6 mo	13.4 (4.9-36.5)	<.001
36 mo		
SAFE commune	4.1 (1.5-9.8)	.005
SA commune	4.2 (1.1-17.3)	.04
Infection at 6 mo	7.4 (3.7-14.8)	<.001
Infection at 18 mo	8.2 (3.3-22.2)	<.001

Abbreviations: CI, confidence interval; OR, odds ratio; SAFE, SA, and S-only are derived from the abbreviation for Surgery for trachomatous trichiasis; Antibiotics for *Chlamydia trachomatis*; Facial cleanliness; and Environmental improvement.

*Covariates included in mixed-effects and generalized estimating equation (GEE) logistic models are SAFE, SA, S-only communes, infection status at previous time point(s), age groups <5 y, 5-15 y, >15 y, sex, and household-targeted azithromycin treatment at baseline and/or 12 mo.

†The S-only commune is the reference group for SAFE and SA communes for each time point. The 5-15 age group is the reference group for age for each time point.

infectious period.³⁸ The duration of infection is age dependent and significantly longer for children younger than 5 years (3.8 weeks) compared with individuals 15 years of age or older (1.2 weeks).^{24,30} Since the birth rate is high among trachoma-endemic countries,³⁹ this represents an important reservoir of infection. There are no reports indicating how rapidly trachoma spreads within a community; how-

ever, we assume that it does not spread very rapidly since *C trachomatis* has a relatively long developmental cycle and is only moderately infectious.⁴⁰

There was a decline in both active trachoma and chlamydial infection rates for all 3 communes up to the 24-month time point. The declines in the SAFE and SA communes suggest that oral azithromycin had some beneficial effect. However, a similar decline in the S-only commune suggests that additional factors such as secular trends or exposure to educational information or knowledge about the SAFE program may have contributed to declines in the S-only commune. These factors may also have affected active trachoma and infection rates in the SAFE and SA communes.

The majority of individuals who became infected after targeted treatment in the SAFE and SA communes had new infection up to the 24-month time point. However, the rate of resolved infection was also high. Since immune protection against *C trachomatis* is only partial^{29,41,42} and usually lasts up to 4 months,⁴³⁻⁴⁵ many individuals were susceptible to reinfection. Both reinfection and new infection almost equally comprised the significant increase in infection rates at 36 months for the SAFE and SA communes, even though infection rates were less than 5% in all communes by 18 months and even lower at 24 months, a year after completion of the annual targeted-treatment program. Importantly, reinfection rates increased significantly for the SAFE and SA communes compared with the S-only commune at 36 months, where the ORs were 4.1 and 4.2, respectively.

Our findings are similar to those of Brunham et al,²⁹ who found that chlamydial sexually transmitted infections in Vancouver initially decreased after azithromycin treatment but increased due to susceptibility to reinfection with an increase in the relative risk of reinfection to 4.6% per year. Using a mathematical model that was also able to simulate the findings in the Vancouver study, this rebound phenomenon occurred even with treatment cov-

erage rates as low as 20%. In our study, targeted azithromycin treatment coverage ranged from 47% to 70% for the overall commune populations for active trachoma but was only 0% to 11% for infection (Table 2). Although treatment effectively decreases the rates of infection in the short term, the subsequent increasing rates of reinfection likely reflect a shortened period of infection, blunting the immune response and preventing the development of immunity. Immunity is normally elicited over many months,⁴⁶ although immunity is not complete in all individuals or sustained even without treatment. These posttreatment susceptible individuals reside in the same trachoma-endemic communities and continue to contribute to ongoing *C trachomatis* transmission.

Additional studies will be needed to assess the spectrum of immune responses at the time of treatment and at subsequent time points after treatment to fully understand this outcome. It has been proposed that treatment for trachoma control must be continued indefinitely until underlying conditions are improved to prevent reintroduction of infection.⁵ Based on our findings, treatment appears to result in increased rates of reinfection that may adversely affect the prevalence of disease over time.

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Author Contributions: Drs Atik and Dean had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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My writing is simply a set of experiments in life—an endeavor to see what our thought and emotion may be capable of.

—George Eliot (1819-1880)