# Mass Antibiotic Treatment and Community Protection in Trachoma Control Programs

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**Azithromycin is highly effective against trachoma, but the practical difficulties of community-wide distribution often leave many individuals untreated. We demonstrate, after mass azithromycin treatment of a population in Ethiopia, an indirect protective effect that occurred among untreated children who resided in villages in which most individuals had been treated. Similarities with the indirect protection within a treated community (i.e., "herd protection") that has been observed in vaccination programs are discussed.**

Repeatedly administered mass antibiotic treatment is a central element of the World Health Organization (WHO) program to eliminate blinding trachoma by the year 2020. Mass treatment of an entire community with single doses of oral azithromycin has been shown to successfully reduce the prevalence of ocular chlamydia that causes trachoma [1]. In practice, trachoma control programs reach only 60%–90% of the community, leaving a large portion of the population untreated [1–3]. In theory, an untreated individual may receive an indirect protective effect by residing in a community in which other individuals have been treated. Even untreated individuals can benefit from a reduction in the reservoir of infection [4]. Here, we estimate the extent of this indirect protective effect by comparing the prevalence of infection among untreated children who resided in villages that received mass antibiotic treatment (hereafter, "treated villages") with the prevalence of infection among untreated children who resided in villages that did not receive mass antibiotic treatment (hereafter, "untreated villages").

***Methods.*** The present study was conducted in the Gurage Zone, a region in Ethiopia in which trachoma is endemic, between the spring and fall of 2003. There were 41 Peasant Associations (PAs) in this region, each consisting of ~5 villages. Eight PAs were randomly selected, and 1 village from each of these PAs was randomly chosen to receive mass azithromycin treatment in the spring of 2003. An additional 8 PAs were randomly chosen, in the same manner, and 1 village from each PA was randomly chosen to receive mass azithromycin treatment in the fall of 2003. All 16 PAs and villages were monitored before the distribution of antibiotics, and the villages that were not chosen to receive mass azithromycin therapy in the spring of 2003 constituted an untreated control group. After the conclusion of the present study, the untreated villages were enrolled in the Ethiopian Trachoma Control Program and were offered treatment. No other specific trachoma control interventions, such as fly control programs, water supply changes, or measures to improve face washing, occurred in any of the 16 villages during the course of the present study. All individuals aged $\geqslant$1 year in the treated villages were offered a single dose of oral azithromycin, in accordance with WHO guidelines [5]. Government guidelines excluded children aged <12 months from receiving treatment with azithromycin. By the time of the survey taken in the fall of 2003, which was 6 months after the first administration of mass treatment, all children aged <18 months had not received treatment with azithromycin. The untreated group was composed of children who had been excluded from receiving azithromycin treatment in the spring of 2003 and children who had been born between the spring and fall of 2003.

Children aged <18 months were monitored for chlamydial infection for the present study; children aged 1–5 years were monitored for chlamydial infection for the trachoma control program in the region. An identical methodology was used for monitoring chlamydial eye infection in both the trachoma control program and in the present study. A trained examiner everted and swabbed the right upper tarsal conjunctiva, using new gloves for each child. Five percent of children aged 0–5 years were randomly chosen to have 2 types of control swab specimens obtained: a "duplicate swab specimen," to validate the results of the first test, and an "air swab specimen," obtained by passing the swab within 2.5 cm of the child's conjunctiva, to assess the frequency of contamination. Control swab spec-

Received 19 April 2004; accepted 24 June 2004; electronically published 6 October 2004.

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**Clinical Infectious Diseases 2004; 39:e95–7**



1058-4838/2004/3909-00E3$15.00

imens were obtained after the first swab specimen was obtained but before the examiner changed gloves for the next patient. All specimens were frozen at −20°C in Ethiopia and were transported at 4°C to the University of California, San Francisco, where they were stored at −80°C before testing. Samples were assayed for chlamydial DNA by use of the Amplicor test (Roche) by laboratory personnel who were masked to the identity and the study arm of each individual whose samples were being tested. Any tests for which the results were equivocal were repeated once, and the results were recorded as negative if they were again found to be equivocal.

A logistic model was used to predict the prevalence of infection; the model used the treatment arm as a covariate and corrected for within-village clustering by applying the Huber-White sandwich estimator of variance (Stata software, version 7.0; Stata). All research was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Committee on Human Research of the University of California, San Francisco, and the Ethiopian Science and Technology Commission, prior to commencement of the study. Verbal consent was obtained from each child's parent or guardian.

***Results.*** Before the administration of any antibiotic treatment, the average prevalence of chlamydial infection among children aged 1–5 years in each village, as determined by PCR, was 34.8% of the children per village ($n = 16$ villages; 95% CI, 22.8%–46.7%). Another study found that the prevalence of infection increased progressively with age and peaked among children aged 3–5 years [6]. The prevalence of infection among children aged 1–2 years (80 [25.7%] of 311 children) was significantly lower than that found among children aged 3–5 years (201 [41.7%] of 482 children; $P < .001$ by Fisher's exact test). In the treated villages, 91.3% of individuals aged 1 year and older received azithromycin treatment (percentage based on the census populations of the villages in 2003). Children aged 1–5 years in the treated villages had a prevalence of infection of 7.6% (95% CI, 0.0% [truncated] to 15.9%), as determined by PCR, 6 months (±1 week) after treatment, in the fall of 2003. Results for 58 of 58 (100%; 95% CI, 94%–100%; binomial exact) duplicate swab specimens were concordant, and results for 58 of 58 (100%; 95% CI, 94%–100%) air swab specimens were negative. In our larger study, which included more villages and more time points but used methodology identical to that of the present study, results for >95% of the duplicate swab specimens were concordant, and results for 99.4% of the air swab specimens were negative [7].

In the fall of 2003, the prevalence of chlamydial eye infection, as determined by PCR, was 3.8% (5 of 132) among the untreated children who were aged <18 months and who resided in treated villages (127 [96.2%] of 132 children were PCR negative for chlamydial eye infection). At the same time, the prevalence of chlamydial eye infection was 10.3% (9 of 87) among children in the same age group in untreated villages (78 [89.7%] of 87 children were PCR negative for chlamydial eye infection). A logistic model that predicted infection rates through the use of the treatment arm as a covariate revealed that, in treated villages, there was a 2.9-fold reduction in the odds of developing chlamydial infection (95% CI, 1.1- to 7.5-fold reduction; $P = .025$).

***Discussion.*** Mass azithromycin treatment for trachoma has a well-documented direct effect of eliminating ocular chlamydial infection in individuals who have received the antibiotic [1, 8, 9]. Our study shows that mass antibiotic distribution may also have an indirect effect on individuals who have not received treatment. We found significantly lower odds of the development of chlamydial infection among children who had not received azithromycin but who resided in a treated village than among children who resided in an untreated village. Because it is exceedingly difficult for any mass treatment program to attain 100% coverage of the community, it is reassuring to find that individuals who do not receive treatment may be indirectly protected.

The lack of approval for the use of azithromycin for young children provided us with a unique opportunity to study untreated individuals. The indirect effect of mass antibiotic treatment has not been previously estimated for a number of reasons. Most trachoma control programs would not usually withhold treatment from individuals in an age group that would, otherwise, be eligible for treatment with azithromycin. Although some individuals who reside in treated villages miss their scheduled appointments for azithromycin treatment, their reasons for doing so may make the results for the group biased; it would be difficult to find residents of untreated villages for whom results may be biased in a similar manner. Trachoma control programs often monitor active trachoma by use of clinical examinations, because of the simplicity and the low cost. However, the follicles that are characteristic of clinical trachoma do not reliably form in individuals until the individuals are 6–12 months of age, and clinical examination has not been shown to be an accurate way to monitor infection after administration of antibiotic treatment to any age group [1, 6]. A study design that takes into account the prevalence of infection at baseline can sometimes provide more power, particularly if there is a high correlation between pretreatment findings and posttreatment findings [10]. However, a good portion of the monitored group had not been born by the time of the pretreatment visit in the spring of 2003. Also, some programs obtain a lower coverage than the 91.3% coverage achieved in the present study; it is not clear how much indirect protection would be offered with lower coverage.

Is it possible that the indirect effect that we observed is analogous to that seen in vaccine programs? Vaccination not only protects the individual from infection, it also removes their

potential as a source of transmission of infection to others. As a result, unvaccinated individuals are less likely to encounter infection. In fact, this indirect effect may even prevent infection from persisting within a community. Such community protection is known as "herd immunity" [11] or "herd protection" [12]. The most important consequence of herd immunity is that it enables the elimination of infection from within a population, even without complete coverage. Although antibiotics do not confer sustained immunity to individuals, the indirect effect that we observed persisted at the community level for at least 6 months. The time point of 6 months after the first administration of mass antibiotic treatment coincides with the next scheduled administration of treatment for many communities in the Ethiopian trachoma control program. The existence of such a prolonged effect suggests that mass antibiotic treatment may offer protection to the entire community if repeated frequently enough, by reducing the chance of individuals coming into contact with the infectious agent. Only long-term follow-up after multiple treatments will reveal whether this community protection is powerful enough to enable elimination of infectious trachoma [4, 13].

## Acknowledgments

***Financial support.*** Research for the Prevention of Blindness, the Osher Foundation, the International Trachoma Initiative, and the National Institutes of Health (grants AI055752 and AI48789).

***Potential conflict of interest.*** All authors: No conflict.

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