BRIEF REPORT

Feasibility of Eliminating Ocular *Chlamydia trachomatis* With Repeat Mass Antibiotic Treatments

Muluken Melese, MD, MPH
Jaya Devi Chidambaram, MBBS
Wondu Alemayehu, MD, MPH
David Chung Lee, BSc
Elizabeth H. Yi
Vicky Cevallos, BSc
Zhaoxia Zhou
Cathy Donnellan
Michael Saidel, MD
John P. Whitcher, MD, MPH
Bruce D. Gaynor, MD
Thomas M. Lietman, MD

Context Mass antibiotic administrations for ocular chlamydial infection play a key role in the World Health Organization's trachoma control program. Mathematical models suggest that it is possible to eliminate trachoma locally with repeat mass treatment, depending on the coverage level of the population, frequency of mass treatments, and rate that infection returns into a community after each mass treatment. Precise estimates of this latter parameter have never been reported.

Objective To determine the rate at which chlamydial infection returns to a population after mass treatment and to estimate the treatment frequency required for elimination of ocular chlamydia from a community.

Design, Setting, and Participants Longitudinal cohort study of 24 randomly selected villages from the Gurage Zone in Ethiopia conducted February 2003 to October 2003. A total of 1332 children aged 1 to 5 years were monitored for prevalence of ocular chlamydial infection pretreatment and 2 and 6 months posttreatment.

Interventions All individuals older than 1 year were eligible for single-dose oral azithromycin treatment. Pregnant women were offered tetracycline eye ointment.

Main Outcome Measures Prevalence of ocular chlamydial infection, measured by polymerase chain reaction, in children aged 1 to 5 years, in each of 24 villages at each time point was used to estimate the rate of return of infection and the treatment frequency necessary for elimination.

Results The prevalence of infection was 56.3% pretreatment (95% confidence interval [CI], 47.5%-65.1%), 6.7% 2 months posttreatment (95% CI, 4.2%-9.2%), and 11.0% 6 months posttreatment (95% CI, 7.3%-14.7%). Infection returned after treatment at an exponential rate of 12.3% per month (95% CI, 4.6%-19.9% per month). The minimum treatment frequency necessary for elimination was calculated to be once every 11.6 months (95% CI, 7.2-30.9 months), given a coverage level of 80%. Thus, biannual treatment, already being performed in some areas, was estimated to be more than frequent enough to eventually eliminate infection.

Conclusion The rate at which ocular chlamydial infection returns to a community after mass treatment suggests that elimination of infection in a hyperendemic area is feasible with biannual mass antibiotic administrations and attainable coverage levels.

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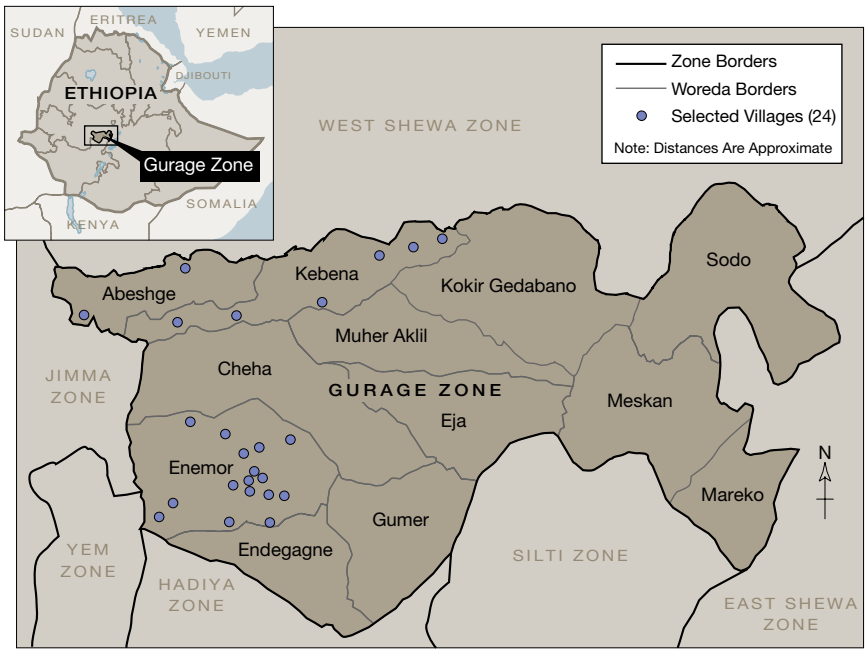
MASS ANTIMICROBIAL ADministrations have been used in several control programs and have been contemplated for many others. They have proven to be effective against some parasitic diseases (eg, onchocerciasis and filariasis), but at times have not lived up to expectations (eg, malaria).[1-3] Various forms of mass treatment have been used for bacterial diseases, including sexually transmitted chlamydia and syphilis.[4,5] The World Health Organization (WHO)[6] and its partners are now using repeated mass azithromycin administrations to control the ocular strains of chlamydia that cause trachoma, the world's leading cause of infectious blindness.[7] Trachoma meets the critical criteria for eradicability: there is an effective treatment for the ocular strains of *Chlamydia trachomatis*, and there is no known animal reservoir. Cur-

Author Affiliations: ORBIS International, Addis Ababa, Ethiopia (Drs Melese and Alemayehu); WHO Collaborating Center, F.I. Proctor Foundation (Drs Chidambaram, Saidel, Whitcher, Gaynor, and Lietman, Mr Lee, and Mss Yi, Cevallos, Zhou, and Donnellan), Department of Ophthalmology (Drs Gaynor, Whitcher, and Lietman), Department of Epidemiology and Biostatistics (Drs Whitcher and Lietman), Institute for Global Health (Drs Whitcher and Lietman), University of California, San Francisco.
Corresponding Author: Thomas M. Lietman, MD, WHO Collaborating Center, F.I. Proctor Foundation, Room 307, 95 Kirkham St, University of California, San Francisco, San Francisco, CA 94143-0944 (tml@itsa.ucsf.edu).

Figure 1. Map of Gurage Zone of Ethiopia Displaying Villages Randomly Selected for the Study



rently, there is little evidence of emerging chlamydial resistance to macrolides;[8] however, susceptibility testing in chlamydia is difficult to measure and rarely performed, and further surveillance may be needed.[9] Trachoma has already disappeared from most developed countries—the last documented case of indigenous active trachoma in the United States appears to have been in the 1970s.[10] Nevertheless, the general consensus among public health workers is that the incidence of ocular chlamydial infection cannot be reduced to zero in the most hyperendemic areas with antibiotics alone.

Can trachoma infection be eliminated from the most hyperendemic areas with repeated mass antibiotic administrations? Mathematical models reveal that it is theoretically possible to eliminate infection locally even without complete antibiotic coverage by progressively reducing the prevalence of infection with each treatment.[11] Elimination is dependent on the efficacy of the antibiotic in an individual, the coverage and frequency of treatment, and the initial rate at which infection returns to a community after mass treatment,[11] but precise estimates of the important latter parameter have never been reported. Here we determine the rate at which chlamydial infection returns to a hyperendemic population in Ethiopia, and from this we estimate the treatment coverage and frequency (ie, biannual, annual) required to eliminate infection. That is, we determine whether elimination of ocular chlamydia from severely affected areas is a feasible goal.

METHODS

A geographical area was selected from the Gurage Zone of Ethiopia that included 3 subdistricts and about 112 000 people (FIGURE 1). A stratified sample of 24 villages was randomly chosen from a complete list of all villages (8 from each of the 3 subdistricts). A census was conducted (February and March 2003), and all village residents aged 1 year and older were eligible to participate in the study. A single oral dose of azithromycin (1 g to adults, 20 mg/kg to children) was offered within 2 weeks of the baseline examination to all members of the community except children younger than 1 year. Children younger than 1 year were excluded because azithromycin was approved for use in Ethiopia only for children 1 year and older. Adherence to therapy was essentially 100% of those treated, since administration of the single-dose antibiotic was directly observed. Pregnant women were offered topical tetracycline ointment. Guardians were asked to bring all children aged 1 to 5 years, the ages most likely to harbor infection, to a central location in their village for examinations at baseline and 2 and 6 months after treatment (±1 week, from March 2003 to October 2003). Verbal consent was obtained from the parent or guardian of each child. The right upper tarsal conjunctiva of each child was everted and swabbed. Swabs were placed immediately at 4°C and at −20°C within 6 hours, and transported at 4° C to the University of California, San Francisco for processing with the Amplicor polymerase chain reaction (PCR) test (Roche Molecular Systems, Branchburg, NJ) according to protocol.

Posttreatment samples from the same village were pooled by random selection into groups of 5, and 200 µL of each of the 5 samples was pooled into a single tube for processing.[12-14] The prevalence in each village was then estimated from the proportion of positive pools, using maximum likelihood estimation as previously described.[15]

Laboratory controls were included according to the Roche Amplicor protocol. In addition, negative field controls were obtained from at least 5 random children from each village. Immediately after the study swab and before changing gloves for the next patient, a second swab was passed within 1 inch of the conjunctiva without touching. These control swabs were processed in a manner identical to the study swabs; if a pooled control was found to be positive, then all samples in that pool were individually retested. All specimens were processed in a masked manner.

The rate of return of infection after treatment was determined from the ob-

served increase in prevalence from 2 to 6 months after treatment. Using this rate, the treatment frequency necessary to achieve elimination was obtained from the following inequality[11]:

$$\frac{1}{1-(\text{coverage}\times\text{efficacy})} > e^{(\text{rate}\times\text{period})}$$

where *efficacy* is the efficacy of the antibiotic in an individual, and *period* is the duration between treatments. The left-hand side of the inequality represents how much a single mass treatment with a given antibiotic efficacy and coverage reduces the level of infection at each treatment. The right-hand side represents the exponential increase of infection during the period between treatments. For eventual elimination, the fraction of infection reduced by each treatment must be greater than the increase of infection on its return between treatments.

To model the future prevalence, the level of infection was extrapolated from the observed prevalence data. The baseline prevalence and the rate of return of infection defined the parameters for a logistic growth model. Mass treatments are incorporated into the model by periodically lowering the prevalence assuming 80% coverage and that the antibiotic will eliminate infection in 95% of individuals treated. By varying the frequency of these mass treatments, the resulting projections predict the feasibility of eliminating infection.

Results from 2 months and 6 months were compared using a *t* test paired by village. Intervillage variance was estimated, and confidence intervals (CIs) were used to express uncertainty due to sampling error. All statistical calculations were performed in STATA 7.0 (Stata Corp, College Station, Tex) using the village as the unit of observation. A local sensitivity analysis was performed by standard techniques[16]: differentiating the necessary treatment frequency function with respect to either coverage or initial rate of return, around the observed coverage and rate of return. $P<.05$ was considered statistically significant.

Table. Antibiotic Coverage, Study Participation, and Prevalence of Ocular Chlamydia by Village in Gurage Zone, Ethiopia

	Baseline Pretreatment	2 mo Posttreatment	6 mo Posttreatment
No. of villages sampled*	24	24	24
Total No. of children aged 1 to 5 y examined	1332	1316	1321
Estimates, mean % (95% CI)†			
Village treatment coverage	91.9 (89.3-94.5)	Monitor only	Monitor only
Village PCR participation	91.1 (88.7-93.5)	91.5 (88.7-94.3)	90.1 (87.6-92.6)
Village prevalence by PCR	56.3 (47.5-65.1)	6.7 (4.2-9.2)	11.0 (7.3-14.7)
Prevalence, No. of villages			
>50%	14	0	0
>20% to ≤50%	10	0	4
>0% to ≤20%	0	18	14
0%	0	6	6

Abbreviations: CI, confidence interval; PCR, polymerase chain reaction.
*The same 24 villages were sampled at each time point.
†Coverage, participation, and prevalence estimates were calculated at the village level. Means and 95% CIs reflect this.

All research was conducted in accordance with the Declaration of Helsinki. We obtained ethical approval from the institutional review board of the University of California, San Francisco, and the National Ethical Clearance Committee of the Ethiopian Science and Technology Commission (registered with the Office for Human Research Protections), prior to commencing the study.

RESULTS

For the mass antibiotic distribution, 92% of the total 10 169 individuals aged 1 year and older were covered by treatment, and 93% of the total 1478 children aged 1 to 5 years were covered, relative to the census (N = 24 villages). The 3 most common reasons for not receiving treatment were temporary absence from the village at the time of treatment, migration, and death. Refusal of treatment was rare. Village PCR participation rates were comparable at each time point, as depicted in the TABLE. We found that 99.1% of negative field controls were PCR negative (449/453).

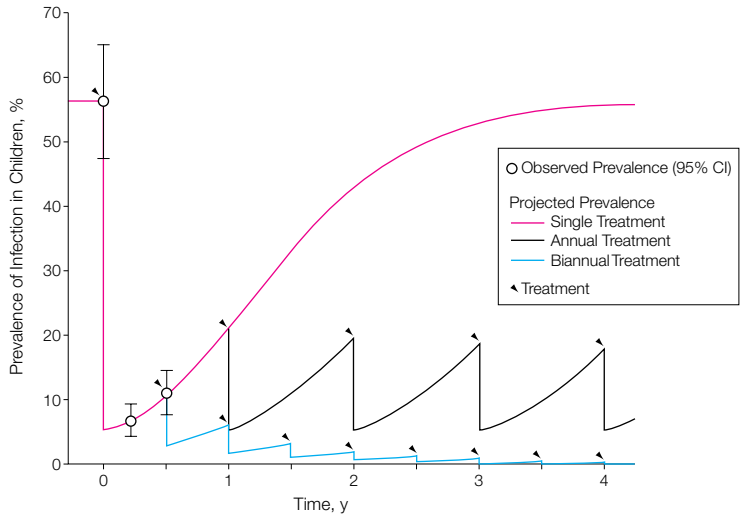
Prior to treatment, the mean village prevalence of infection based on PCR positivity was 56.3% (N = 24 villages; 95% CI, 47.5%-65.1%). After treatment, the mean prevalence dropped to 6.7% (95% CI, 4.2%-9.2%) at 2 months; by 6 months, it had risen to 11.0% (95% CI, 7.3%-14.7%) ($P=.005$ for 2 vs 6 months). Village-level prevalences at each time point are categorized into various strata in the Table. After mass treatment, the exponential rate of return of infection was calculated to be 12.3% per month (95% CI, 4.6%-19.9% per month) (FIGURE 2). Treatment every 6 months is more than enough to eventually eliminate infection.

Using these empirical data and the inequality above, we estimated the minimum treatment frequency necessary for elimination to be once every 11.6 months (95% CI, 7.2-30.9 months), given 80% treatment coverage of the population (FIGURE 3). This coverage level of 80% was chosen for the projections because it has been achieved by other trachoma programs[17] and is the target recommended by the WHO. The estimation of the necessary treatment frequency is locally sensitive both to the initial rate of return after treatment (changing by 0.12 months for every 1% relative change in rate) and to the coverage level (changing by 0.32 months for every 1% absolute change in coverage level). The dependence of the necessary treatment frequency on the coverage level is displayed in Figure 3. Also, the effect that the uncertainty in the estimation of the rate of return has on the necessary treatment frequency is depicted in Figure 3 by the 95% CIs.

COMMENT

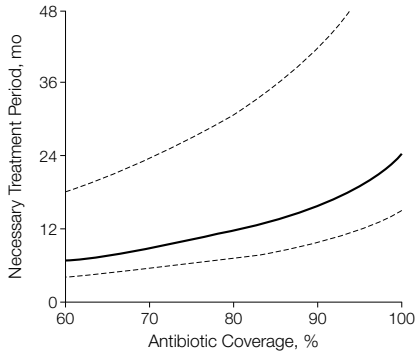
These results imply that elimination of ocular chlamydia in this area of Ethiopia is feasible. Biannual treatment with

Figure 2. Mathematical Projections of Trachoma Prevalence Derived From Empirical Pretreatment, 2-Month, and 6-Month Posttreatment Results



Projections are based on the assumptions that treatment is administered once, annually, or biannually; coverage is 80%; and antibiotic efficacy in an individual is 95%.[11] Projections follow logistic growth determined by the equation: baseline prevalence/$(1 + C\,e^{-[\text{rate of return}][\text{time}]})$, where C is a constant that is fit by the empirical data.

Figure 3. Treatment Frequency Necessary to Eliminate Infection Over a Range of Antibiotic Coverage Levels



The World Health Organization currently recommends annual treatment. Calculations assume an antibiotic efficacy of 95% in an individual and use inequality (i). The solid black line indicates the calculated treatment frequency necessary for elimination; the dashed lines indicate 95% confidence intervals.

80% coverage should be more than sufficient to eventually reduce the local incidence of infection to zero (Figure 2). This coverage level is realistic and within the range of previous trachoma programs.[17] Greater coverage would allow less frequent treatment (Figure 3). These calculations require estimation of the rate of return of infection into a community after mass treatment, which has not been available previously for several reasons. First, most trachoma programs monitor disease by following clinical activity, which does not correlate well with infection after antibiotic treatment.[18,19] Also, intervillage variance is sufficiently high that multiple villages need to be monitored to make a reasonable estimate.[20,21] Finally, in some areas that have been studied, trachoma appears to be disappearing even in the absence of an organized control program, in which case infection may never return after treatment.[22-24]

Currently, the WHO's goal for trachoma programs is neither eradication (global reduction of infection to zero) nor true elimination (local reduction of infection to zero), but the more conservative target of "elimination of trachoma as a public health concern".[4] This is defined as less than 5% clinical activity in children. The rationale of the program is that infection can be reduced with several mass antibiotic treatments, and that other sustainable, nonantibiotic measures such as face-washing and fly control can prevent infection from returning to a community. So far, it has been difficult to prove that any particular nonantibiotic measure has a significant effect on chlamydial infection, although there are reasons to be optimistic.[25] If true local elimination of ocular strains of chlamydia is feasible with antibiotics alone, then this would provide a rationale for the trachoma program even without adjunctive measures. If other measures prove to be as effective as hoped, then antibiotics could be given less frequently and to a lower percentage of the population.

The prevalence of ocular chlamydia in a community before treatment may be a key factor determining the rate that infection returns after treatment—the greater the baseline prevalence, the more rapid the return.[11,26] Trachoma in this area of Ethiopia is as severe as anywhere else in the world, so if biannual treatments can eliminate infection in this region, success should be possible elsewhere, perhaps requiring even less frequent treatments. Longer term empirical studies will be necessary to determine whether infection can indeed be eliminated locally and to determine appropriate dosing frequencies for less endemic areas. Although studies have found only minimal pneumococcal resistance after mass treatment,[27] the potential for emerging chlamydial resistance should be monitored, particularly when multiple rounds of treatment are used.

If mass periodic treatments with incomplete coverage of the population can eliminate trachoma as these results suggest, then researchers can concentrate on whether similar results can be obtained by targeting only a core group most likely to be infectious. Mathematical models imply that this too is possible, although treatment may need to be given more than twice per year.[11] For many bacterial diseases, treatment targeted to the entire population may not be appropriate. However, if only a core group needs to be treated, then mass repeat antibiotic administration may prove to be a valuable tool for a variety of bacterial scourges.

Author Contributions: Dr Lietman 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.

Study concept and design: Melese, Chidambaram, Alemayehu, Yi, Whitcher, Gaynor, Lietman.
Acquisition of data: Melese, Chidambaram, Alemayehu, Yi, Cevallos, Zhou, Donellan, Saidel, Whitcher, Gaynor, Lietman.
Analysis and interpretation of data: Melese, Chidambaram, Alemayehu, Lee, Yi, Whitcher, Gaynor, Lietman.
Drafting of the manuscript: Melese, Chidambaram, Alemayehu, Yi, Donellan, Whitcher, Gaynor, Lietman.
Critical revision of the manuscript for important intellectual content: Melese, Chidambaram, Alemayehu, Lee, Yi, Cevallos, Zhou, Donellan, Saidel, Whitcher, Gaynor.
Statistical analysis: Alemayehu, Lee, Yi, Whitcher, Lietman.
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