Complete Elimination Is a Difficult Goal for Trachoma Programs in Severely Affected Communities

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The World Health Organization has distributed millions of doses of azithromycin to control the ocular chlamydial infection that causes trachoma. Theoretically, a loftier goal of elimination is feasible. Here, we demonstrate that, although local elimination of infection in the most severely affected communities is difficult, it is possible with biannual antibiotic distributions.

The World Health Organization (WHO) has recommended repeated, community-wide antibiotic distributions to control ocular chlamydial infection so that blinding trachoma is no longer a major public health concern [1]. The WHO does not anticipate that infection can be eradicated or even locally eliminated from an area. Instead, the WHO relies on other measures, such as hygiene and environmental improvements, to prevent infection from returning after antibiotics are discontinued. Although there are reasons to hope that nonantibiotic measures may be beneficial, there is currently no evidence that any particular intervention prevents infection from returning to a community once antibiotics have been discontinued [2]. Thus, if achievable, local elimination of infection would be an important end point. Mathematical models suggest that local elimination of infection is possible even in severely affected communities if antibiotics are distributed frequently enough and to a large enough portion of the community [3, 4]. In villages with low rates of infection, ≥1 treatments have come close to eliminating infection [5–7]. In areas of hyperendemicity, if infection is not eliminated from a community, it can clearly return, even if a decrease to a low rate of infection is achieved [4, 8, 9]. To date, no study has demonstrated that infection can be locally eliminated from all members of a severely affected community. In our study, we surveyed all members of 3 Ethiopian villages where ocular chlamydial infection is hyperendemic that are likely candidates for elimination of the infection.

Methods. Twenty-four communities in the Enemore district of the Gurage Zone, Ethiopia, received biannual mass oral azithromycin distributions, as described elsewhere [8]. Briefly, a stratified sample of 24 villages was randomly chosen from a complete list of villages in 3 subdistricts. A census was conducted, and all individuals aged ≥1 year were offered 4 biannual, single-dose azithromycin treatments (1 g to adults and 20 mg/kg to children) over 24 months. Pregnant women were offered topical tetracycline ointment.

Children aged 1–5 years, the age group most likely to harbor infection, were monitored prior to each mass antibiotic administration and at 6 months after the last antibiotic administration. After verbal consent was obtained from the parent or guardian of each child, an upper conjunctival swab specimen was obtained for PCR testing. At 24 months after the study start, there was no PCR-proven infection in preschool-age children in 8 villages for at least 2 consecutive visits, and these villages were considered as candidates for elimination. Three of these 8 villages were chosen for this study on the basis of their populations (<400 individuals) and the prevalence of infection (>30%) in the village before treatment. At the 30-month visit in October 2005, we attempted to examine every individual from these 3 villages. If an individual was not present, we returned to the village on a subsequent day within the same 7-day period. Villages were visited until survey coverage was complete or up to 4 times. The upper right tarsal conjunctiva was everted and swabbed. Swab specimens were placed at 4°C immediately and then at −20°C within 6 h and were transported at 4°C to the University of California, San Francisco, for processing using the Amplicor PCR (Roche Molecular Systems).

Posttreatment samples from the same village were randomly pooled into groups of 5 for processing. For samples collected from children aged 1–5 years at baseline or from the entire community at 30 months, every sample in a positive pool was then processed to determine the infected individual(s). For
samples collected from children aged 1–5 years during the 2–24 months after treatment, the prevalence of infection in the village was estimated directly from the percentage of positive pools using maximum likelihood estimation, as described elsewhere [4, 8]. Note that this pooling strategy is considerably cost-effective. Laboratory control samples were included according to the Roche Amplicor protocol. In addition, 2 sets of field controls were obtained. Before changing gloves for the next patient, a second swab was passed within 1 inch of the conjunctiva (without touching) in 5 random individuals from each village (negative field control group). A duplicate swab specimen was obtained from 5 different randomly chosen individuals from each village (duplicate field control group). All specimens were processed in a masked manner.

Results. Antibiotic coverage of the intended population (persons aged ≥1 year) in the 3 villages ranged from 85% to 100% at each village visit, with a mean coverage of >90% (table 1). 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, and adherence to treatment when given was essentially 100%, because it was single-dose, observed therapy. The 3 villages chosen for the study had a mean estimated population of 211 persons at 30 months, with a mean baseline prevalence of infection of 43%. At 30 months, 19.8% of the population in the 3 villages was aged 1–5 years. The 24 villages in the original study had a mean baseline prevalence of PCR-positive infection of 52.9% and a mean baseline population of 250 persons. The 5 villages that had no evidence of infection at 18 and 24 months and were not chosen for this study had a mean baseline prevalence of infection of 26.9% and a mean estimated population of 358 persons.

Characteristics of the 3 villages chosen for this study are shown in table 1. The estimated prevalence of ocular chlamydial infection among children aged 1–5 years from pretreatment to 24 months is shown in figure 1. Note that no infections were found in children aged 1–5 years at the 18- and 24-month visits.

At 30 months, coverage with swabbing was nearly complete in village 1. We were unable to examine an 85-year-old woman whose family felt she was too ill and a 45-year-old man who was absent from the village at all 4 visits. The survey was 100% complete in village 2. In village 3, a total of 4 individuals (aged 12, 22, 26, and 48 years) were unable to be examined. The parents of the 12-year-old boy refused to allow examination. The 26-year-old woman had undergone a trichiasis surgical procedure 2 weeks prior to the study visits and refused to be examined, fearing discomfort. The men aged 22 and 48 years also refused examination, even after receiving further information regarding the examination procedure. In village 1, there were 3 preschool children aged 2 years (female), 4 years (female), and 4 years (male) who tested positive for chlamydia. In village 2, a single 15-year-old girl was found to be infected. In village 3, all individuals tested negative for infection.

All 90 negative field control specimens obtained from individuals in the 3 villages from baseline through the 30-month visit showed no evidence of chlamydia. There was 98.8% concordance (82 of 83 pairs of specimens had the same result) between the duplicate field control specimens for all visits.

Table 1. Population of and coverage of antibiotic treatment for ocular chlamydial infection in the 3 study villages.

<table>
<thead>
<tr>
<th>Village</th>
<th>Population</th>
<th>Coverage, %</th>
<th>No. of infections remaining at 30 months/no. of persons</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At 30 months</td>
<td>At 6 months</td>
<td>At 12 months</td>
</tr>
<tr>
<td>1</td>
<td>166</td>
<td>162</td>
<td>93.0</td>
</tr>
<tr>
<td>2</td>
<td>265</td>
<td>208</td>
<td>93.4</td>
</tr>
<tr>
<td>3</td>
<td>279</td>
<td>262</td>
<td>85.8</td>
</tr>
</tbody>
</table>
Discussion. It may be possible to eliminate ocular chlamydial infection from communities using repeated mass antibiotic distributions. However, it will be difficult to do so in the most severely affected areas. The WHO recommends at least 3 annual treatments with at least 80% coverage, with subsequent treatments dependent on reassessment. In our study, we distributed 4 biannual treatments with >90% coverage and still found infected individuals in 2 of the 3 communities. In the community in which there were no infected individuals, there was no evidence of infection 12 months after the last treatment.

It is unclear why residual infections after mass treatments occur. Possibilities include incomplete coverage, ineffective treatment, and reintroduction of infection from outside the community; all have been hypothesized [4, 6, 9]. Molecular epidemiological studies that use the genetic heterogeneity of chlamydia to track cases have not resolved the issue [10]. In this study, children found to be infected in village 1 at the end of the study period had previously received treatment and tested negative for infection. In village 2, the infected young adult would not have been found by screening the high-risk younger age group. Interestingly, children who had been too young to receive azithromycin at the last treatment were not found to be a source of infection. The role of reintroduction from outside the community is unclear. Most immigrants come from neighboring villages where individuals were treated at least twice in the spring and fall of 2003.

The WHO's trachoma control program has been extremely successful. In regions where infection has been monitored, azithromycin distribution has reduced the prevalence of infection with ocular strains of chlamydia. However, if infection is not eliminated by treatment, it has been shown to return, at least in communities of hyperendemicity [4, 8, 9]. In our study, we found that complete elimination was difficult. Infection persisted in 2 of 3 villages. However, we were unable to locate 4 of the individuals from the village where infection did not remain. Although the accuracy of the PCR test used in this study is thought to be high, it is not perfect, and cases may have been missed. Future studies with even more sensitive RNA-based testing may be necessary to prove elimination of infection beyond doubt [11]. In villages larger than the 3 included in this study, it may be harder to eliminate infection, as has been suggested in mathematical models [12]. Models also suggest that >4 mass antibiotic distributions may be necessary to predictably eliminate infection from the most severely affected areas [12, 13]. Complete elimination of ocular chlamydial infection from severely affected areas may be possible; however, it will be difficult and will likely require treatment at a higher frequency and coverage than is necessary for control.

Acknowledgments

We thank the Ethiopian Ministry of Health and the many health care professionals who helped us organize and implement our fieldwork in Ethiopia, including Tadesse Kebede, Berhanu Fikre, Mifta Shifa, and Tadesse Birru.


Potential conflicts of interest. All authors: no conflicts.

References