Number of Years of Annual Mass Treatment With Azithromycin Needed to Control Trachoma in Hyper-endemic Communities in Tanzania

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Background. The World Health Organization recommends mass treatment as part of a trachoma control strategy. However, scant empirical data from hyperendemic communities exist on the number of rounds of treatment needed to reach a goal of <5% prevalence in children. We determined the prevalence of trachoma and infection with Chlamydia trachomatis in communities after 3–7 years of annual mass treatment in Tanzania.

Methods. Seventy-one communities with trachoma and annual azithromycin coverage data were enrolled. A cross-sectional survey of ≥ 100 randomly selected children aged <5 years in each community was performed. Children were examined for clinical trachoma, and swab samples were taken for determination of ocular C. trachomatis infection.

Results. After 3 years of mass treatment, the prevalence of trachoma decreased in a linear fashion with number of years of mass treatment, whereas decreased prevalences of C. trachomatis infection were related to the extent of the previous year’s azithromycin coverage. Our model suggests that, for communities with baseline trachoma prevalence of 50% and annual treatment coverage of 75%, >7 years of annual mass treatment will be needed to reach a prevalence of trachoma of <5%.

Conclusions. Country programs in trachoma-endemic regions must realistically expect that several years of annual mass treatment may be necessary to eliminate trachoma.
The perception exists that 1 round may be enough, based on data from a single village in a hypoendemic area, where a single round of mass treatment with azithromycin at 98% coverage (plus provision of tetracycline ointment to all patients with clinical cases of infection at 6, 12, and 18 months) reduced the infection rate to <1% for up to 60 months and reduced the prevalence of trachoma in children aged 1–9 years from >20% to <2.6% 5 years later [2, 10]. The perception of the adequacy of a single round of mass treatment is unfortunate, as it has raised expectations for the short length of commitment needed by drug donors, program funders, and the countries themselves. Thus, data from many communities in programs where starting prevalences are known and coverage data are available are urgently needed to address the question of how many rounds may be needed to decrease the prevalence of trachoma to <5%.

We conducted a cross-sectional study of sentinel children, aged 6 months to 5 years, living in 71 communities that have been the recipient of between 3 and 7 years of mass treatment with azithromycin under a National Trachoma Control Program in Tanzania. The purpose was to determine the effect of the number of years of mass treatment on the prevalence of *C. trachomatis* infection and clinical trachoma, and to model the trajectory of decline and number of years needed to reach 5% prevalence in these communities.

**METHODS**

**Trachoma Control Program**

The Tanzania National Trachoma Control Program started with azithromycin in 1999, in 6 trachoma hyperendemic districts, and in 6 communities in each district. The program was scaled up during the ensuing years, adding districts and communities within districts, to 54 districts at present, with all communities in the districts slated for annual antibiotic distribution. The number of years of mass treatment in the communities prior to our survey was determined precisely from antibiotic distribution records showing the date that mass treatment began in a community and the date for each subsequent year. Logistic and funding considerations dictated the process of scale-up, particularly in terms of adding districts. The program also had a component of education on keeping children’s faces clean and improving environmental sanitation that was national in scope, with training for village health workers.

Baseline surveys for trachoma were carried out by the program in sentinel communities, which were randomly selected in the district prior to the start of the intervention. The surveys were carried out using trained trachoma graders who determined the presence of follicular trachoma and intense trachoma in a random sample of children aged 1–5 years in each community. Infection was not assessed at baseline.

**Study Communities**

To be eligible for this study, a community had to have a baseline survey prior to the intervention conducted by the Kongwa Trachoma Project Team, have received ≥3 rounds of mass treatment, have data on estimated coverage of the community with azithromycin for >50% of the annual rounds of mass treatment, and consent to participate. Three rounds of mass treatment were chosen as a minimum, because WHO guidelines suggest that 3 rounds of mass treatment must be provided and then the communities resurveyed for ongoing need. All communities approached for the study agreed to participate.

We stratified all eligible communities according to number of rounds of mass treatment. In the stratum of 3 rounds, 6 of the 12 communities were not eligible, because they had inadequate baseline surveys and likely had no trachoma [11]. In the stratum of 4 rounds, all communities came from 1 district that was the 1 new district enrolled that year, a district known to have a lower prevalence of trachoma than did the other districts at baseline. In all other strata, communities from multiple districts were included. In all, 71 communities were selected and studied.

**Follow-up Surveys**

Starting in 2007 in each village, our census team created a list of all households in the village. We randomly selected sufficient households in each village to yield ≥100 households with children in the age range 6 months to 5 years. A complete census of all selected households was performed, and if there was >1 child within the age range, 1 was randomly selected to avoid clustering of data by household. At the time of the census, the interviewer asked whether the household had a latrine and verified an affirmative answer visually.

The children were examined by 1 experienced grader, using 2.5 loupe, who graded the conjunctiva of both eyes for the presence of trachoma using the WHO Simplified grading scheme [12]; follicular trachoma is defined as the presence of 5 or more follicles of size >0.5 mm. Intense trachoma is defined as the presence of inflammation severe enough to obscure >50% of the deep tarsal vessels. Trachoma is defined as the presence of follicular trachoma and/or intense trachoma. Photographs of the left upper eyelid were taken for every child, and a sample of 50 photographs regraded at 3 time points to ensure the absence of drift in grading over time. At the time of the exam, the child’s face was also assessed for cleanliness, using the presence or absence of 3 signs: nasal discharge, ocular crusting, and/or flies on the face when observed for 3 seconds [13]. The absence of all 3 signs was considered to signify a clean face.

Swab samples were taken of the upper conjunctiva of the left eye, using standard procedures to avoid field contamination, and stored dry at −20°C until shipped to the International Chlamydia Laboratory at Johns Hopkins. A total of 213 field
control samples were taken randomly throughout the study, and none had positive results. At the laboratory, a C. trachomatis qualitative polymerase chain reaction assay (Amplicor; Roche Molecular Systems) was performed, according to the manufacturer’s directions, to identify samples with positive results. Results were considered negative if the optical density was $<0.2$ A$_{450}$ and positive if $\geq 0.8$ A$_{450}$.

All procedures and protocols were reviewed and approved by the Johns Hopkins institutional review board and the National Institute for Medical Research of Tanzania. Parents provided informed, written consent for participation of their children.

**Treatment Coverage**

Azithromycin was provided as a single dose, 20 mg/kg up to 1 g. Children aged $<1$ year were treated with topical tetracycline, twice per day for 4–6 weeks. Women who reported being pregnant were also treated with topical tetracycline; no pregnancy testing was performed.

Data on annual mass treatment coverage of communities with azithromycin was obtained from 1999 through 2004 from the International Trachoma Initiative office in Tanzania. The data were recorded as the number of persons treated and the estimated population in the community. In some cases, the estimated population was the population resident in the community at the time of mass treatment and did not include those who were temporarily absent. In 2005, the mass treatment program devolved to the communities, and data on coverage were collected from each community. In this case, the community health workers kept a treatment book in which information about individuals who were treated was recorded. Antibiotic treatment was observed by health workers in each community. They were given doses of azithromycin at the outset and 2 weeks to complete mass treatment before the remaining antibiotic was returned to the district headquarters. At the time of this study, there was no other source of azithromycin in the communities. No payment was provided to health care workers for this activity, and supervision was provided by the districts. However, with these caveats, the national program did provide sufficient doses on the basis of estimated need to undertake mass treatment in each community, which was as recorded.

The Tanzania program suspended mass drug administration in 2006 in order to conduct impact surveys. We started our surveys before resumption of mass drug administration, so communities would have not been treated during a period of 1–2 years prior to our surveys.

**Data Analyses**

The rate of coverage with azithromycin was defined as the number of persons treated divided by the number of persons in the community, according to community records. As indices of coverage rate we examined percentage of annual coverage $>80\%$, $>75\%$, average coverage of all mass treatments, and last treatment coverage. Associations with each index were explored, and the most reasonable fit, in terms of significance level, was the model using average treatment coverage.

An ordinary linear regression model was used to estimate trachoma prevalence at follow-up as a function of baseline prevalence, number of years of mass treatment, and a descriptor of treatment coverage. Smoothed scatter plots (LOWESS function in S) were used to examine the assumption of a linear relationship between trachoma and possible independent predictors; the plots indicated that linear models were appropriate. For a model of prevalence of C. trachomatis infection, a linear model was attempted, but after a number of transformations were attempted, a linear model was never a good fit because of the number of communities with zero cases of infection. Instead, we used a binary logistic regression model to predict the odds of zero cases of infection. In addition, the best index of coverage for infection was coverage at last treatment round.

**RESULTS**

The average prevalence of trachoma in children aged $\leq 5$ years prior to any mass treatment in these communities was 51% (range, 19%–83%), and 1.6% of trachoma was intense trachoma alone (Table 1). Reported coverage of the communities with annual mass treatment varied widely (Table 1). Although achieving 80% coverage was the program target, the overall mean was 78% and estimates of the percentage of annual coverage that exceeded even 75% varied from 41% to 75%.

At follow-up, the prevalence of trachoma varied from 20% in communities with 3 prior rounds of mass treatment to 9% in communities with 7 prior rounds of annual mass treatment (Table 2). The prevalence of infection averaged 8% in those communities with 3 rounds of mass treatment, compared with 6% in those with 7 rounds of annual mass treatment. The decline in the prevalence of infection was not linear and seemed to stabilize after 5 rounds. The average proportion of children with clean faces was lowest in the communities with 3 rounds of treatment and highest in the communities with 7 rounds of treatment. The communities with 3 rounds of treatment also had the lowest proportion of households with latrines, with no clear trend by rounds of treatment.

Because baseline rates of trachoma are a predictor of subsequent rates, we constructed a model predicting trachoma prevalences that controlled for preprogram rates. A multivariate linear model of trachoma prevalence, adjusted for baseline trachoma rate and the average treatment coverage, suggested that each additional round of mass treatment beyond 3 years decreased the prevalence by an absolute value of 1.6% (Table 3). According to our model, the most dramatic decrease in the prevalence of trachoma occurred during the first 3 rounds of treatment, as shown by the intercept, from a 50% prevalence before mass treatment to an estimated...
15.3% prevalence at the end of 3 rounds. The model suggests that, with average coverage of 75% and a starting trachoma prevalence of 50%, it will take >7 rounds and likely closer to 10 rounds of annual mass treatment to reach a prevalence of trachoma <5%. There was no additional benefit seen when adding to the model variables on clean faces or latrines.

Creating an appropriate model for infection was not straightforward, because of the number of communities with no cases of infection and the absence of infection data at baseline to use for adjustment. In a logistic model predicting absence of infection, only baseline level of trachoma was a significant predictor. No measure of coverage or number of rounds of mass treatment was statistically significantly related to absence of infection. The best metric for coverage was using the estimate of coverage on the last round of mass treatment; an increase of 10% in coverage with the last round was associated with a 41% increase in the odds of zero cases of infection in a community but was not statistically significant (P = .22) (Table 4). The model suggested that at a baseline trachoma prevalence of 50%, after R3 rounds of mass treatment, and the last round with coverage of 75%, the probability of having zero infection in a community was only 0.10 (95% confidence interval, 0.04–0.24).

DISCUSSION

The results of this study suggest that, in a realistic country program setting, it will take longer than 7 years and may take as long as 10 years of annual mass treatment in communities where baseline prevalence is >50% and treatment was stopped for 1 year to reduce the prevalence of trachoma to 5%. Findings from studies evaluating 1 or more rounds of mass treatment in hyperendemic settings support this finding. In a hyperendemic community in a high-prevalence district in Tanzania, a single round of mass treatment with overall coverage of 89% reduced infection rates but did not eliminate infection, and there was evidence for reemergence at 12 months [8]. After 2 rounds of mass treatment, a survey at 5 years revealed trachoma prevalences that were still >30% [14]. In hyperendemic communities in Ethiopia, after 4 rounds of biannual mass treatment, with high coverage, the prevalence of infection decreased to 2.6%, but once treatment stopped, the prevalence of infection returned to 25% by 18 months [9]. In data from Mali, the national program had seemingly reduced the prevalence of trachoma to <5% from 17% in the highest prevalence area after 3 rounds of mass treatment, but 3 years later trachoma had started to reemerge [6]. Our data clearly suggest that baseline prevalence of trachoma is an important predictor of current trachoma and infection rates in a community. For every 10% increase in the baseline prevalence of trachoma, the ending prevalence of trachoma after 3 years was higher by an absolute value of 2%, independent of number of rounds of treatment or coverage. The finding that subsequent infection or trachoma is predicted by previous trachoma/infection status has been reported by us and others previously [9, 15, 16] and remains a critical observation: The

Table 1. Prevalence of Trachoma in Preschool-Age Children in 71 Communities Prior to Start of Mass Treatment With Azithromycin, and Estimates of Annual Azithromycin Treatment Coverage, by Number of Years of Mass Treatment Rounds

<table>
<thead>
<tr>
<th>No. of years of annual mass treatment</th>
<th>No. of villages</th>
<th>Baseline prevalence of active trachoma, mean % (range)</th>
<th>Estimates of coverage, mean % (range)</th>
<th>Proportion of mass treatments with &gt;75% coverage, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>6</td>
<td>59.9 (48.9–77.7)</td>
<td>71.3 (67.0–86.3)</td>
<td>41.7</td>
</tr>
<tr>
<td>4</td>
<td>17</td>
<td>40.7 (18.9–74.0)</td>
<td>79.4 (56.1–97.6)</td>
<td>75.0</td>
</tr>
<tr>
<td>5</td>
<td>15</td>
<td>49.6 (24.9–74.6)</td>
<td>81.1 (58.9–94.0)</td>
<td>71.7</td>
</tr>
<tr>
<td>6</td>
<td>16</td>
<td>58.9 (34.1–83.3)</td>
<td>76.9 (59.0–84.7)</td>
<td>62.8</td>
</tr>
<tr>
<td>7</td>
<td>17</td>
<td>53.0 (23.2–80.4)</td>
<td>78.2 (65.1–85.4)</td>
<td>67.2</td>
</tr>
<tr>
<td>Total</td>
<td>71</td>
<td>51.2 (18.9–83.3)</td>
<td>78.2 (66.1–97.6)</td>
<td>66.9</td>
</tr>
</tbody>
</table>

Table 2. Average Prevalence of Trachoma and Chlamydia trachomatis Infection, and Measures of Clean Faces and Latrines in Communities at Follow-up, Stratified by Number of Rounds of Mass Treatment

<table>
<thead>
<tr>
<th>No. of previous rounds of annual mass treatment</th>
<th>Prevalence of clean faces, mean % (95% CI)</th>
<th>Prevalence of households with latrines, mean % (95% CI)</th>
<th>Prevalence of trachoma, mean % (95% CI)</th>
<th>Prevalence of infection, mean % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>37.5 (24.6–50.3)</td>
<td>9.7 (0.3–19.0)</td>
<td>20.3 (7.9–32.8)</td>
<td>7.8 (0.8–14.8)</td>
</tr>
<tr>
<td>4</td>
<td>50.6 (45.2–55.9)</td>
<td>59.1 (43.8–74.4)</td>
<td>9.3 (5.1–13.5)</td>
<td>2.8 (1.3–4.3)</td>
</tr>
<tr>
<td>5</td>
<td>45.1 (40.2–50.0)</td>
<td>69.6 (56.7–82.5)</td>
<td>12.8 (8.2–17.5)</td>
<td>6.4 (2.2–10.6)</td>
</tr>
<tr>
<td>6</td>
<td>46.1 (40.6–51.6)</td>
<td>62.9 (53.4–72.5)</td>
<td>12.6 (8.9–16.2)</td>
<td>5.8 (2.8–8.7)</td>
</tr>
<tr>
<td>7</td>
<td>51.6 (45.9–57.6)</td>
<td>67.9 (59.0–76.7)</td>
<td>9.1 (6.4–11.7)</td>
<td>6.1 (4.1–8.2)</td>
</tr>
</tbody>
</table>

NOTE. Trachoma refers to active disease (follicular trachoma or intense trachoma). CI, confidence interval.
prevalence of trachoma at the outset of a program will dictate the prevalence after 3 or more rounds of mass treatment, so program managers should not expect the same results for the same coverage in communities where the starting prevalence is 20% as in those where the starting prevalence is 50%. These data suggest that the WHO guideline to resurvey after 3 rounds of annual mass treatment might be refined on the basis of starting prevalence and whether there was any interruption in annual mass treatment, as there is no value in using resources for surveys to determine whether 5% prevalence has been achieved after 3 years of mass treatment in hyperendemic areas.

Although the number of rounds of mass treatment was significantly related to lower prevalence of trachoma, the coverage rate was not related. We showed data for average treatment coverage, but even using the percentage of coverage rates 75% and >80%, the coverage indicator was not significantly related to trachoma prevalence. The lack of association may in part be attributed to the imprecision of the program data on coverage. The trachoma control program in Tanzania was under pressure to achieve high coverage rates, which may have affected reporting by the districts. Thus, coverage may be overestimated in this study. Also, in some cases individuals who missed mass treatment in one village may have traveled to another nearby village for treatment, thus skewing the data for both villages. Finally, the effect in all villages of a “national treatment holiday” may have muted the effect of coverage. Because of these uncertainties, our data should not be interpreted to mean that coverage levels were not important.

These findings should also be interpreted against the backdrop of the Tanzania National Trachoma Control Program’s attempts to implement a hygiene improvement campaign. We did not collect data on the implementation of their program to improve face washing and sanitation, but some of the decrease (or lack thereof) may be due to variations in the success of this program component. At follow-up, we did not observe a linear increase in proportion of households with latrines or proportion of children whose faces were clean by stratum.

Our model for infection also supported the finding that multiple rounds of mass treatment, beyond 3, would be needed to increase the likelihood that infection would be eliminated. However, after 3 rounds of mass treatment we did not find any metric related to coverage, or number of rounds of mass treatment, to be significantly related to infection. The best metric, in terms of approaching the closest to significance, was percent coverage at the last round of mass treatment. In longitudinal studies, infection rates decrease dramatically after treatment and, even if there is reemergence, take time to return [8, 9, 17]. Thus, it makes sense that the infection rates that we observed cross-sectionally may be sensitive to the last round of mass treatment; it is possible that a particularly high coverage rate in the immediate past year, or low coverage, would have negated somewhat the effects of previous rounds in the community. In addition, the imprecision of adjustment by baseline trachoma prevalence, rather than infection prevalence, may have affected our ability to detect differences. Ideally, infection data at baseline would have informed these analyses, but they were not collected by the program. Although there is reasonable correlation between cases of infection and the presence of trachoma, and our infection model supports an association, baseline infection data would have likely enabled better predictions. In the stratum of 4 rounds of mass treatment, for example, where baseline trachoma prevalences were lowest, almost one-quarter of communities had no cases of infection at follow-up. If the communities in this district had already had low infection rates at the outset, this high rate of clearance would be more understandable. As it is, with only the ability to adjust for baseline trachoma prevalence, the relationship of number of rounds of mass treatment to prevalence of infection is likely somewhat blurred. The effect of the treatment holiday in potentially allowing reemergence is also likely to have affected the infection rate that we observed and to have blunted the effect of multiple rounds of mass treatment. Nevertheless, the absence of a clear decline after multiple rounds

Table 3. Multivariable Linear Model Predicting Trachoma According to Number of Years (Past 3) of Annual Mass Treatment With Azithromycin

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>β (95% CI), %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept*</td>
<td>15.2 (11.8–18.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Baseline trachoma prevalence (per 10% increase)</td>
<td>2.2 (1.1–3.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No. of rounds of mass treatment (per round)</td>
<td>−1.6 (−2.9 to −0.02)</td>
<td>.02</td>
</tr>
<tr>
<td>Average treatment coverage (per 10% increase)</td>
<td>−0.8 (−2.8 to 1.1)</td>
<td>.41</td>
</tr>
</tbody>
</table>

NOTE. CI, confidence interval.

* Centered at 50% prevalence at baseline, 3 rounds of treatment, and average treatment coverage with azithromycin of 75%.

Table 4. Multivariable Logistic Model Predicting Odds of Zero Cases of Infection With Chlamydia trachomatis in Communities

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>β (95% CI), %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept*</td>
<td>−2.13 (−3.10 to −1.16)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Baseline trachoma prevalence (per 10% increase)</td>
<td>−0.72 (−1.27 to −0.19)</td>
<td>.008</td>
</tr>
<tr>
<td>Last treatment coverage (per 10% increase)</td>
<td>0.35 (−0.21 to 0.90)</td>
<td>.22</td>
</tr>
</tbody>
</table>

NOTE. CI, confidence interval.

* Centered at 50% baseline prevalence of trachoma and last treatment coverage with azithromycin of 75%. The probability of no infection after at least 3 rounds of treatment in a community with 50% baseline prevalence of active trachoma and last treatment coverage of 75% is equal to $e^{-2.13/(1 + e^{-2.13})} = 0.10$. 13.
of mass treatment is worrisome and may be an indicator that higher coverage than the program is currently able to achieve may be needed to have an effect.

The sample of 71 communities, with data from up to 7 years of mass treatment, is a strength of our study. Other studies have used single villages or much shorter periods of time to report on the disappearance or reemergence of trachoma and to make projections [4, 8, 10, 18, 19]. For example, a recent paper suggesting that 2 rounds of treatment would be enough for trachoma control in Tanzania was based on a sample of 15 neighborhoods all in the same village [20]. Our data, based on random samples from 71 communities scattered all over Tanzania, suggest that a far greater commitment of time will be needed in a programmatic context to achieve trachoma control. Because trachoma control program managers only have clinical trachoma rates to guide program success, these data are more relevant than the data on \textit{Chlamydia trachomatis} infection, at least until a field-usable, rapid test is available.

In summary, data from this cross-sectional survey of children in 71 communities where the average starting prevalence was >50% and a “treatment holiday” occurred suggest that, after 3 rounds of mass treatment, no communities had a prevalence that would warrant stopping mass treatment under program conditions. With each additional round of treatment, the prevalence of trachoma declined, but >7 rounds (we estimated 10 rounds of mass treatment) will be needed to reach 5% rates of prevalence. This work was funded by a grant from the National Eye Institute (EY16429) and the Division of Intramural Research, National Institute of Allergy and Infectious Diseases. S. K. W. is a Research to Prevent Blindness Senior Scientific Investigator.

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References