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# Short Report: Adverse Events after Mass Azithromycin Treatments for Trachoma in Ethiopia

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*Abstract.* During a cluster-randomized clinical trial for trachoma in Ethiopia, two rounds of adverse event surveillance were performed in a random sample of communities after community-wide mass azithromycin treatment. The prevalence of any reported adverse event ranged from 4.9% to 7.0% in children 1–9 years of age and from 17.0% to 18.7% in persons ≥ 10 years of age. Adverse events appeared to cluster by household and perhaps by village. Mass azithromycin distributions were well tolerated in this setting.

The World Health Organization (WHO) recommends mass azithromycin distributions for the treatment of trachoma in areas with endemic disease.[1] Azithromycin is given as a single directly observed dose, 1 g for adults and 20 mg/kg for children. Mass distribution of oral azithromycin is effective in reducing the burden of ocular *Chlamydia* in a community.[2–4] Mass azithromycin treatments are also effective for several systemic infections, and may even reduce childhood mortality.[5–7] Furthermore, azithromycin is thought to be well tolerated in most persons.[8] However, previous studies have rarely assessed adverse events in multiple communities in a population-based fashion.[6] We recently performed a cluster-randomized clinical trial in Ethiopia to compare the efficacy of different trachoma treatment strategies. The current report describes population-based adverse event surveillance performed after two separate rounds of mass azithromycin treatment of trachoma.

We conducted a cluster-randomized clinical trial for trachoma in Goncha Siso Enese *Woreda* (District), Amhara Region, Ethiopia, during May 2006–November 2009 (clinicaltrials.gov NCT00322972). The study area was located in a homogenous rural setting that had hyperendemic trachoma. In the trial, 72 *subkebeles* (geographic administrative units) were randomly allocated to one of six treatment arms: 1) annual mass azithromycin for four years; 2) biannual (every six months) mass azithromycin for four years; 3) quarterly (every three months) mass azithromycin for children 1–9 years of age for one year followed by mass treatment of the entire community at the 12-month time point; 4) a delayed single-mass azithromycin treatment at the 12-month time point (control arm); 5) a single-mass azithromycin treatment at baseline; and 6) a single-mass azithromycin treatment at baseline plus a latrine promotion intervention.[9] In addition, mass azithromycin was distributed to the latter two treatment arms at 24 months as part of the collaborative trachoma program.

For all antibiotic distributions in the current study, azithromycin was offered to all persons ≥ 1 year of age; administration was directly observed and noted in a treatment log book. Each *subkebele* consisted of approximately 3–5 administrative subunits known as *state teams*, which are referred to as villages in this report. Although all villages in a *subkebele* were treated identically, only one randomly selected sentinel village per subkebele was monitored during the study. Ethical approval was obtained from the Committee for Human Research of the University of California, San Francisco; the Ethiopian Science and Technology Commission; and Emory University. Informed consent in Amharic was obtained from all study participants.

We performed household surveys in July 2007 (12 months after the baseline study visit) and June 2008 (24 months after baseline) to monitor for potential adverse events after mass oral azithromycin. The 12-month survey was performed one month after completion of the mass azithromycin distribution, and the 24-month survey was performed immediately after the completion of mass treatment. Each mass azithromycin distribution lasted 3–4 weeks, and each survey was conducted over 2–3 days. At the 12-month time point, we selected a simple random sample of 12 *subkebeles* from the 4 treatment groups that had received treatment at 12 months (annually-treated, biannually-treated, quarterly treatment of children, and delayed treatment). At the 24-month time point, we selected a stratified random sample of 12 *subkebeles* from the 4 treatment groups that had received treatment at 24 months, with 3 *subkebeles* from each treatment arm (annually-treated, biannually-treated, single treatment only, single treatment with latrine intervention). We conducted the surveys in a single sentinel village from each subkebele. At each visit, we attempted to survey 10 randomly chosen households per village. Heads of households were asked whether any member of the household had shown development of an adverse event, defined as any new illness or symptom in the time since mass drug administration. Heads of households were encouraged to ask other family members about adverse events, especially the primary caretaker of children.

We estimated the proportion of persons in the village reporting an adverse event separately for children 1–9 years of age and for persons ≥ 10 years of age. We report adverse events separately for persons who received azithromycin versus those who did not. Although those who did not receive azithromycin may constitute a biased group, this group provides a comparison group to assess the adverse effect profile of azithromycin.[10] We computed bias-corrected bootstrapped 95% confidence intervals (CIs) with re-sampling of villages to account for the clustered design of the survey (10,000 repetitions). If no adverse events were recorded, we calculated exact binomial confidence intervals, ignoring clustering. We assessed for risk factors for experiencing an adverse event using multivariate mixed effects logistic regression models with household nested in village as random effects, and the

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TABLE 1
Adverse events reported by treated community members after a mass azithromycin distribution, Ethiopia*

| Adverse event | 12-month survey, % (95% CI) | | 24-month survey, % (95% CI) | |
|---|---|---|---|---|
| | 1–9 years of age, n = 142 | ≥ 10 years of age, n = 267 | 1–9 years of age, n = 142 | ≥ 10 years of age, n = 312 |
| Any | 7.0 (1.9–12.5) | 18.7 (10.8–29.8) | 4.9 (2.2–8.0) | 17.0 (10.0–24.8) |
| Abdominal pain | 2.8 (0.8–4.9) | 6.0 (2.1–12.2) | 0.7 (0–2.9) | 6.7 (3.4–10.9) |
| Vomiting | 2.1 (0.6–4.2) | 4.5 (2.2–7.1) | 1.4 (0–3.4) | 1.6 (0.3–3.9) |
| Nausea | 0.7 (0–2.5) | 4.1 (2.4–5.9) | 2.1 (0.7–4.1) | 2.9 (1.0–5.2) |
| Diarrhea | 0.7 (0–2.6) | 2.6 (0.3–5.8) | 0.7 (0–3.0) | 2.2 (0.7–4.1) |
| Dyspepsia | 0.7 (0–2.5) | 0.7 (0–2.0) | 0.7 (0–2.6) | 0 (0–1.2) |
| Constipation | 0 (0–2.6) | 0.7 (0–2.0) | 0 (0–2.6) | 1.3 (0.3–2.4) |
| Hemorrhoid | 0 (0–2.6) | 0 (0–1.4) | 0 (0–2.6) | 0.3 (0–1.1) |
| Rash | 0 (0–2.6) | 0 (0–1.4) | 0 (0–2.6) | 0.3 (0–1.2) |
| Other | 0 (0–2.6) | 0.4 (0–1.4) | 0 (0–2.6) | 5.1 (2.2–8.5) |

*CI = confidence interval. Because persons may have more than one adverse event, the sum of individual adverse events does not equal the percentage with any adverse event.

following explanatory variables: age, sex, number of persons in the household, azithromycin treatment of the person at the most recent treatment, and number of previous mass azithromycin distributions to the community. Clustering of adverse events was estimated in the total population by calculating the intraclass correlation coefficient (ICC) on the logit scale from the mixed effects logistic regression model.[11] The ICC was calculated separately for responses in the same village (across different households), and for responses within the same household (and within the same village).

We assessed adverse events in 118 households from 12 villages at the 12-month survey and in 119 households from 12 villages at the 24-month survey. Approximately 70% of eligible persons in the surveyed households received their allocated dose of azithromycin at each time point (409 of 589 during the 12-month time point, and 454 of 656 during the 24-month time point). At least one adverse event was documented in 56 households of 11 villages at the 12-month survey and in 48 households of 12 villages at the 24-month survey. At the 12-month survey, adverse events were recorded in 10 (7.0%) of 142 treated children 1–9 years of age and in 50 (18.7%) of 267 treated persons ≥ 10 years of age; at the 24-month survey, an adverse event was noted in 7 (4.9%) of 142 treated children 1–9 years of age and in 53 (17.0%) of 312 treated persons ≥ 10 years of age (Table 1). Adverse events were also reported by persons who did not receive recent azithromycin treatment, although at lower frequencies (Table 2). The presence of an adverse event was associated with age and recent azithromycin treatment in both surveys, but not with sex, number of persons in the household, or number of previous community mass azithromycin distributions (Table 3). There was evidence of clustering of adverse events within villages at the 12-month survey (ICC = 0.23, 95% CI = 0.03–0.42) but not at the 24-month survey (ICC = 0.07, 95% CI = –0.04 to 0.18). Clustering of adverse events was observed within households of the same village at the 12-month survey (ICC = 0.23, 95% CI = 0.01–0.45) and at the 24-month survey (ICC = 0.20, 95% CI = 0.01–0.38).

The low prevalence and relatively mild nature of adverse events observed in this study is similar to that of western populations given a single high dose of azithromycin (0–17%).[12–14] Results of this study are also consistent with those of several reports of mass azithromycin treatment of trachoma, which have reported adverse events in 0–9% of treated persons.[15–18] Other trachoma studies have reported a higher occurrence of adverse events, although these reports are not directly comparable to this study because of differences in reporting adverse events, and because interviewers used a method in which they asked about specific conditions.[6,19] In our study, we asked an open-ended question, which may have elicited fewer positive responses compared with other methods.[20]

Those reports that have described adverse events after azithromycin treatment for trachoma were conducted in settings in which the entire community did not receive azithromycin[15–19,21] or in which only 1–2 communities were monitored,[17,19] or in which only children[6,16,17,21] or adults[15] were monitored. The current study design is noteworthy for several reasons. First, we offered treatment to all members of the community ≥ 1 year of age, as recommended by the WHO, and we monitored adverse events among all ages. The results are therefore

TABLE 2
Adverse events reported by untreated community members after a mass azithromycin distribution, Ethioipia*

| Adverse event | 12-month survey, % (95% CI) | | 24-month survey, % (95% CI) | |
|---|---|---|---|---|
| | 1–9 years of age, n = 30 | ≥ 10 years of age, n = 150 | 1–9 years of age, n = 41 | ≥ 10 years of age, n = 161 |
| Any | 6.7 (0–14.0) | 12.0 (3.1–24.2) | 0 (0–8.6) | 5.6 (2.4–9.8) |
| Abdominal pain | 3.3 (0–7.0) | 6.0 (0–15.0) | 0 (0–8.6) | 1.2 (0–4.5) |
| Vomiting | 3.3 (0–7.0) | 0.7 (0–2.6) | 0 (0–8.6) | 1.9 (0–5.7) |
| Nausea | 0 (0–11.6) | 2.0 (0–5.4) | 0 (0–8.6) | 1.2 (0–3.6) |
| Diarrhea | 0 (0–11.6) | 0 (0–2.4) | 0 (0–8.6) | 0.6 (0–2.5) |
| Dyspepsia | 0 (0–11.6) | 0.7 (0–2.0) | 0 (0–8.6) | 0 (0–2.3) |
| Constipation | 0 (0–11.6) | 0.7 (0–2.0) | 0 (0–8.6) | 0 (0–2.3) |
| Hemorrhoid | 0 (0–11.6) | 2.0 (0.5–3.9) | 0 (0–8.6) | 0 (0–2.3) |
| Rash | 0 (0–11.6) | 0 (0–2.4) | 0 (0–8.6) | 0 (0–2.3) |
| Other | 0 (0–11.6) | 1.3 (0–3.6) | 0 (0–8.6) | 1.9 (0–3.7) |

*CI = confidence interval. Because persons may have more than one adverse event, the sum of individual adverse events does not equal the percentage with any adverse event.

TABLE 3
Factors associated with the presence of an adverse event in an area recently treated with mass oral azithromycin for trachoma, Ethiopia*

| Variable | OR (95% CI) | |
|---|---|---|
| | 12-month survey | 24-month survey |
| Age, per decade | 1.33 (1.15–1.53) | 1.52 (1.28–1.80) |
| Female sex | 1.22 (0.71–2.10) | 1.59 (0.88–2.88) |
| Persons per household | 0.91 (0.80–1.04) | 1.11 (0.97–1.27) |
| Number of previous mass treatments | 0.94 (0.55–1.59) | 1.03 (0.66–1.61) |
| Recent azithromycin treatment | 2.77 (1.16–6.63) | 6.83 (2.63–17.76) |

*Odds ratio (OR) and 95% confidence intervals (CIs) are from multivariate mixed effects logistic regression with the presence of any adverse event as the response variable and household nested in village as random effects.

generalizable to trachoma programs that follow WHO guidelines. Second, we monitored 12 communities in each round of adverse event surveillance, which may provide a more accurate estimate by allowing for variation among and clustering within communities. Finally, the current study was conducted on a random sample of households from a random sample of communities and can therefore provide valid estimates of the underlying population.

We observed fewer adverse events in children compared with older persons, even though azithromycin coverage was higher among children. This result could have arisen if survey respondents ignored, underestimated, or did not recall adverse events in children. Nonetheless, the low prevalence of adverse events in children is encouraging because this age group is the most likely to be infected with ocular strains of *Chlamydia* and presumably would be the most likely to benefit from treatment.[9]

We found that adverse events clustered within households of the same village, and may cluster within villages. This result could be explained by reporting bias if some respondents or interviewers ignored all household complaints, but others overestimated illnesses within the household. Alternatively, this finding could be caused by common genetic or environmental factors among household members. Perhaps more likely, however, is a scenario in which complaints of an adverse event by one household or village member prompted others in the household or village to become more aware of their own symptoms.

Adverse events were slightly more common at the 12-month survey than at the 24-month survey. Adverse events monitoring was conducted 1 month after antibiotic distribution at the 12-month survey, but several days after the 24-month survey. The longer interval of time for the first survey provided a greater chance of experiencing an illness, which may have been correctly or incorrectly attributed to azithromycin. In addition, other external factors (e.g., an unrelated epidemic of gastroenteritis) could have occurred at either survey and caused differences between the two surveys unrelated to azithromycin treatment.

In conclusion, during two rounds of active, population-based surveillance of multiple communities, we found a low prevalence of adverse events after mass azithromycin distribution. The presence of an adverse event was more common in persons who had recently received azithromycin treatment and in older persons. Adverse events appeared to cluster by household, and perhaps by village. This study provides further evidence that community-wide azithromycin treatments for trachoma, as advocated by the WHO, are safe.

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