Latrine Promotion for Trachoma: Assessment of Mortality from a Cluster-Randomized Trial in Ethiopia

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Abstract. Trachoma control strategies, including latrine construction and antibiotic distribution, are directed at reducing ocular chlamydia, but may have additional benefits. In a cluster-randomized clinical trial, 24 subkebeles (administrative geographic units) in Ethiopia were offered a single mass azithromycin treatment, and half were randomized to receive an intensive latrine promotion. At a follow-up census 26 months after the baseline treatment, 320 persons had died. The mortality rate of children 1–5 years of age was 3.87 (95% confidence interval [CI] = 2.19–6.82) per 1,000 person-years in the latrine promotion arm, and 2.72 (95% CI = 1.37–5.42) per 1,000 person-years in the control arm. In a multi-level mixed effects logistic regression model controlling for age, there was no difference in mortality in persons randomized into the latrine or control arms (odds ratio = 1.18, 95% CI = 0.89–1.58). Latrine promotion provided no additional effect on mortality in the context of an azithromycin distribution program (clinicaltrials.gov, #NCT00322972).

INTRODUCTION

The World Health Organization recommends the SAFE strategy (eyelid surgery, mass antibiotics, facial hygiene promotion, and environmental improvement) for the control of trachoma, the world’s leading infectious cause of blindness.1 Although the SAFE strategy is directed at control of trachoma, there are reasons to suspect that each of the SAFE components may help reduce transmission of non-chlamydial infections. For example, trichiasis surgery may prevent bacterial superinfections of the cornea.2 Systemic azithromycin has efficacy against a broad spectrum of bacteria, as well as malaria.3,5 Facial hygiene and hand washing would be expected to reduce transmission of respiratory pathogens present in nasal secretions.6 Environmental improvements such as safe water and latrine provision are associated with a reduction in diarrhea morbidity, presumably from breaking the transmission cycle of the responsible organisms.7,8

If trachoma treatment strategies sufficiently reduce the burden of non-chlamydial infections, they might even reduce mortality caused by these infections. This is especially true for children in trachoma-endemic areas, who often die of infectious causes.9 We recently conducted a cluster-randomized trial in Ethiopia where half the communities were randomized to latrine promotion and all communities were offered a single oral dose of azithromycin. The main aim of the trial was to investigate the efficacy of latrine promotion for preventing the return of ocular chlamydia after mass azithromycin treatment.10 An additional pre-specified outcome of this trial was age-specific mortality. In this report, we assess the effect of a latrine promotion intervention on all-cause mortality.

METHODS

The trial was sponsored by the National Eye Institute and registered with clinicaltrials.gov (NCT00322972). 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. The study was conducted in accordance with the Declaration of Helsinki and overseen by a Data Safety and Monitoring Committee appointed by the National Institutes of Health-National Eye Institute. Informed consent in Amharic was obtained for all participants.

Study design. The study area comprised 72 contiguous subkebeles (Ethiopian administrative geographic units) from the Goncha Siso Enese woreda (district) in the Amhara Region of Ethiopia. Each subkebele consisted of approximately 5 state teams (administrative subunit), and each state team contained approximately 50 households and 275 persons. Each subkebele was randomized to one of six treatment arms (Figure 1).1,12 In the current report, we compare mortality in two of the treatment arms. In one treatment arm, 12 subkebeles were randomized to receive an intensive latrine intervention and single mass azithromycin treatment at baseline, and in the other arm, 12 subkebeles were randomized to receive only a single mass azithromycin treatment at baseline without a latrine intervention (control arm).13 In a separate report, we describe the association between azithromycin treatment and reduced childhood mortality in these 24 subkebeles.13 That study does not address the impact of latrine promotion on mortality, which is the subject of the current report. Subkebeles were randomized as a simple random sample, without replacement, blocking, or stratification. The randomization sequence was generated by one of the authors (KJR) with the RANDOM and SORT functions in Excel Version 2003 and concealed until assignment. Participant enrollment and treatment assignment was performed by one of the authors (BA). By design, subkebeles were not masked to the intervention. The prevalence of ocular chlamydial infection was monitored from 24 sentinel state teams randomly selected from each of the 24 subkebeles. Ocular chlamydia and trachoma outcomes from the sentinel state teams are reported elsewhere.10 We conducted baseline and follow-up census in all communities, which enabled assessment of mortality. We chose the subkebele as the randomization unit in part to reduce contamination between sentinel communities within each subkebele, and in part to increase the statistical power of analyses of mortality.

Census. A door-to-door census was conducted in May 2006 for each of the 24 subkebeles included in this study. The census
Assessed for Eligibility: 72 subkebeles

Enrolled: 72 subkebeles

Randomized: 72 subkebeles

Excluded: 0 subkebeles
Did not meet inclusion criteria: 0 subkebeles
Refused to participate: 0 subkebeles

Single Treatment Arm
12 subkebeles 60 state teams
18,682 persons

Single Treatment and Latrines Arm
12 subkebeles 58 state teams
16,370 persons

Annual Treatment Arm
12 subkebeles

Biannual Treatment Arm
12 subkebeles

Children-Treated Arm
12 subkebeles

Control Arm
12 subkebeles

Received allocated intervention
17,506 persons

Did not receive allocated intervention
0 subkebeles
1,176 persons

Lost to follow-up
0 subkebeles

Discontinued intervention
0 subkebeles

Received allocated intervention
14,189 persons

Did not receive allocated intervention
0 subkebeles
2,181 persons

Lost to follow-up
0 subkebeles

Discontinued intervention
0 subkebeles

Analyzed 24 months
12 subkebeles
38,685 person years

Excluded from analysis
0 subkebeles

Analyzed 24 months
12 subkebeles
33,928 person years

Excluded from analysis
0 subkebeles

Excluded from study by design

Figure 1. Trial profile.
was updated for new deaths and migration one month later, at the time of the baseline mass azithromycin distribution. A repeat door-to-door census was conducted approximately 26 months after the baseline treatment. If a person was present at baseline, but absent at the follow-up census, the reason for absence was determined. In the case that an absent person had died, an abbreviated verbal autopsy was obtained by asking household members to report the probable cause of death (respiratory disease, diarrhea, malaria, old age, accident, or unknown). Both censuses were performed by Ethiopian auxiliary health care workers masked to treatment assignment and antibiotic coverage, and unaware that mortality was an outcome of interest in the study.

Interventions. Mass azithromycin. A single mass azithromycin distribution was completed in all subkebeles approximately one month after the initial census. All persons ≥1 year of age were offered a single dose of directly observed oral azithromycin (1 g for adults and height-based dosing to approximate 20 mg/kg for children), except for self-reported pregnant women, children <1 year of age, and those known to be allergic to macrolide antibiotics, who were offered a six-week course of tetracycline ophthalmic ointment (twice a day). The Carter Center-Ethiopia and the Amhara Regional Health Bureau coordinated the mass treatments and had a goal of achieving a minimum of 80% antibiotic coverage. Because antibiotics were distributed before the subkebeles were randomized for the trial, all antibiotic distributors were masked to treatment allocation. Persons were considered covered by azithromycin treatment if they were >1 year of age, present at the initial census, and recorded as having received a dose of oral azithromycin in the treatment logbook.

Intensive latrine promotion. The latrine intervention had two components. First, auxiliary health workers and sanitation volunteers intensified an already existing pit latrine program by attempting to train each head of household in the community in latrine construction, and by conducting follow-up visits to encourage latrine construction. Second, iron-reinforced cement slabs were provided for each household in the community. Households were instructed how to build a latrine with a 3-meter deep pit with tapering sides and an opening of 1 × 1.5 meters, which was covered with stout eucalyptus logs, a bed of mud plaster, and a cement slab measuring 60 × 60 × 5 cm with a drop hole of 18 × 38 cm. Eucalyptus logs were used to build a superstructure, including a roof, walls, and door. Construction started six months after the baseline treatment, and during the next six months, auxiliary health workers made multiple visits to encourage latrine construction and use. At 12 months after baseline, health workers recorded the proportion of households that had built a latrine. No payments were made to the heads of household, and participation in the intensified latrine construction program was entirely voluntary.

Outcomes. The mortality rate was defined as deaths per 1,000 person-years at risk, and the population at risk was estimated as the mid-interval population (the baseline population minus half of those who had died or moved away). Specifically, we calculated mortality rate as 1,000 × D/(26/12 × (P − (½ × (D + M)))), where D represents deaths during the 26-month study period, P represents the baseline population, and M represents persons who permanently moved from the study area during the 26-month study period. The primary outcome of the study was age-specific all-cause mortality. Subkebele-specific latrine characteristics and ocular chlamydial infection were estimated from the 24 sentinel communities. Latrine coverage (defined as the presence of a latrine) and recent use (defined as presence of recent feces in the latrine) were estimated from surveys of 10 randomly selected households from each sentinel community at 12 and 24 months after baseline. The prevalence of ocular chlamydial infection was monitored in each sentinel community shortly before the baseline antibiotic treatment, as reported elsewhere. Ocular chlamydial infection was not an outcome of this study, but is reported to enable a comparison of the baseline health status of the two treatment arms.

Statistical analysis. For each treatment arm, we calculated the proportion of the total population ≥1 year of age who belonged to pre-specified age strata (1–5 years, 6–10 years, 11–20 years, and >20 years), the proportion who were female, and the proportion who received treatment with oral azithromycin. For the latrine intervention arm, we calculated the mean proportion of households with a latrine. Using data from the sentinel communities, we estimated the mean proportion of ocular chlamydial infection, latrine coverage, and recent use of a latrine for each treatment arm (reported elsewhere). All 95% confidence intervals (CIs) were adjusted for within-subkebele correlation.

We estimated the annual mortality rate in each treatment arm for 4 cohorts defined by age at baseline (1–5, 6–10, 11–20, and >20 years). We accounted for subkebele clustering by modeling mortality rates by using negative binomial regression, a generalization of Poisson regression that estimates an additional aggregation parameter to enable modeling of over-dispersion of count data. We assessed for differences in the mortality rate between the two treatment arms separately for each age group by using a negative binomial regression with mortality rate as the response variable and treatment arm as the explanatory variable. All negative binomial regression models were performed by using the Huber/White/sandwich estimate of variance.

We then assessed the association between latrine promotion and mortality by using a multi-level mixed-effects logistic regression model with death as the response variable, treatment arm and age group (1–5, 6–10, 11–20, and >20 years) as the fixed effects, and three levels of nested random effects: 1) households within 2) state teams within 3) subkebeles. In an additional analysis, we added individual azithromycin coverage and sex to the model. We chose to analyze a model that included azithromycin treatment because antibiotic coverage differed between the two treatment arms, and because a cluster-randomized trial from neighboring subkebeles found decreased mortality in those communities randomized to mass azithromycin. We explored the interaction terms azithromycin × age, azithromycin × treatment group, and treatment group × age, keeping only those interaction terms with a Wald \( P < 0.05 \). Goodness-of-fit for regression models was ensured by examining plots of residual versus fitted values. The causes of death were compared between the two treatment arms by using Fisher’s exact test. All statistical tests were performed using Stata 10.0 (Statcorp, College Station, TX).

By design, we did not analyze the group <1 year of age because they were not eligible to receive mass azithromycin treatments. In addition, much of the mortality in this age group would have occurred before the latrine construction. Sample size calculations were based on the main outcome of the trial, the prevalence of ocular chlamydial infection. Twelve subkebeles provided 80% power to detect a 0.2% absolute
reduction in the annual mortality rate, assuming a mortality rate of 5 per 1,000 person-years in the control group, 1,400 persons per subkebele, and a variance inflation factor for mortality of 2 from previous studies. 17

RESULTS

During the initial census, we recorded 16,370 persons ≥ 1 year of age in the latrine promotion arm and 18,682 persons ≥ 1 year of age in the control arm. Baseline demographic features and prevalence of ocular chlamydia were similar in the two treatment arms (Table 1). Each of the subkebeles was treated according to protocol, and none were lost to follow-up (Figure). Azithromycin coverage was lower in the latrine promotion arm (95% CI = 82.4–87.9%) than in the control arm (92.0%, 95% CI = 89.9–94.2%, Table 1). The baseline prevalence of ocular chlamydia among children < 1–9 years of age was similar in the two treatment groups (45.5%, 95% CI = 34.1–56.8% in the latrine group and 43.0%, 95% CI = 31.1–54.8% in the control group). 10

According to records from auxiliary health workers that included all subkebeles in the latrine promotion arm, a latrine was present at 79.3% (95% CI = 71.7–86.9%) of households in the latrine promotion arm after 12 months baseline. The survey conducted in sentinel communities showed that latrine presence and use was considerably higher in the latrine promotion arm compared with the control arm at 12 and 24 months (Table 2).

Twenty-six months after the baseline treatment, 320 persons ≥ 1 year of age at the time of the initial census had died. Mortality incidence rates for each treatment arm stratified by age are shown in Table 3. Differences in mortality rates between the two treatment groups were not statistically significant in any of the age groups by negative binomial regression (Table 3). Furthermore, no relationship between latrine promotion and mortality was detected using a multi-level mixed-effects logistic regression model clustered by subkebele, state team, and household adjusted for age group (odds ratio = 1.18, 95% CI = 0.89–1.58), or adjusted for age group, sex, azithromycin treatment, and the interaction between age group and azithromycin treatment (OR = 1.17, 95% CI = 0.88–1.57) (Table 4). In this last analysis, the interaction between age and azithromycin treatment was significant (Wald P = 0.03), warranting inclusion of this term in the model. The interaction between 1) treatment arm and age and 2) treatment arm and azithromycin treatment were not statistically significant, and not included in the model.

Verbal autopsies showed a cause of death in 250 cases, with mortality attributed to old age in 31.6%, accident in 22.0%, respiratory disease in 10.0%, diarrhea in 9.2%, malaria in 7.2%, and other causes in the remainder. No statistically significant differences in cause of death were seen between the two treatment groups (P = 0.52, by Fisher’s exact test).

DISCUSSION

In this cluster-randomized trial in which all participants were offered a single oral dose of azithromycin, we were unable to demonstrate a difference in age-specific all-cause mortality in communities randomized to intensive latrine promotion.

### Table 1
Baseline characteristics from a cluster-randomized clinical trial in Ethiopia comparing intensive latrine promotion with no latrine intervention *

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Latrine promotion</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>Proportion (95% CI)</td>
<td>No.</td>
</tr>
<tr>
<td>Total population ≥ 1 year of age</td>
<td>16,370</td>
<td>18,682</td>
</tr>
<tr>
<td>Female</td>
<td>8,253</td>
<td>9,278</td>
</tr>
<tr>
<td>Received oral azithromycin</td>
<td>13,943</td>
<td>17,190</td>
</tr>
<tr>
<td>Ages 1–5 years</td>
<td>2,578</td>
<td>2,929</td>
</tr>
<tr>
<td>Female</td>
<td>1,288</td>
<td>1,461</td>
</tr>
<tr>
<td>Received oral azithromycin</td>
<td>2,160</td>
<td>2,754</td>
</tr>
<tr>
<td>Ages 6–10 years</td>
<td>3,074</td>
<td>3,686</td>
</tr>
<tr>
<td>Female</td>
<td>1,589</td>
<td>1,794</td>
</tr>
<tr>
<td>Received oral azithromycin</td>
<td>2,798</td>
<td>3,521</td>
</tr>
<tr>
<td>Ages 11–20 years</td>
<td>4,111</td>
<td>4,577</td>
</tr>
<tr>
<td>Female</td>
<td>2,101</td>
<td>2,281</td>
</tr>
<tr>
<td>Received oral azithromycin</td>
<td>3,449</td>
<td>4,142</td>
</tr>
<tr>
<td>Ages &gt; 20 years</td>
<td>6,607</td>
<td>7,490</td>
</tr>
<tr>
<td>Female</td>
<td>3,275</td>
<td>3,742</td>
</tr>
<tr>
<td>Received oral azithromycin</td>
<td>5,536</td>
<td>6,773</td>
</tr>
</tbody>
</table>

* No. = number of persons; CI = confidence interval.

### Table 2
Latrine coverage and use in a cluster-randomized trial in rural Ethiopia comparing intensive latrine promotion with no latrine intervention *

<table>
<thead>
<tr>
<th>Time after baseline</th>
<th>Survey descriptor</th>
<th>No.</th>
<th>Proportion (95% CI)</th>
<th>No.</th>
<th>Proportion (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 months</td>
<td>Surveyed households</td>
<td>122</td>
<td>77.1% (66.9–87.4%)</td>
<td>120</td>
<td>29.2% (18.5–39.8%)</td>
</tr>
<tr>
<td></td>
<td>Latrine present</td>
<td>94</td>
<td>61.5% (46.4–76.6%)</td>
<td>35</td>
<td>15.8% (6.7–25.0%)</td>
</tr>
<tr>
<td></td>
<td>Latrine recently used</td>
<td>75</td>
<td>61.5% (46.4–76.6%)</td>
<td>19</td>
<td>15.8% (6.7–25.0%)</td>
</tr>
<tr>
<td>24 months</td>
<td>Surveyed households</td>
<td>120</td>
<td>80.8% (72.1–89.6%)</td>
<td>120</td>
<td>36% (15.7–44.3%)</td>
</tr>
<tr>
<td></td>
<td>Latrine present</td>
<td>97</td>
<td>61.7% (49.0–74.3%)</td>
<td>36</td>
<td>30.0% (10.8–39.2%)</td>
</tr>
<tr>
<td></td>
<td>Latrine recently used</td>
<td>74</td>
<td>61.7% (49.0–74.3%)</td>
<td>30</td>
<td>25.0% (10.8–39.2%)</td>
</tr>
</tbody>
</table>

* No. = number of households; CI = confidence interval.
† Survey of randomly selected households in randomly selected sentinel communities. Full survey results are reported elsewhere. 10
estimated mortality rates from a clinical trial in rural Ethiopia comparing intensive latrine promotion with no latrine intervention, stratified by age cohort at baseline.

<table>
<thead>
<tr>
<th>Age group, years</th>
<th>Latrine promotion</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>Mortality rate†</td>
<td>No.</td>
</tr>
<tr>
<td>1–5</td>
<td>22</td>
<td>17</td>
</tr>
<tr>
<td>6–10</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>11–20</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>&gt; 20</td>
<td>112</td>
<td>113</td>
</tr>
</tbody>
</table>

* No. = number of deaths.
† Mortality rate per 1,000 person-years (95% confidence interval) estimated from negative binomial regression to account for cluster randomization.
‡ Negative binomial regression with mortality rate as the response variable and treatment arm as the explanatory variable.

For unclear reasons, the proportion of persons treated with azithromycin was lower in the subkebeles randomized to the latrine promotion arm than in the control arm. Because azithromycin treatment occurred before randomization, antibiotic distributors were necessarily masked to the treatment allocation. We assume the differential levels of antibiotic coverage occurred by chance. Because of this imbalance between the two treatment arms, we chose to adjust for individual azithromycin treatment in one of the regression analyses, especially given the results from neighboring subkebeles that showed a reduction in childhood mortality in communities treated with mass azithromycin compared with communities not treated with azithromycin. In the model additionally adjusted for azithromycin treatment, we found that azithromycin treatment was significantly associated with reduced mortality among children 1–5 years of age. However, inclusion of azithromycin treatment in the model did not alter the interpretation of the relationship between latrine promotion and mortality.

Strengths of this trial include the cluster-randomized study design, high latrine coverage, and relatively high proportion of latrine use. There are also some limitations. The clinical trial was powered for trachoma outcomes and may have had insufficient power to detect an association between latrine promotion and mortality. Latrine construction did not start until six months after baseline. Because the two treatment arms were treated similarly for the first six months of the study, this may have resulted in a bias toward the null hypothesis of no association. We did not have the resources to actively document cases of diarrhea or anthropometric indices of children in the study, and were therefore unable to assess whether latrine use had an impact on deaths caused by diarrhea or malnutrition. We performed abbreviated verbal autopsies on deceased persons, which are prone to misclassification errors. However, in this environment, the verbal autopsy method was the only feasible way to estimate a cause of death.

In a cluster-randomized trachoma trial in which communities were randomized to intensive latrine promotion plus mass azithromycin versus mass azithromycin alone, we failed to find that latrine promotion reduced mortality. The azithromycin treatment itself may have resulted in reduced mortality in both treatment groups, which may have overwhelmed any benefit of latrines. In addition, this negative finding may be a result of an insufficient sample size and duration of follow-up, or to a lack of hygiene education. Further trials are needed to investigate the effects of sanitation interventions on community health in developing areas of the world.

**Table 3**

Odds of all-cause mortality from a clinical trial in rural Ethiopia comparing intensive latrine promotion versus no latrine intervention.

<table>
<thead>
<tr>
<th>Model parameter</th>
<th>Odds ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latrine promotion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–5 years</td>
<td>1.17 (0.88–1.57)</td>
<td>0.28</td>
</tr>
<tr>
<td>6–10 years</td>
<td>0.33 (0.16–0.71)</td>
<td>0.004</td>
</tr>
<tr>
<td>11–20 years</td>
<td>1.41 (0.19–10.76)</td>
<td>0.74</td>
</tr>
<tr>
<td>&gt; 20 years</td>
<td>1.31 (0.39–4.36)</td>
<td>0.66</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.23 (0.78–1.94)</td>
<td>0.38</td>
</tr>
<tr>
<td>0.98 (0.78–1.23)</td>
<td>0.85</td>
<td></td>
</tr>
</tbody>
</table>

*CI = confidence interval. Multi-level mixed-effects logistic regression model with mortality as the response variable, treatment arm, age group, sex, azithromycin treatment, and the azithromycin × age group interaction term as fixed effects, and three levels of nested random effects: households within state teams within subkebeles.
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Disclosures: None of the authors has any conflicts of interest.

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