Effect of Mass Distribution of Azithromycin for Trachoma Control on Overall Mortality in Ethiopian Children

A Randomized Trial

Travis C. Porco, PhD, MPH
Teshome Gebre, MBA
Berhan Ayele, MSc
Jenafir House, MPH
Jeremy Keenan, MD
Zhaoxia Zhou, BS
Kevin Cyrus Hong, BS
Nicole Stoller, MPH
Kathryn J. Ray, MA
Paul Emerson, PhD
Bruce D. Gaynor, MD
Thomas M. Lietman, MD

Context Mass oral azithromycin distribution to affected communities is a cornerstone of the World Health Organization's trachoma elimination program. Antibiotics are provided to target the ocular strains of chlamydia that cause trachoma, but may also be efficacious against respiratory disease, diarrhea, and malaria—frequent causes of childhood mortality in trachoma-endemic areas.

Objective To compare mortality rates of participants aged 1 to 9 years in treated communities with those in untreated communities.

Design, Setting, and Participants We conducted a cluster-randomized clinical trial of mass azithromycin administration for trachoma control. Forty-eight communities (known as subkebeles) were randomized into 1 of 3 treatment schedules (annual treatment of all residents [15 902 participants], biannual treatment of all residents [17 288 participants], or quarterly treatment of children only [14 716 participants]) or into 1 group for which treatment was delayed by 1 year (control, 18 498 participants). Twelve subkebeles were randomized to each of the 4 schedules with all children in each of the 3 communities being eligible for treatment. The trial was conducted in a field setting in rural Ethiopia, May 2006 to May 2007.

Interventions A single dose of oral azithromycin (adults, 1 g; children, 20 mg/kg) was administered for treatment of ocular *Chlamydia trachomatis* infection. Antibiotic coverage levels for children aged 1 to 9 years exceeded 80% at all visits.

Main Outcome Measure The main outcome measure was the community-specific mortality risk for children aged 1 to 9 years over the course of 1 year. Mortality was measured by enumerative census at baseline and again after 1 year. Comparison of the risk of mortality was a prespecified outcome for the clinical trial.

Results The odds ratio for childhood mortality in the intervention communities was 0.51 (95% confidence interval, 0.29-0.90; $P=.02$; clustered logistic regression) compared with the control group. In the treated communities, the estimated overall mortality rate during this period for children aged 1 to 9 years in the untreated group was 8.3 per 1000 person-years (95% confidence interval, 5.3-13.1), while among the treated communities, the estimated overall mortality rate was 4.1 per 1000 person-years (95% confidence interval, 3.0-5.7) for children aged 1 to 9 years.

Conclusion In a trachoma-endemic area, mass distribution of oral azithromycin was associated with reduced mortality in children.

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THE WORLD HEALTH ORGANIZATION has recommended mass distribution and administration of oral azithromycin as part of efforts to control blinding trachoma.[1] Such distribution has proven effective against the ocular strains of *Chlamydia trachomatis* that cause the disease at both the individual and village levels.[2-4] A single mass treatment dramatically reduces the prevalence of *C trachomatis* infection in a community.[3-6] Although infection returns in severely affected villages, repeated mass treatment with azithromycin progressively reduces and may even eliminate ocular chlamydia.[5,7-9] The treatment may also have unintended consequences, both harmful and beneficial.[10-13] Adverse effects are inevitable and antibiotic resistance may be in-

See also Patient Page.

Author Affiliations: F.I. Proctor Foundation (Drs Porco, Gaynor, Keenan, and Lietman, Mss House, Zhou, Stoller, and Ray and Mr Hong), Departments of Ophthalmology (Drs Porco, Gaynor, Keenan, and Lietman, and Ms Zhou) and Epidemiology and Biostatistics (Drs Porco and Lietman), Institute for Global Health (Dr Lietman), University of California, San Francisco; Carter Center, Ethiopia-USA (Messrs Gebre and Ayele and Dr Emerson). **Corresponding Author:** Thomas M. Lietman, MD, 513 Parnassus Ave, Room S309 Medical Sciences, University of California San Francisco, San Francisco, CA 94143-0412 (tom.lietman@ucsf.edu).

duced (although no data suggest resistance to azithromycin in ocular *C trachomatis*).[14] Conversely, antibiotics may reduce both respiratory and gastrointestinal infections, and possibly reduce rates of malaria—all of which are major causes of death in children in trachoma-endemic areas such as rural Ethiopia.[10,12,15] Therefore, the effect of oral azithromycin distribution on mortality was assessed in a cluster-randomized trial of trachoma control in Ethiopia.

METHODS

Participants and Interventions

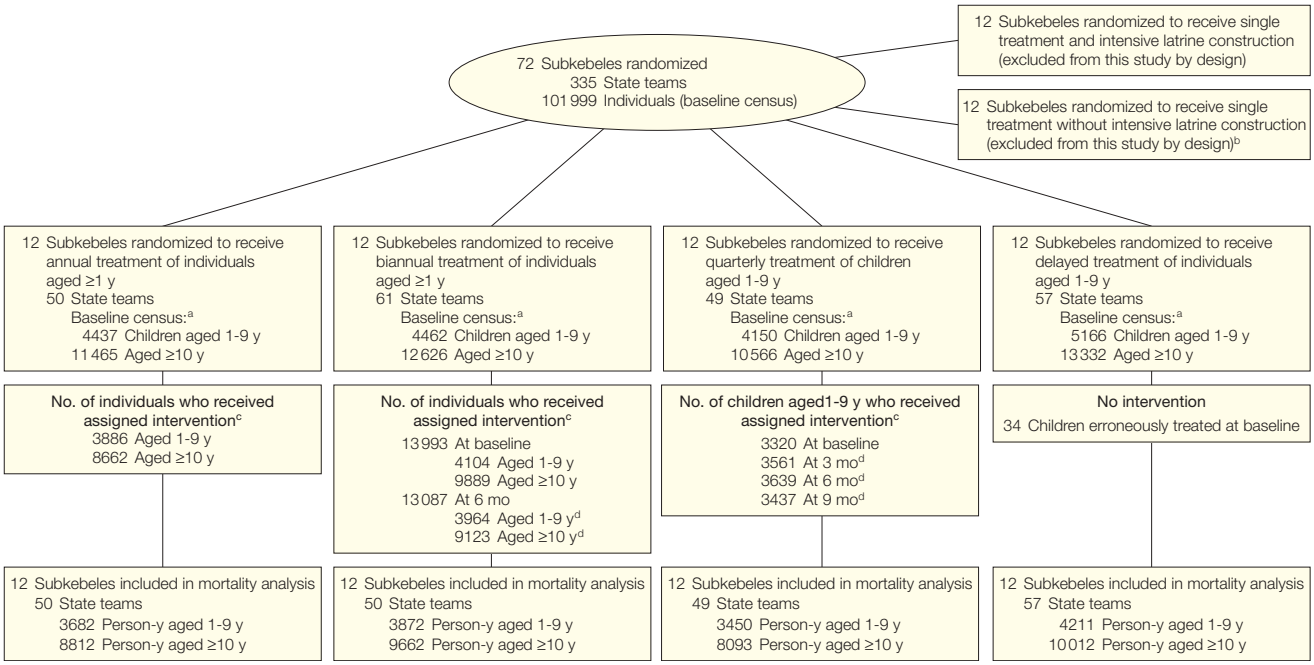
We enrolled 72 contiguous subkebeles (small Ethiopian administrative districts consisting of approximately 1500 individuals in 4-5 contiguous small villages [known as *state teams*]) in the Amhara region in a clinical trial of trachoma infection, featuring mass oral administration of azithromycin (Trachoma Amelioration in Northern Amhara [TANA]). These subkebeles were randomized to 1 of 6 treatment groups each containing 12 subkebeles. Four randomization groups contributed data to this mortality study (FIGURE): annual azithromycin distribution to all individuals aged 1 year and older, biannual treatment of those aged 1 year and older, quarterly treatment of those aged 1 to 10 years, and a delayed-treatment group in which treatment was scheduled for 12 months after the study began (control group).

The other 24 subkebeles were randomized to treatment groups assessing the additional benefit of latrines in trachoma control, and by design, no mortality data were collected from these groups for inclusion in this study because latrines may have an independent effect on mortality. *C trachomatis* infection rates were estimated from polymerase chain reaction analysis of conjunctival swabs collected from a sentinel state team chosen randomly from each subkebele; these results are reported elsewhere.[16]

Individuals were offered directly observed treatment with a single dose of oral azithromycin (adults, 1 g; children, 20 mg/kg). All individuals in the intended target age groups were eligible for treatment unless contraindicated by allergy or pregnancy. Within each subkebele, the intent was to treat 80% or more of the eligible population (ideally, all individuals would receive treatment).

All subkebeles in the study district (Goncha Siso Enese Woreda, Amhara region) that were accessible to the study team were eligible for inclusion (accessibility defined as requiring no more than a 3-hour walk beyond the furthest point available to 4-wheel drive vehicles). This region is homoge-

Figure. Participant Flow



Entire communities were randomized to 1 of the 4 study groups (annual, biannual, quarterly [children only], and delayed [untreated for the 1-year duration of this study; at 1 year mass administration of azithromycin for trachoma elimination was undertaken]). A total of 66 404 individuals were enumerated in these communities including 18 415 children aged 1-9 years. These groups form part of an evaluation trial for trachoma elimination in which trachoma-related results are to be reported elsewhere.

[a] Primary analysis was based on baseline census population.

[b] Specifies that subkebeles did not receive an intensive sponsored effort to construct large numbers of latrines. Cannot denote "without latrine construction" because some individuals constructed latrines on their own.

[c] Number of participants who received assigned intervention differs from number enrolled because of exclusions for allergy or pregnancy.

[d] Number of patients who received interval interventions following baseline differ slightly because of relocation or unavailability due to work.

neously Amharic-speaking and almost all members of the population share a common religion.

Because mass administration of antibiotics for trachoma elimination is conducted at the community level, we conducted a community-randomized trial. We did not randomize individuals within a community to different treatment schedules because treated individuals could rapidly become reinfected with chlamydia from untreated sources in the community. In addition, reinfection of individuals in treated groups by untreated individuals in the same community would result in biased efficacy estimates,[17] a problem avoided by analysis and randomization at the community level. These considerations also apply in principle to the analysis of mortality due to infectious causes.

Objectives and Outcomes

The primary objective was to test the hypothesis that mass administration of oral azithromycin would reduce the mortality risk among children aged 1 to 9 years. The primary mortality outcome was the subkebele-specific risk of death among children aged 1 to 9 years between 2 implementations of population census approximately 1 year apart. We determined these mortality risks (and rates) using data from a population census carried out before the distribution of antibiotics. These census counts were conducted for each of the 48 subkebeles included in the mortality comparison, and census personnel were masked to the treatment assignments. Consent for participation was obtained from the Regional Health Bureau, community leaders, and a parent or guardian of each child participant.

A repeat census was performed at a scheduled visit approximately 1 year after the initial census, according to the protocol. Any absence of an individual who had been recorded on the initial census was noted and the reason for the absence was determined. For each reported death, an abbreviated verbal autopsy was obtained, asking household members to report symptoms (respiratory, diarrhea, malaria, cardiovascular, or unknown). Recorded adverse outcomes following azithromycin administration included transient gastrointestinal complaints.[16]

For secondary analyses, we included additional variables measured at the community level at baseline as statistical predictors of the mortality rate in each subkebele. Because the abundance of the *Musca sorbens* flies, thought to transmit infection, may decrease with altitude,[18] we measured altitude in meters above sea level in the randomly chosen sentinel state team in each subkebele using a global positioning system. We also measured the distance (km) to the nearest population center (Gandewayn) using global positioning system coordinates and used an ordinal scale for accessibility of each subkebele. Specifically, the accessibility of the subkebeles was classified as (1) possible in less than 1 hour from the town of Gandewayn; (2) requiring more than 1 hour but not requiring an overnight stay; or (3) requiring an overnight stay. We also estimated the fraction of the population aged 1 to 9 years and the fraction of children aged 1 to 9 years who were female. Our study was not designed to address these factors, but instead was intended to randomly allocate participants to the treatment and control groups.

Sample Size

The number of subkebeles in each group needed for randomization was determined with respect to the main trachoma outcome of the trial (the prevalence of *C trachomatis* infection measured in a sentinel state team). Twelve subkebeles in each group provided 80% power to detect a 6% difference in the prevalence of trachomatous infection and a reduction of 0.5% in the annual risk of death (based on simulation). All state teams in a subkebele were treated in the same manner and all were used in this mortality assessment. This design was chosen to increase power for the mortality comparison, as well as to ensure that trachoma sentinel state teams were largely surrounded by communities treated in the same way. Comparison of mortality between the entire treatment group (annual, biannual, and quarterly [children only] groups) and the control group was planned and prespecified to maintain statistical power. There were no prespecified interim analyses or stopping rules that could be enacted during the 12 months of this report.

Randomization

Following the baseline census, randomization of the communities was conducted by sampling the subkebele names without replacement, assigning the first 12 names to annual treatment, the next 12 to biannual treatment, and so forth (conducted by K.J.R., and concealed until interventions were assigned to the field teams). All 72 enrolled communities were simultaneously randomized. No blocking or stratification was undertaken. Once a community was assigned to the annual or biannual treatment group, field teams of treatment workers visited the community to enroll participants and administer oral azithromycin to adults and children aged 1 year or older; only children aged 1 to 10 years were enrolled and treated in communities randomized to the quarterly group (the mortality measurements were intended only for 1- to 9-year-olds, inclusive). Treatment workers were masked to all trachoma outcome variables; and census workers were masked to treatment coverage throughout the study. By design, the communities were not masked to the intervention chosen.

Human Participants

Ethical approval for this study was obtained from the Committee for Human Research of the University of California, San Francisco, the Ethiopian Science and Technology Commission, and Emory University (Atlanta, Georgia). The study was carried out in accordance with the Declaration of Helsinki. A data and safety monitoring committee appointed by the National Institutes of Health–National Eye In-

stitute oversaw the design and implementation of the study. Informed consent was obtained in Amharic for all adult participants; for children, informed consent from the parent or guardian was obtained, as well as informed assent for children who were at least 7 years of age.

Statistical Analysis

The prespecified primary mortality outcome was the proportion of children aged 1 to 9 years who were present at baseline, but not present at the second survey due to death. The prespecified analysis plan was to compare the risk of death over 1 year in those present at baseline in the control group with the combined risk of death in the 3 treated groups (annual, biannual, and quarterly [children only], aggregated together). We modeled mortality risk using clustered logistic regression at the individual level for the primary comparison, taking into account the possible statistical dependence of individuals in the same subkebele. All significance testing was 2-sided with an α of .05.

To ensure that the results were not dependent on the particular choice of statistical model, we also constructed other regression models to fit subkebele-specific estimated mortality rates, taking clustering at the level of the randomization unit into account. Mortality rates were estimated by dividing the number of deaths by the number of person-years at risk, which was estimated as the intercensus interval in years multiplied by the number of individuals at the baseline census, minus half of the sum of the number determined to have died and permanently moved. We used negative binomial regression (a generalization of the commonly used Poisson regression)[19] to model the mortality rates in the 48 subkebeles. By estimating an additional aggregation parameter, negative binomial regression allowed us to model possible overdispersion of the mortality counts; as the aggregation parameter becomes very large, the negative binomial distribution approaches the Poisson distribution. Goodness of fit was assessed using the standard deviance χ^2 statistic[20] ($P < .05$ was used as the criterion to indicate lack of fit), and by examination of plots of the deviance residuals against the fitted values.

In a randomized trial, chance may result in a substantially uneven allocation of important covariates between the treatment and control groups. We therefore conducted 2 additional supplementary analyses using negative binomial regression: (1) we included additional subkebele-level covariates in negative binomial regression models for the mortality rates at the subkebele level; and (2) we compared subkebele-level covariates at the start of the trial using *t* tests, negative binomial regression, or Fisher exact tests for an $r \times c$ table. The causes of death, as determined from the verbal autopsy, were compared between the treated and untreated groups using the Fisher exact test. All analyses were conducted using R statistical software, version 2.6.0 for MacIntosh (R Foundation for Statistical Computing [http://www.r-project.org/]).

RESULTS

A total of 66 404 individuals were identified at baseline in the 48 subkebeles participating in the study (Figure), including 18 415 children aged 1 to 9 years (May 2006). Each of the 48 subkebeles were treated according to protocol (annually, biannually, or quarterly [children only] for the treatment groups, and no intervention for the delayed treatment [control] group); we conducted the analysis of subkebele-specific mortality rates on an intention-to-treat basis. All 48 subkebeles were observed until the follow-up census (March 2007). A small number of individuals (34/18 498) in 1 state team in the control group were mistakenly treated at baseline, contrary to protocol.

Baseline characteristics of the subkebeles are shown in TABLE 1. No statistically significant differences were found between the treatment and control subkebeles at baseline when comparing the proportion of children who

Table 1. Baseline Characteristics of the Treatment and Control Subkebeles

Variable	Value (95% Confidence Interval) in Treatment Group[a]				*P* Value
	Annual	Biannual	Quarterly[b]	Delayed[c]	
Fraction of population aged 1 to 9 y, mean, %[d]	27.9 (26.5-29.3)	26.4 (25.1-27.7)	28.3 (27.0-29.5)	28.0 (27.1-28.9)	.27[e]
Fraction female among children aged 1 to 9 y, mean, %[d]	50.2 (48.7-51.6)	51.0 (49.3-52.7)	49.3 (46.8-51.7)	48.8 (47.4-50.2)	.58[e]
Altitude of sentinel state team, mean, m[f]	2522 (2358-2687)	2592 (2455-2730)	2592 (2455-2730)	2536 (2388-2684)	.85[g]
Distance of sentinel state team, mean, km[h]	11.2 (8.5-13.8)	10.1 (6.5-13.7)	12.4 (9.0-15.9)	11.3 (8.5-14.1)	.97[g]
Fraction of villages difficult to access, %[i]	33 (10-65)	25 (5-57)	25 (5-57)	25 (5-57)	>.99[j]

[a] Confidence intervals for continuous variables were computed using the *t* test for distribution; confidence intervals for proportions were computed using exact binomial intervals.
[b] Treatment was only administered for participants aged 1 to 9 years.
[c] Denotes control group, untreated for the 1-year duration of this study, at which time mass administration of azithromycin was conducted.
[d] The fraction of female participants aged 1 to 9 years and the fraction of the population known to be aged 1 to 9 years are reported as the average (mean) over subkebele.
[e] *P* value was calculated comparing baseline values in 1 of the 3 treatment groups with those in the control group using negative binomial regression for individual-level dichotomous values (taking into account clustering).
[f] State teams are smaller government units approximately equivalent to a village (see "Participants and Interventions" section).
[g] *P* value was calculated comparing baseline values in 1 of the 3 treatment groups with those in the control group using the Student *t* test.
[h] Distance is from sentinel state team to Gandewayn, the nearest population center (see "Objectives and Outcomes" section).
[i] For explanation of accessibility, see "Objectives and Outcomes" section; fraction denotes 4 of 12 for the annual treatment group, 3 of 12 for the biannual treatment group, 3 of 12 for the quarterly treatment group (children only), and 3 of 12 for the delayed treatment (control) group.
[j] *P* value was calculated comparing baseline values in the treatment groups with those in the control group using the $r \times c$ Fisher exact test.

were female, the fraction of the population between the ages of 1 and 9 years (inclusive), the altitude of the sentinel state team, the distance to the nearest population center, or the accessibility (see "Methods" section). Antibiotic coverage rates exceeded 81% among children aged 1 to 9 years (inclusive) at all visits (TABLE 2).

A total of 82 deaths were recorded for children aged 1 to 9 years at the 2007 census (TABLE 3). The primary prespecified mortality outcome was the comparison of the mortality risk among children aged 1 to 9 years in the treatment vs the control groups using clustered logistic regression; this procedure yielded an odds ratio for mortality in the treatment group of 0.51 (95% confidence interval [CI], 0.29-0.90; $P=.02$) compared with the control group. The estimated overall mortality rate during this period for participants aged 1 to 9 years in the untreated group was 8.3 per 1000 person-years (95% CI, 5.3-13.1), while among the treated communities, the estimated overall mortality rate was 4.1 per 1000 person-years (95% CI, 3.0-5.7) for participants aged 1 to 9 years. As a sensitivity analysis, we also compared the mortality rates between the groups using negative binomial regression; the treated group mortality rate was 50% lower (relative rate, 0.496; 95% CI, 0.29-0.86; $P=.01$, negative binomial regression). The deviance goodness-of-fit statistic indicated no evidence of lack of fit ($P=.18$).

We conducted post hoc analyses using other age ranges. Negative binomial regression of mortality rates in children aged 1 to 5 years yielded a relative mortality rate a factor of 0.47 lower in the treatment groups than in the untreated group (95% CI, 0.26-0.84; $P=.01$). The mortality rate among 1- to 5-year-olds in the untreated group was 12.1 per 1000 person-years (95% CI, 7.4-19.6), while among the treated group, the mortality rate was 5.7 per 1000 person-years (95% CI, 4.1-8.0). As a sensitivity analysis, we also examined mortality in the age range of 1 to 10 years; this analysis also revealed statistically significant differences between the treatment and control groups (relative rate, 0.50; 95% CI, 0.29-0.86; $P=.01$; treated average mortality rate, 3.8 per 1000 person-years; untreated, 7.6 per 1000 person-years), indicating that results were not dependent on the exact choice of age range monitored. Clustered logistic regression yielded very similar results as negative binomial regression yielded in these analyses.

We conducted 4 additional exploratory analyses in which we included singly each of the following predictors to the negative binomial regression model in addition to the treatment group: altitude, distance to the nearest town (Gandewayn), accessibility (as defined in the "Methods" section), and fraction aged 1 to 9 years who were female. No significant differences were seen with respect to these additional predictors, suggesting that the mortality differences observed need not be attributed to these factors. Specifically, the adjusted relative mortality rate per 100 m of altitude was 0.94 (95% CI, 0.84-1.05; $P=.24$), and the adjusted relative rate per 1 km of distance to Gandewayn was 1.02 (95% CI, 0.97-1.07; $P=.45$). Comparing the most difficult to access villages with the easiest to access, the adjusted relative mortality rate was 1.34 (95% CI, 0.69-2.62; $P=.38$). Finally, the adjusted relative rate (for every 10% change in the fraction female) was 0.88 (95% CI, 0.31-2.50; $P=.81$).

Children younger than 1 year never received azithromycin treatment (by design), and no differences in mortality were to be expected based on the treatment. A total of 98 deaths were identified in this age group out of a total of 3241 children. The estimated mortality rate was 42.9 per 1000 person-years (95% CI, 29.4-62.6) in the untreated group and 35.8 per 1000 person-years (95% CI, 26.8-47.7) in the treated groups ($P=.51$; negative binomial re-

Table 2. Azithromycin Coverage Rates by Interval and Study Group[a]

Treatment Group by Age	Coverage Fraction by Interval mo, % (95% Confidence Interval)			
	0	3	6	9
Annual				
1-9 y	88.0 (83.7-92.2)	NA	NA	NA
≥10 y[b]	81.7 (76.7-86.7)	NA	NA	NA
Biannual				
1-9 y	88.7 (85.6-91.8)	NA	87.8 (83.4-92.1)	NA
≥10 y[b]	84.9 (82.1-87.6)	NA	79.3 (75.0-83.6)	NA
Quarterly[c]	81.4 (72.9-89.8)	86.9 (82.6-91.2)	88.7 (85.1-92.4)	84.3 (80.1-88.6)
Delayed[d]	NA	NA	NA	NA

Abbreviation: NA, not applicable.
[a] Not applicable indicates that treatment was not scheduled for that group at that time.
[b] Denotes azithromycin coverage rates for individuals aged 10 years and older.
[c] Treatment was only administered for participants aged 1 to 9 years.
[d] A small fraction of individuals (0.3%) were erroneously treated at baseline (see "Results" section); denotes control group, untreated for the 1-year duration of this study, at which time mass administration of azithromycin was conducted.

Table 3. Estimated Mortality Rates in the 4 Groups

Treatment Group	Participant Mortality Rate per 1000 Person-Years (95% Confidence Interval) [No. of Deaths][a]		
	Age <1 y[b]	Age 1-9 y	Age >9 y
Annual	34.6 (20.9-57.2) [22]	3.2 (1.8-5.8) [12]	4.3 (3.1-6.0) [38]
Biannual	26.3 (17.0-40.8) [20]	4.9 (3.1-7.7) [19]	6.2 (4.5-8.8) [60]
Quarterly[c]	46.9 (29.5-74.7) [29]	4.7 (2.0-11.1) [14]	6.5 (5.0-8.6) [53]
Delayed[d]	42.9 (29.4-62.6) [27]	8.3 (5.3-13.1) [37]	6.1 (4.5-8.4) [62]

[a] Mortality rates were estimated by negative binomial regression. Mortality in 1- to 9-year-old participants was a prespecified outcome of the trial and was found to be significantly lower in the treated communities than in control communities.
[b] Children younger than 1 year were not treated with azithromycin in any study group.
[c] Treatment was only administered for participants aged 1 to 9 years.
[d] Denotes control group, untreated for the 1-year duration of this study, at which time mass administration of azithromycin was conducted.

gression, posthoc comparison). Deviance goodness-of-fit statistics yielded no evidence of lack of fit in either case. For children younger than 1 year, clustered logistic regression yielded an odds ratio of 0.84 (95% CI, 0.51-1.40; $P=.50$), yielding the same conclusion as negative binomial regression. The lack of a mortality difference among untreated children in the treatment and control groups suggests that the observed differences in the 1- to 9-year-olds were unlikely to have resulted from chance variation in village-specific random effects that may have arisen during randomization.

Verbal autopsy revealed no cause of death for 30.3% (27/82) deaths of children aged 1 to 9 years. For 40.2% (33/82), the cause of death was attributed to malaria, fever, diarrheal or respiratory causes, and the remainder to other causes. For the 55 individuals whose cause of death was revealed by verbal autopsy, 36% (20/55) were attributed to respiratory causes, 9% (5/55) to diarrheal causes, 15% (8/55) to fever or malaria, and an additional 40% (22/55) were attributed to other causes. No statistically significant differences in cause of death (based on the abbreviated verbal autopsy) were seen between untreated and treated communities ($P=.09$, Fisher exact test) among children aged 1 to 9 years.

COMMENT

A large, cluster-randomized trachoma trial in Ethiopia offered the opportunity to assess the effect on mortality of antibiotics given community wide for a nonlethal indication. Mass oral azithromycin distribution for management of infection with *C trachomatis* was associated with fewer deaths in children. It is not clear precisely why azithromycin decreased mortality, although infectious diseases are the leading cause of death in Ethiopian children, in particular pneumonia (28%), diarrhea (20%), and malaria (20%).[21] In Ethiopia, azithromycin is likely effective against the major pathogenic causes of lower respiratory tract infections such as *Streptococcus pneumoniae* and *Haemophilus influenzae*, and may have some effect against major causes of bacterial diarrhea such as *Escherichia coli* and *Clostridium jejuni*.[22,23] Azithromycin has also been shown to have efficacy in the prevention and treatment of malaria due to both *Plasmodium falciparum* and *Plasmodium vivax*.[24-26]

Mass azithromycin treatment for trachoma may reduce the symptoms of diarrhea and respiratory disease.[12,27] Although antibiotic treatments were given regardless of symptoms, it is inevitable that some individuals with severe respiratory infection, gastrointestinal disease, or malaria received azithromycin treatment, which may explain the observed results. Since azithromycin, in principle, may act on several of the major causes of childhood death, it may be difficult to identify a single reason why its use decreases mortality in this setting, and there is no a priori reason to expect particular differences in the cause of death between the study groups. No evidence of a difference was found based on the limited data available in our abbreviated verbal autopsy reports.[28]

Our estimate of the crude mortality rate in children 1 to 5 years of age was 12.2 per 1000 person-years in the untreated communities and 5.7 per 1000 person-years in the azithromycin-treated communities. This is consistent with a recent survey from an area near this study, which reported a crude mortality rate in children aged 1 to 4 years ranging from 5.0 to 9.2 per 1000 person-years.[29] We note that although children younger than 1 year were not directly treated with azithromycin, indirect protection may be possible because other children were treated (such effects were seen for trachoma[16]); our trial was not powered to detect indirect protection for infectious causes of mortality, and the nonsignificant finding in this post hoc comparison does not provide evidence of the absence of such an effect.

Although antibiotics are clearly effective against the ocular strains of chlamydia that cause trachoma, there has been debate about the risks and benefits of mass distribution. The increased antibiotic pressure could theoretically induce macrolide resistance in *C trachomatis*, although this has yet to be demonstrated.[14] Increased resistance has been seen in other organisms such as *S pneumoniae*,[12,13,30] although the levels of resistance are thought to return to near baseline levels after antibiotic distributions are discontinued.[12,13] Mass distributions may be justifiable in the context of trachoma control. However, careful consideration of the cost, adverse effects, and the potential for inducing drug resistance would need to be considered before advocating their use in nontrachoma-endemic areas.

Azithromycin is not the first drug for which mass distribution has been shown to affect mortality. Chemoprophylaxis with semimonthly pyrimethamine/dapsone can reduce malaria and malarial deaths in children.[31,32] Vitamin A distributions not only decrease childhood blindness but also childhood mortality.[33] That azithromycin can also prolong survival is perhaps not surprising, since respiratory bacterial infections and malaria are a major cause of childhood mortality in Ethiopia.

Several limitations apply to the findings of this study. The limited power of the verbal autopsy makes it difficult to determine why azithromycin may decrease mortality. The limited duration of the study (12 months) does not allow assessment of a longer-term effect. The development of antibiotic resistance could, for example, reduce the effect in subsequent years. Also, communities in the treated groups had visits for antibiotic distribution that those in the untreated (delayed treatment) group did not. Even though no other measures such as education were planned during these visits, we cannot rule out the possibility of a Hawthorne-like effect. Placebo was not distributed in the untreated group, therefore, we are also unable to rule out any placebo effect on mortality.

The dangers of nonspecific antibiotic use have been well-described in the scientific literature. The common wis-

dom is that overprescribing antibiotics results in increased morbidity and mortality from drug-resistant organisms, and that society would be better off were physicians to restrain their use of the drugs. However, the effect of nonspecific mass antibiotic use on mortality has never before been assessed in a group-randomized clinical trial. In an area in which residents have very limited access to antibiotics, mass distribution of oral azithromycin appears to reduce mortality in preschool children. Further assessment of the mechanism, generalizability, effects of drug resistance or other adverse outcomes, and cost-effectiveness of antibiotic administration in impoverished rural settings may be needed to provide further insight to guide public health policy.

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: Porco, House, Hong, Emerson, Gaynor, Lietman.
Acquisition of data: Gebre, Ayele, House, Zhou, Hong, Stoller, Ray, Lietman.
Analysis and interpretation of data: Porco, Keenan, Ray, Lietman.
Drafting of the manuscript: Porco, Lietman.
Critical revision of the manuscript for important intellectual content: Gebre, Ayele, House, Keenan, Zhou, Hong, Stoller, Ray, Emerson, Gaynor, Lietman.
Statistical analysis: Porco.
Obtained funding: Lietman.
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Study supervision: Gebre, Ayele, House, Stoller, Lietman.
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