MAJOR ARTICLE

Childhood Mortality in a Cohort Treated With Mass Azithromycin for Trachoma

Jeremy D. Keenan,[1,2] Berhan Ayele,[3] Teshome Gebre,[3] Mulat Zerihun,[3] Zhaoxia Zhou,[1] Jenafir I. House,[1] Bruce D. Gaynor,[1,2] Travis C. Porco,[1,2,4] Paul M. Emerson,[5] and Thomas M. Lietman[1,2,4,6]

[1]F.I. Proctor Foundation; [2]Department of Ophthalmology, University of California, San Francisco, California; [3]The Carter Center, Addis Ababa, Ethiopia, Africa; [4]Department of Epidemiology and Biostatistics, University of California, San Francisco, California; [5]The Carter Center, Atlanta, Georgia; and [6]Institute for Global Health, University of California, San Francisco, California

Background. Mass azithromycin distributions are used to clear ocular strains of chlamydia that cause trachoma, but treatments may also affect respiratory infections, diarrhea, and malaria. Here, we monitor a large cohort in which almost 90% of individuals received azithromycin. We assess whether receiving treatment is associated with reduced all-cause and infectious childhood mortality.

Methods. As part of a clinical trial for trachoma, a census was conducted in 24 communities in rural Ethiopia. All individuals ⩾1 year of age were eligible for single-dose oral azithromycin, although antibiotic coverage was not universal. A follow-up census was performed 26 months after treatment to estimate all-cause mortality among children 1–5 years of age, and verbal autopsies were performed to identify infectious mortality.

Results. The cohort included 35,052 individuals ⩾1 year of age and 5507 children 1–5 years of age, of whom 4914 received a dose of azithromycin. All-cause mortality was significantly lower among those 1–5-year-old children who received azithromycin (odds ratio [OR] = 0.35 [95% confidence interval {CI}, 0.17–0.74]), as was infectious mortality (OR = 0.20 [95% CI, 0.07–0.58]). When individuals were compared only with members of the same household, azithromycin treatment was still associated with reduced all-cause mortality in children 1–5 years of age (OR = 0.40 [95% CI, 0.16–0.96]), although this relationship was not statistically significant for infectious mortality (OR = 0.35 [95% CI, 0.10–1.28]).

Conclusions. This study demonstrated an association between mass oral azithromycin treatment and reduced all-cause and infectious childhood mortality. This relationship could not be attributed to bias at the level of the household. Mass azithromycin distributions may have benefits unrelated to trachoma.

Repeated mass azithromycin distributions are an important component of the World Health Organization's trachoma control strategy [1, 2]. Azithromycin is efficacious against the ocular strains of chlamydia that cause trachoma [3–5]. However, azithromycin also has activity against respiratory infections, diarrhea, and malaria [6–9]. There is some evidence that mass distributions for trachoma may affect these conditions [10–12]. Moreover, a cluster-randomized clinical trial has demonstrated reduced mortality in children who resided in communities randomized to mass azithromycin treatments, compared with children in communities who were randomized to delayed treatment, even though trachoma itself is not a lethal disease [13].

Here, we conduct an observational analysis of a cohort of individuals monitored in a large cluster-randomized trial. All communities were offered a single dose of oral azithromycin per person. Although the project's goal was to treat all individuals 1 year of age or older, in practice, antibiotic coverage was not perfect. This allowed assessment of mortality in preschool-aged children who received azithromycin, compared with those who did not. To control for any household-level confounders, we assessed this relationship relative to other individuals in the deceased individual's household.

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Correspondence: Jeremy D. Keenan, MD, 513 Parnassus Ave, Rm S309, Medical Sciences, University of California, San Francisco, CA 94143-0412 (jeremy.keenan@ucsf.edu).

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METHODS

Study Design

In a cluster-randomized clinical trial for trachoma conducted in the Goncha Siso Enese *woreda* (district) in the Amhara Region of Ethiopia, 72 *subkebeles* (government administrative units) were randomized to 1 of 6 treatment arms (clinicaltrials.gov #NCT00322972). A previous report analyzed the association between mass azithromycin and 1-year mortality in subkebeles from 4 of these treatment arms [13]. In the remaining 2 treatment arms, 12 subkebeles were randomized to a single mass azithromycin distribution plus intensive latrine construction, and 12 subkebeles were randomized to a single mass azithromycin distribution without a latrine intervention. In these 24 subkebeles, censuses were performed at baseline and again 26 months after the mass azithromycin distribution. In the current report, we perform an observational epidemiological analysis of the census and coverage data from these 24 subkebeles to assess the association between childhood mortality and azithromycin treatment. Childhood mortality was a pre-specified outcome of the trial.

Census

We conducted a door-to-door population census in May 2006. Each household and each individual in the household were assigned a unique identification number. A second door-to-door census was conducted in August 2008. If an individual was present for the first census but absent at the follow-up census, the reason for absence was determined. If an individual had died, an abbreviated verbal autopsy was conducted to identify the cause of death (respiratory disease, diarrhea, malaria, old age, accident, or unknown). Both censuses were performed by local Ethiopian auxiliary health workers masked to treatment assignment and antibiotic coverage and familiar with the residents and geography of their assigned area. Mortality rate was defined as deaths per person-years at risk, calculated as the inter-census 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 or permanently moved. The baseline census was updated at the mass azithromycin distribution that occurred 1 month later. Therefore, the current analysis includes the 26 months between the azithromycin distribution and the follow-up census.

Interventions

All individuals $\geqslant$1 year of age who were not pregnant or known to be allergic to macrolide antibiotics were offered a single, directly observed dose of oral azithromycin (1 g for adults, 20 mg/kg for children approximated by height-based dosing [14]). The azithromycin distribution occurred $\sim$1 month after the baseline census and is referred to as the baseline treatment in this report. Individuals who reported being pregnant or having a macrolide allergy were given topical tetracycline ointment, to be applied twice daily for 6 weeks. Antibiotic distributors recorded the dose of antibiotic given to each community member. For those individuals not receiving either antibiotic, the reason was recorded as current illness, refusal, migration out of the community, death, or unknown. In the 12 subkebeles randomized to the latrine intervention arm, concrete slabs were provided to each household for the purpose of latrine construction. Auxiliary health workers provided training in latrine construction for heads of households.

Statistical Analysis

We treated all study participants from the cluster-randomized clinical trial as a single cohort. By design, we did not include infants $<$1 year of age in the main analysis, because they were not eligible to receive azithromycin. We used univariate and multivariate mixed effects logistic regression models to determine predictors of having received antibiotic treatment, with household nested in subkebele as random effects. We determined whether having received antibiotics was associated with household membership by calculating the intraclass correlation coefficient (ICC) on the logit scale from the mixed effects logistic regression model.

We estimated all-cause and infectious mortality rates for ages 1–5, 6–10, 11–20, and $>$20 years stratified by whether the individual had received azithromycin. We accounted for subkebele clustering by modeling mortality rates with negative binomial regression, a generalization of Poisson regression that estimates an additional aggregation parameter to allow modeling of overdispersion of count data [15]. The primary prespecified outcome of this study was the association between mortality and azithromycin treatment in preschool-aged children 1–5 years of age. This was assessed in a negative binomial regression adjusted for age as a categorical variable (1–5 years, 6–10 years, 11–20 years, and $>$20 years), the interaction between age group and azithromycin treatment, sex, and clinical trial arm. To assess for bias, we used similar techniques to estimate the mortality rate among those infants $<$1 year of age who had sibling(s) 1–5 years of age, stratified by whether any of their siblings had received azithromycin. We assessed whether treatment of any siblings (versus no siblings) was associated with mortality among infants $<$1 year of age in a negative binomial regression adjusted for sex and clinical trial arm.

The relationship between azithromycin treatment and childhood mortality could be confounded by any household factors that were responsible for childhood mortality and also for absence from azithromycin treatment (eg, poverty, isolation, and illness, etc). We accounted for any potential household-level bias using a conditional logistic regression analysis, with mortality as the response variable and individual azithromycin treatment at baseline as the explanatory variable, conditioned on household

[16]. Note that this is analogous to a matched case-control study nested in our treatment cohort, where each individual who died is compared only to individuals in the same household who did not die. This analysis, therefore, accounts for any household-level confounders. To account for individual-level confounders, the model was also adjusted for sex, age group (as defined above), and the interaction between age group and azithromycin treatment. The sandwich estimate of variance for cluster-correlated data was used [17]. To ensure that results were not dependent on the particular choice of age groups, sensitivity analyses were performed using age categorized by quartile, decade, and by a cubic spline (*mkspline* command in Stata; 4 knots; knot location assigned by the statistical software).

We created similar negative binomial and conditional logistic regression models to assess the relationship between azithromycin treatment and infectious mortality, which was defined as death due to malaria, respiratory infection, or diarrhea. Sample size calculations were based on the primary outcome of the trial, which was ocular chlamydia prevalence. All analyses were conducted with Stata software, version 10.0 (Stata software).

Ethics Statement

Ethical approval was obtained from the Committee for Human Research of the University of California, San Francisco; the Ethiopian Science and Technology Commission, Addis Ababa; and Emory University, Atlanta, Georgia. The study was carried out 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. Verbal informed consent in Amharic was obtained from all study participants by local auxiliary health workers during each census; verbal consent was used because of the high prevalence of illiteracy in the study area and was approved by all institutional review boards.

RESULTS

The treatment cohort consisted of 35,052 individuals ⩾1 year of age and 5507 children 1–5 years of age and represented 6519 households from the 24 subkebeles in the study area. Overall, 31,133 (88.8%) of the cohort members received azithromycin at baseline, including 4914 children 1–5 years of age (89.2% of this age group). Of the 3919 individuals ⩾1 year who did not receive antibiotics, 78.9% (3092 people) were known to be alive but did not receive treatment, 14.3% (560 people) received topical tetracycline ointment instead, 6.7% (263 people) refused treatment, and 0.08% (3 people) were ill at the time of distribution; proportions for the 593 children 1–5 years of age who did not receive antibiotics were 83.3% (494 children), 3.9% (23 children), 1.9% (11 children), and 0.2% (1 child), respectively. Characteristics of individuals who received azithromycin during the mass distribution, as well as those who did not, are shown in Table 1. Azithromycin treatment was significantly associated with household membership (ICC = 0.37 [95% CI, 0.34–0.40]), age, and sex (Table 1).

In a census conducted 26 months after the baseline azithromycin distribution, 320 individuals present during the baseline treatment had died. During the intercensus interval, 2083 persons who had received antibiotics and 674 persons who had not received antibiotics moved away from the study area and were lost to follow-up. No deaths were observed among individuals documented as missing azithromycin treatment due to illness. Mortality rates for the cohort are shown in Table 2, stratified by age and whether the baseline dose of azithromycin was received. Children 1–5 years of age who had received azithromycin at baseline had a lower all-cause mortality rate (2.79 deaths per 1000 person years) compared with those who had not (8.18 deaths per 1000 person years). Azithromycin treatment was significantly associated with reduced all-cause mortality in children 1–5 years of age (OR = 0.35 [95% CI, 0.17–0.74]; $P = .006$, by adjusted negative binomial regression). This

Table 1. Characteristics of Individuals Who Did and Did Not Receive Treatment during a Mass Azithromycin Distribution

Variable	Received azithromycin (*n* = 31,133)	Did not receive azithromycin (*n* = 3,919)	Odds ratio(95% CI)[a]
Age distribution, %			
1–5 Years	15.8 (14.9–16.6)	15.1 (12.2–18.0)	1.0
6–10 Years	20.3 (19.7–20.9)	11.3 (9.6–12.9)	1.91 (1.65–2.20)[b]
10–20 Years	24.4 (23.3–25.5)	28.0 (25.4–30.6)	0.83 (0.73–0.93)[b]
>20 Years	39.5 (38.8–40.3)	45.6 (41.6–49.7)	0.81 (0.73–0.91)[b]
Female sex, %	49.5 (48.9–50.0)	54.4 (51.3–57.4)	0.79 (0.73–0.86)
Household size, mean no. of individuals	6.3 (6.1–6.5)	6.3 (6.1–6.5)	1.01 (0.99–1.04)

NOTE. Data are population-averaged proportions/means and 95% confidence intervals (CIs), adjusted for sampling at the level of the subkebele.

[a] Univariate logistic regression assessing the relationship between antibiotic treatment and each characteristic, with clustering at the level of the subkebele and household.

[b] The reference group is 1–5-year-old children.

Table 2. Estimated Age-Specific All-Cause and Infectious Mortality Rates from a Clinical Trial in Ethiopia, Stratified by Whether Azithromycin Treatment was Received

Variable	Received azithromycin		Did not receive azithromycin			
	No. of deaths	Mortality rate[a]	No. of deaths	Mortality rate[a]	OR (95% CI)[b]	*P*
All-cause mortality, by age						
1–5 Years	29	2.79 (1.90–4.09)	10	8.18 (4.34–15.43)	0.35 (0.17–0.74)	.006
6–10 Years	21	1.56 (1.00–2.43)	1	1.13 (0.16–8.06)	1.42 (0.19–10.66)	.73
10–20 Years	31	2.03 (1.40–2.94)	3	1.49 (0.48–4.64)	1.40 (0.42–4.63)	.58
>20 Years	202	7.98 (6.68–9.55)	23	6.44 (4.19–9.90)	1.26 (0.79–2.01)	.33
Mortality attributed to infection, by age						
1–5 Years	9	0.89 (0.36–2.15)	6	4.86 (2.09–11.27)	0.20 (0.07–0.58)	.003
6–10 Years	5	0.38 (0.15–0.94)	1	1.14 (0.16–8.24)	0.35 (0.04–3.11)	.35
10–20 Years	6	0.39 (0.17–0.91)	1	0.49 (0.07–0.91)	0.85 (0.10–7.25)	.88
>20 Years	33	1.34 (0.89–2.02)	5	1.45 (0.58–3.63)	0.98 (0.36–2.64)	.96

NOTE. CI, confidence interval; OR, odds ratio.

[a] Mortality rate per 1000 person-years (95% CI), estimated from negative binomial regression to account for cluster randomization.

[b] Odds of mortality in those who received azithromycin treatment compared with those who did not, estimated from a negative binomial regression model adjusted for age group, sex, clinical trial arm, and the interaction between age group and azithromycin treatment.

association remained significant if those lost to follow up were treated as having died, treated as present for the duration of the study, or omitted. The relationship did not change when comparing younger children with older children (OR = 0.48 [95% CI, 0.18–1.28] for 1–2-year-old children [of whom 82.4% received antibiotics] and OR = 0.30 [95% CI, 0.10–0.93] for 3–5-year-old children [of whom 92.8% received antibiotics]). To assess the potential for bias, we assessed mortality in infants <1 year of age (none of whom were eligible for azithromycin treatment) who had siblings 1–5 years of age. Of the 597 infants who had 1 or more treated sibling, 24 died (19.5 deaths per 1000 person years [95% CI, 11.4–33.6]); of the 35 infants whose siblings all went untreated, 1 died (13.0 deaths per 1000 person years [95% CI, 1.8–92.3]; OR = 1.73 [95% CI, 0.21–14.05], by adjusted negative binomial regression).

Table 3. All-Cause and Infectious Mortality in 1–5-Year-Old Children from a Cohort of 24 Subkebeles in Rural Ethiopia, Comparing Individuals Who Received Azithromycin with Those Within Their Household Who Did Not

Model parameter	Odds ratio (95% CI)	*P*
All-cause mortality		
Primary explanatory variable		
Azithromycin (1–5 years old)	0.40 (0.16–0.96)	.04
Other covariates		
Azithromycin (6–10 years old)	1.86 (0.23–14.73)	.56
Azithromycin (11–20 years old)	1.68 (0.46–6.08)	.43
Azithromycin (>20 years old)	1.69 (0.91–3.15)	.10
Female sex	0.80 (0.62–1.02)	.07
Mortality attributed to infection		
Primary explanatory variable		
Azithromycin (1–5 years old)	0.35 (0.10–1.28)	.11
Other covariates		
Azithromycin (6–10 years old)	0.73 (0.07–7.44)	.79
Azithromycin (11–20 years old)	0.88 (0.06–12.56)	.93
Azithromycin (>20 years old)	1.06 (0.36–3.14)	.92
Female sex	1.01 (0.56–1.82)	.98

NOTE. Conditional logistic regression model predicting mortality, with individual azithromycin treatment coverage, sex, age group, and the interaction between azithromycin coverage and age group as explanatory variables, grouped by household. CI, confidence interval.

When comparing individuals with other members of their own household, single-dose azithromycin treatment was associated with reduced mortality in children 1–5 years of age (OR = 0.40 [95% CI, 0.16–0.96]; $P = .04$, by conditional logistic regression) (Table 3). The interaction between age and azithromycin treatment was significant ($P = .03$, by Wald test), indicating a differential association between azithromycin and mortality in different age groups. No statistically significant association between azithromycin treatment and mortality was observed in the other age groups (Table 3). In sensitivity analyses, mass azithromycin was still associated with reduced childhood mortality in conditional logistic regression models with age categorized by quartiles (OR = 0.41 in children 1–7 years of age [95% CI, 0.19–0.90]), by decade (OR = 0.41 in children 1–9 years of age [95% CI, 0.18–0.92]), or by a cubic spline (OR = 0.31 for children 1 year of age [95% CI, 0.10–0.93]).

Of the 250 individuals for whom a cause of death was specified, 10.0% (25 people) died from respiratory infection, 9.2% (23 people) died from diarrhea, 7.2% (18 people) died from malaria, 22.0% (55 people) died from accident, 31.6% (79 people) died from old age, and 20.0% died from other causes. Of the 28 children aged 1–5 years for whom a cause of death was specified, 53.6% died of an infectious cause. Estimated rates of mortality attributed to infection are shown in Table 2. A single

mass azithromycin treatment was associated with reduced infectious mortality in 1–5-year-old children (OR = 0.20 [95% CI, 0.07–0.58], $P = .003$, by adjusted negative binomial regression). Conditional logistic regression analyses were consistent with this finding, although identified infectious deaths were fewer in number, and the results did not achieve statistical significance (OR = 0.35 [95% CI, 0.10–1.28], $P = .11$) (Table 3).

DISCUSSION

We studied a large cohort of individuals from rural Ethiopia who were each offered a single dose of mass oral azithromycin for trachoma. Data were collected in a clinical trial setting, which provided detailed records of antibiotic coverage and a baseline and follow-up census. We compared 2-year mortality in individuals who did and those who did not receive azithromycin treatment. Compared with those who did not receive treatment, those 1–5 year old children who received azithromycin were significantly less likely to die from all causes and from infectious causes. Moreover, children 1–5 years of age who received azithromycin were less likely to die than were members of their own household who did not receive azithromycin, adjusting for age and sex.

We report a strong association between mass azithromycin and reduced childhood mortality (Table 2). We found no evidence that this relationship was due to bias in identification of deaths, because mass azithromycin of children 1–5 years of age was not associated with reduced mortality in their untreated infant siblings. However, because azithromycin treatment was not randomly allocated in this study, this association is subject to confounding by unmeasured factors. For example, a family's nonparticipation in the trachoma program may have been a function of other factors related to increased mortality, such as poverty or poor access to health services. We accounted for confounding at the household level by performing a conditional logistic regression analysis that estimated the association between azithromycin and mortality relative to members in the same household. This analysis confirmed a protective effect of azithromycin in 1–5-year-old children. Although the analysis removed the influence of confounding factors present at the household level, it is important to note that individual-level confounders other than age and sex are not addressed by our analysis and could still account for some or all of the observed association. However, residual confounding might be less of an issue for preschool-aged children, compared with older individuals, because many behavioral confounders for a preschool-aged child would likely be a function of the parents and household and not of the individual child. We acknowledge that the magnitude of association in this observational study was high—seemingly too high for a single antibiotic treatment. However, because most childhood deaths occur among the youngest children, it is likely that most of the childhood deaths in this cohort study occurred at the beginning of the study, when the children were youngest. We hypothesize that the magnitude of the association would have been similar had we performed a repeat census earlier in the study.

The plausibility of mass azithromycin treatments directly reducing childhood mortality is supported by several observations. First, azithromycin has efficacy as a treatment for respiratory infections, diarrhea, and malaria, which account for the majority of childhood deaths in Ethiopia [8, 9, 18–20]. Oral azithromycin has a long tissue half-life, which may reduce the burden of infectious organisms for weeks [6, 21]. Indeed, azithromycin treatments for trachoma have already been shown to reduce morbidity caused by fever, diarrhea, and malaria [7, 10, 11]. Mass azithromycin treatments may also prevent infections. For example, mass treatments reduce nasopharyngeal colonization with *Streptococcus pneumoniae*, which may decrease the risk for invasive pneumococcal disease [6]. Azithromycin is also effective for the prophylaxis of malaria, which could have played a role in this study, because the azithromycin was administered just prior to the rainy season [22]. Finally, the anti-inflammatory properties of azithromycin may modulate the host response to infection, resulting in milder and less frequently fatal disease [23].

We recognize several limitations in this observational study of a large cohort. Although the study had a large sample size, deaths were uncommon, and therefore the estimate of any protective effect had a relatively wide confidence interval. We performed abbreviated verbal autopsies on deceased individuals, at times many months after deaths occurred. The verbal autopsy technique is prone to misclassification errors, and the abbreviated verbal autopsy used in this study was unable to attribute a cause of death in 22% of deaths [24, 25]. However, given the lack of access to health care facilities in the study area, verbal autopsy was the only feasible way to estimate a cause of death. Individuals who were not treated with antibiotics were more likely to be lost to follow-up; if those lost to follow-up also had a higher risk for mortality, then the observed protective effect of antibiotics could have been stronger. We adjusted for age as a categorical variable. Differential antibiotic coverage and mortality rates within the age group could therefore account for some of the observed association. However, we found a similar relationship between azithromycin treatment and reduced mortality in younger children (1–2 years of age) and older children (3–5 years of age). Azithromycin distributions were not randomized in this study, and children who received treatment may be different from children who did not. For example, it is possible that ill children did not receive treatment and were also more likely to die. However, no individuals documented as missing azithromycin treatment due to illness died during this study. Although individual-level confounders could still account for some of the observed association, the use of the conditional logistic regression did remove any confounding present at the household level.

In this observational cohort study, receiving azithromycin treatment was associated with a decreased risk of all-cause mortality in preschool-aged children. This association could only partly be explained by bias at the household-level, because a conditional logistic regression found the protective effect to exist when individual deaths were matched against members of the same household. Our findings are plausibly explained by a direct protective effect of azithromycin against the organisms responsible for a majority of lethal childhood infections, although we cannot rule out an association due in part to individual-level bias in who presented for treatment. We note that azithromycin treatment was associated with an even greater protective effect against infectious mortality in preschool-aged children, which is an age group with an especially large burden of infectious mortality. The protective effect seen here lends support to a recent cluster-randomized trial that found reduced childhood mortality in communities randomized to mass azithromycin distributions, compared with control communities randomized to delayed treatment [13]. Future studies are needed to clarify the effect of mass azithromycin distributions on morbidity and mortality in developing areas of the world.

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