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Adult Mortality in a Randomized Trial of Mass Azithromycin for Trachoma

Jeremy D. Keenan, MD, MPH, **Paul M. Emerson, PhD**, **Bruce D. Gaynor, MD**, **Travis C. Porco, PhD, MPH**, and **Thomas M. Lietman, MD**
Francis I. Proctor Foundation (Drs Keenan, Gaynor, Porco, and Lietman), Department of Ophthalmology (Drs Keenan, Gaynor, Porco, and Lietman), Department of Epidemiology and Biostatistics (Drs Porco and Lietman), and Institute for Global Health (Dr Lietman), University of California, San Francisco; and the Carter Center, Atlanta, Georgia (Dr Emerson)

Annual mass azithromycin treatments are provided to entire communities to clear the ocular strains of *Chlamydia trachomatis* that cause blinding trachoma. Mass treatments reduce the community burden of ocular chlamydia and have proven efficacious in community-randomized trials.[1] Since 1999, more than 150 million doses of azithromycin have been distributed for trachoma worldwide.[2]

Mass azithromycin distributions are directed at clearing ocular chlamydia but may have other effects. For example, in the Trachoma Amelioration in Northern Amhara (TANA) trial, we found that mass azithromycin distributions reduced childhood mortality.[3] In contrast, a recent observational study suggested that azithromycin use may cause sudden death in adults.[4] This finding could have major implications for trachoma elimination efforts. In our previous report, an intention-to-treat analysis found no evidence of increased mortality among individuals older than 9 years.[3] However, in light of the recent observational study, we thought it worthwhile to reassess our data to determine the mortality rates and causes of death in an older subgroup of individuals and to compare mortality in individuals who received azithromycin with that in those who did not.

Methods

TANA was a National Institutes of Health–funded, cluster-randomized trial conducted in Ethiopia from 2006 through 2009 (clinicaltrials.gov Identifier: NCT00322972). The design

Correspondence: Dr Keenan, Box 0412, 513 Parnassus Ave, Med Sci S334, University of California, San Francisco, San Francisco, CA 94143-0412 (jeremy.keenan@ucsf.edu)..

Author Contributions: Drs Keenan and Lietman had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Emerson, Gaynor, and Lietman. *Acquisition of data:* Lietman. *Analysis and interpretation of data:* Keenan, Emerson, Porco, and Lietman. *Drafting of the manuscript:* Keenan. Critical revision of the manuscript for important intellectual content: Emerson, Gaynor, Porco, and Lietman. *Statistical analysis:* Keenan and Porco. *Obtained funding:* Emerson and Lietman. *Administrative, technical, and material support:* Emerson and Gaynor. *Study supervision:* Lietman.

Conflict of Interest Disclosures: None reported.

Additional Contributions: Donald Everett, MA (National Eye Institute, Bethesda, Maryland) was the program officer for the clinical trial. The data safety and monitoring committee included William Barlow, PhD (University of Washington, Seattle; chair), Donald Everett, MA (National Eye Institute, Bethesda, Maryland), Larry Schwab, MD (International Eye Foundation, Kensington, Maryland), Arthur Reingold, MD (University of California, Berkeley), and Serge Resnikoff, MD (Brien Holden Vision Institute, Sydney, Australia; and International Health and Development, Geneva, Switzerland). These individuals received reimbursement for the expenses associated with their work on this article but otherwise did not receive compensation. The Goncha woreda health office, the Amhara Regional Health Bureau, and the Ethiopian Ministry of Health allowed and organized health workers to be employed by the study as data collectors.

and implementation of the trial, including the prespecified mortality outcome, have been described previously.[3] Herein we report results from the following 4 study arms, each composed of 12 randomly selected "subkebeles" (government-defined units): (A) annual or (B) biannual directly observed mass distribution of azithromycin to persons 1 year or older, (C) quarterly mass distribution of azithromycin to children aged 1 to 9 years, and (D) no treatment. Mortality was defined as presence at the baseline census and absence at the 12-month census due to death. For each death, household members were asked about the cause of death.

In an intention-to-treat analysis, we compared communities where individuals aged at least 10 years received azithromycin (arms A and B) with communities where this age group did not receive treatment (arms C and D). We used negative binomial regression to calculate age-stratified mortality rates and mixed effects logistic regression to compare the 2 groups, with subkebele as a random effect. As a second independent analysis, we treated arms A and B as a cohort and compared mortality in persons who received any dose(s) of azithromycin relative to those who received no doses. This analysis could be biased if the baseline health status differed between participants and nonparticipants.[5] Therefore, we performed a conditional logistic regression grouped on household, which removes all household-level confounding. We included sex and the interaction of age stratum by antibiotic treatment to account for individual-level confounding, and we report the odds ratio for the 30-years-and-older group. The TANA trial provided 80% power to detect a 0.7% reduction in the mortality rate of participants aged at least 30 years, assuming a mortality rate of 10 per 1000 person-years, 350 persons aged at least 30 years per subkebele, and a variance inflation factor of 2. Statistical analyses were performed with Stata software, version 10.1 (StataCorp).

Ethical approval for this study was obtained from the University of California, San Francisco Committee for Human Research, the Emory University Institutional Review Board, and the Ethiopian Science and Technology Commission.

Results

Baseline characteristics of the 4 treatment groups were similar (reported elsewhere).[3] Of 8217 persons aged at least 30 years who were present at baseline in arms A and B, 7252 (88.3%) received azithromycin during the year. Of 8320 persons aged at least 30 years who were present at baseline in arms C and D, 109 (1.3%) mistakenly received azithromycin. By the 12-month census, 166 individuals aged 30 years or older had died. Although we were unable to detect a significant difference, mortality was lower in arms A and B than in arms C and D (odds ratio, 0.91 [95% CI, 0.63–1.30]). Causes of death were similar in the 2 groups (Table).

A separate analysis of arms A and B found no difference in mortality between individuals aged at least 30 years who received azithromycin and those who did not, although those who received azithromycin had a lower risk of mortality than did members of the same household who never received the drug (adjusted odds ratio, 0.59 [95% CI, 0.17–2.00], conditional logistic regression).

Comment

We were unable to detect an association between azithromycin use and increased risk of all-cause or cause-specific mortality among adults in this study; to the contrary, individuals treated with azithromycin had a lower rate of mortality compared with those who did not receive treatment. This lack of an association is in contradiction to a previous report that

found an increased risk of sudden death in patients treated with azithromycin.[4] The 2 studies are clearly different. Ours was a randomized clinical trial of healthy adults in Ethiopia, whereas theirs was a propensity score-adjusted observational study of hospitalized patients in Tennessee. Other studies have demonstrated that mass azithromycin distributions for trachoma have collateral benefits (eg, decrease in childhood respiratory infections, diarrhea, malaria, and mortality) and potential harms (eg, transient macrolide resistance).[3,6–8] An argument could be made for trachoma programs to stop distributing azithromycin to adults, especially since the greatest burden of ocular chlamydia is found in children, and treatment of children provides some degree of indirect herd protection for adults.[9] However, our findings provide no evidence to support discontinuation of mass distributions to entire communities for trachoma control, suggesting that if anything, benefit outweighs harm.

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References

1. Chidambaram JD, Alemayehu W, Melese M, et al. Effect of a single mass antibiotic distribution on the prevalence of infectious trachoma. JAMA. 2006; 295(10):1142–1146. [PubMed: 16522834]
2. Haddad D. Ten years left to eliminate blinding trachoma. Community Eye Health. 2010; 23(73):38. [PubMed: 21119924]
3. Porco TC, Gebre T, Ayele B, et al. Effect of mass distribution of azithromycin for trachoma control on overall mortality in Ethiopian children: a randomized trial. JAMA. 2009; 302(9):962–968. [PubMed: 19724043]
4. Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the risk of cardiovascular death. N Engl J Med. 2012; 366(20):1881–1890. [PubMed: 22591294]
5. Sommer A, Zeger SL. On estimating efficacy from clinical trials. Stat Med. 1991; 10(1):45–52. [PubMed: 2006355]
6. Coles CL, Levens J, Seidman JC, Mkocha H, Munoz B, West S. Mass distribution of azithromycin for trachoma control is associated with short-term reduction in risk of acute lower respiratory infection in young children. Pediatr Infect Dis J. 2012; 31(4):341–346. [PubMed: 22173140]
7. Skalet AH, Cevallos V, Ayele B, et al. Antibiotic selection pressure and macrolide resistance in nasopharyngeal *Streptococcus pneumoniae:* a cluster-randomized clinical trial. PLoS Med. 2010; 7(12):e1000377. [PubMed: 21179434]
8. Coles CL, Seidman JC, Levens J, Mkocha H, Munoz B, West S. Association of mass treatment with azithromycin in trachoma-endemic communities with short-term reduced risk of diarrhea in young children. Am J Trop Med Hyg. 2011; 85(4):691–696. [PubMed: 21976574]
9. House JI, Ayele B, Porco TC, et al. Assessment of herd protection against trachoma due to repeated mass antibiotic distributions: a cluster-randomised trial. Lancet. 2009; 373(9669):1111–1118. [PubMed: 19329003]

Table

Age-Stratified Mortality Rates in Individuals Randomized to Mass Azithromycin Treatment or No Treatment

Cause of Mortality by Age Group	Mortality Rate per 1000 Person-Years (95% CI) [Deaths][a]			
	Azithromycin (A+B)[b]	No Azithromycin (C+D)[C]	Odds Ratio (95% CI)[d]	*P* Value
Age 10–29 y				
All causes	1.42 (0.91–2.20) [19]	2.04 (1.30–3.23) [28]	0.69 (0.37–1.29)	.24
Infection	0.15 (0.04–0.59) [2]	0 (0–0.26) [0]	4.92 (0.24–102.5)	.30
Unintentional injury	0 (0–0.26) [0]	0.08 (0.01–0.50) [1]	0.33 (0.01–8.05)	.50
Other	1.27 (0.82–1.96) [17]	1.99 (1.27–3.12) [27]	0.63 (0.33–1.19)	.15
Age ≥30 y				
All causes	9.69 (7.19–13.1) [79]	10.7 (8.71–13.3) [87]	0.89 (0.62–1.29)	.55
Infection	1.19 (0.54–2.60) [9]	1.24 (0.66–2.32) [10]	0.91 (0.33–2.47)	.85
Unintentional injury	2.00 (1.25–3.19) [16]	2.20 (1.20–4.03) [17]	0.94 (0.44–1.99)	.87
Other	6.49 (4.53–9.30) [54]	7.41 (5.86–9.38) [60]	0.90 (0.59–1.35)	.60

[a] Mortality rates were estimated by means of negative binomial regression assuming that deaths and migration occurred at the midpoint of the census; for strata with zero deaths, binomial exact 97.5% confidence intervals were calculated.

[b] A, Annual directly observed mass distribution of azithromycin to persons 1 year or older; B, biannual directly observed mass distribution of azithromycin to persons 1 year or older. In arms A and B, 11 977 of 14115 persons (84.9%) aged 10 to 29 years and 7252 of 8217 persons (88.3%) 30 years or older received azithromycin.

[C] C, Quarterly directly observed mass distribution of azithromycin to children aged 1 to 9 years; D, no treatment. In arms C and D, 757 of 13996 persons (5.4%) aged 10 to 29 years and 109 of 8320 persons (1.3%) 30 years or older mistakenly received azithromycin.

[d] Estimated with mixed effects logistic regression using subkebele as a random effect, except for deaths due to infection or unintentional injury in the 10 to 29 year age stratum, which were estimated by means of the Firth penalized maximum likelihood logistic regression.