ORIGINAL ARTICLE

Azithromycin to Reduce Childhood Mortality in Sub-Saharan Africa

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ABSTRACT

BACKGROUND
We hypothesized that mass distribution of a broad-spectrum antibiotic agent to preschool children would reduce mortality in areas of sub-Saharan Africa that are currently far from meeting the Sustainable Development Goals of the United Nations.

METHODS
In this cluster-randomized trial, we assigned communities in Malawi, Niger, and Tanzania to four twice-yearly mass distributions of either oral azithromycin (approximately 20 mg per kilogram of body weight) or placebo. Children 1 to 59 months of age were identified in twice-yearly censuses and were offered participation in the trial. Vital status was determined at subsequent censuses. The primary outcome was aggregate all-cause mortality; country-specific rates were assessed in prespecified subgroup analyses.

RESULTS
A total of 1533 communities underwent randomization, 190,238 children were identified in the census at baseline, and 323,302 person-years were monitored. The mean (±SD) azithromycin and placebo coverage over the four twice-yearly distributions was 90.4±10.4%. The overall annual mortality rate was 14.6 deaths per 1000 person-years in communities that received azithromycin (9.1 in Malawi, 22.5 in Niger, and 5.4 in Tanzania) and 16.5 deaths per 1000 person-years in communities that received placebo (9.6 in Malawi, 27.5 in Niger, and 5.5 in Tanzania). Mortality was 13.5% lower overall (95% confidence interval [CI], 6.7 to 19.8) in communities that received azithromycin than in communities that received placebo (P<0.001); the rate was 5.7% lower in Malawi (95% CI, −9.7 to 18.9), 18.1% lower in Niger (95% CI, 10.0 to 25.5), and 3.4% lower in Tanzania (95% CI, −21.2 to 23.0). Children in the age group of 1 to 5 months had the greatest effect from azithromycin (24.9% lower mortality than that with placebo; 95% CI, 10.6 to 37.0). Serious adverse events occurring within a week after administration of the trial drug or placebo were uncommon, and the rate did not differ significantly between the groups. Evaluation of selection for antibiotic resistance is ongoing.

CONCLUSIONS
Among postneonatal, preschool children in sub-Saharan Africa, childhood mortality was lower in communities randomly assigned to mass distribution of azithromycin than in those assigned to placebo, with the largest effect seen in Niger. Any implementation of a policy of mass distribution would need to strongly consider the potential effect of such a strategy on antibiotic resistance. (Funded by the Bill and Melinda Gates Foundation; MORDOR ClinicalTrials.gov number, NCT02047981.)

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*A complete list of investigators in the MORDOR Study Group is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

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Trachoma-control programs have distributed more than 600 million doses of oral azithromycin in an effort to eliminate the ocular strains of chlamydia that cause the disease.[1,2] Azithromycin has been effective against trachoma, although it has caused gastrointestinal side effects and selected for macrolide-resistant strains of *Streptococcus pneumoniae* and *Escherichia coli*.[3-8] Investigators have also noted possible benefits of azithromycin for prevention of a number of infectious diseases including malaria, infectious diarrhea, and pneumonia.[9-14] The results of a case–control study and a cluster-randomized trial in an area of Ethiopia in which trachoma is endemic suggested that mass distribution of azithromycin might reduce childhood mortality.[15,16] Some experts believed that a mortality benefit was, indeed, possible, although it would probably be smaller in magnitude than what was found in these studies.[17]

We tested the hypothesis that twice-yearly mass distributions of oral azithromycin would reduce mortality in children 1 to 59 months of age. The trial was performed in three geographically distinct areas: Malawi in southern Africa, Niger in West Africa, and Tanzania in East Africa. Azithromycin affects transmissible diseases, so the treatment of one person might have an effect on others in the same community. Thus, randomization and intervention were conducted at the community level, and inferences of efficacy were made at the community level. Since death is a relatively rare event even in these settings, a large trial population was required. Therefore, we adopted a trial strategy with a straightforward intervention and primary outcome.[18]

METHODS

ELIGIBILITY

MORDOR (Macrolides Oraux pour Réduire les Décès avec un Oeil sur la Résistance) was a cluster-randomized trial conducted in the Malawian district of Mangochi, in the Nigerien districts of Boboye and Loga, and in the Tanzanian districts of Kilosa and Gairo, with communities as the unit of randomization. The community that served as the randomization unit was a health surveillance assistance area in Malawi, a *grappe* (i.e., a cluster of households representing the smallest government health unit) in Niger, and a hamlet in Tanzania. None of the districts were eligible for mass distributions of azithromycin for trachoma on the basis of the most recent mapping, and none of the children who participated in the trial had previously received azithromycin. Enrollment was based on census information available before the trial. Communities with a population between 200 and 2000 inhabitants on the most recent census were eligible for enrollment (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Communities remained in the trial even if the population drifted out of this range. All children 1 to 59 months of age (truncated to month) who weighed at least 3800 g were eligible to receive azithromycin or placebo.

RANDOMIZATION AND MASKING

Lists of communities from the most recent pretrial census were submitted to the data coordinating center at the University of California, San Francisco (UCSF). For each country, communities were randomly assigned in equal proportions to 1 of 10 letters, with 5 letters coded for azithromycin and 5 for placebo (more information is provided in the statistical analysis plan in the protocol, available at NEJM.org). Randomization was performed with the sample function in R software, version 3.1 (R Foundation for Statistical Computing). Only key trial personnel were aware of which letters corresponded to each group. Participants, observers, investigators, and data-cleaning team members were unaware of the group assignments. Centralized randomization and simultaneous assignment of communities facilitated complete concealment of the assignments. The placebo contained the vehicle of the oral azithromycin suspension and was bottled and labeled identically to azithromycin. Both placebo and azithromycin were donated by Pfizer, which reviewed the protocol but had no other role in the trial.

CENSUS

A house-to-house census was performed during five prescribed 6-month periods, with allowance for a 2-month grace period for the initial census. At the initial census, all households in the community were recorded in a custom-built mobile application (Conexus); the name of the head of household and the global positioning system coordinates were used to facilitate location of the household for the following census. All children

1 to 59 months of age in the household were identified. Pregnant women and children younger than 1 month of age were also documented in anticipation of the next census. At follow-up censuses, the vital status (alive, dead, or unknown) and residence (living in community, moved outside community, or unknown) were recorded for the children who had been present in the previous census records. Pregnant women and children younger than 1 month of age were documented, and children 1 to 59 months of age who had moved into the community after the previous census were also documented and were offered participation. Census data were collected in communities in the same general order throughout the trial. Data were uploaded to the Salesforce cloud database service (Salesforce). Data cleaning was performed with the use of the Salesforce platform; Stata software, version 13.1 (Statacorp); and R software.

INTERVENTION

Each child 1 to 59 months of age at the time of the census was offered a single directly observed dose of oral azithromycin or placebo (according to the randomization of their community). Children were given a volume of suspension corresponding to at least 20 mg per kilogram of body weight, calculated with the use of a height stick (see the protocol), in accordance with the country's trachoma program guidelines, or by weight for children unable to stand. Children who were known to be allergic to macrolides were not given azithromycin or placebo. Azithromycin or placebo was administered at the time of the census or during additional visits in an attempt to achieve at least 80% coverage. Administration of trial medication or placebo was documented in the mobile application for each child, and community coverage was calculated relative to the census. The parents or guardians of the children and the local health posts were instructed to contact a village representative regarding any adverse events noted within 7 days after administration of azithromycin or placebo; the village representative reported the events to the site coordinator, who in turn reported the events to UCSF.

PRIMARY OUTCOME

The prespecified primary outcome was the community-level, aggregate, three-country mortality rate determined with the use of data from twice-yearly censuses. Each intercensal period was analyzed separately, with a death counted only when a child was recorded as having been alive and living in the household at the time of one census and recorded as having died while residing in the community by the time of the next census. By design, no attempt was made to track down a child's status after the child moved out of the community. Person-time at risk was measured as the days between consecutive censuses; children who moved, died, or had an unknown follow-up status contributed to one half of the intercensal period. All children documented as being alive and residing in the household at the time of the initial census of each intercensal period were included in the analysis. No changes to trial outcomes were made after the trial had begun.

SUBGROUP ANALYSES

Mortality rates were assessed according to country site and age group. An abbreviated version of the 2007 World Health Organization (WHO) verbal autopsy questionnaire for children 4 weeks to 14 years of age was used to collect data for verbal autopsies.[19] Causes of death were assigned according to an algorithm based on a published verbal autopsy hierarchy.[20]

TRIAL OVERSIGHT

Approval for the trial was obtained from the ethics committees at the College of Medicine, University of Malawi, Blantyre; the Niger Ministry of Health; the Tanzanian National Institute for Medical Research; the London School of Hygiene and Tropical Medicine; the UCSF Committee on Human Research; Emory University; and Johns Hopkins University School of Medicine. Oral informed consent was obtained in Malawi and Niger, and written informed consent was obtained in Tanzania. The trial was conducted in accordance with the principles of the Declaration of Helsinki. No incentives were offered for participation. All children in the communities in Niger were offered treatment with azithromycin at the conclusion of the trial. By design, communities in Malawi were entered into the country's trachoma-control program, even though prior district-level data had not met the criteria for mass distribution.

A data and safety monitoring committee provided oversight. The members of the steering committee (see the Supplementary Appendix), who were also investigators in the trial, designed the trial and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. Full details of the trial design and analyses are provided in the protocol and the statistical analysis plan. The last author wrote the initial draft of the manuscript. All the authors contributed to subsequent revisions and agreed to submit the manuscript for publication.

STATISTICAL ANALYSIS

We estimated that the inclusion of 620 communities per country would provide at least 80% power to detect 10% lower all-cause mortality overall with azithromycin than with placebo. Specifically, we assumed that mortality rates would be between 14 and 20 deaths per 1000 person-years in the placebo group, that the average community sizes would be 600 to 799 people (of whom 16.7 to 19.0% would be children 1 to 59 months of age), that coefficients of variation would be between 0.40 and 0.51, and that the loss to follow-up would be 10%.

The prespecified primary analysis was negative binomial regression of the number of deaths per community, with treatment group and country as predictors and total person-time at risk as an offset. All three country sites contributed to the primary outcome. Hypothesis testing was two-sided, with an overall alpha level of 0.05 for the interim and final analyses. P values were determined with Monte Carlo permutation testing (10,000 replications). An interim efficacy analysis after the 12-month census was designed to spend 0.001 of the overall alpha level, with an alpha level of 0.049 reserved for the primary 24-month analysis. Community-level clustering was taken into account by the dispersion parameter in the negative binomial regression model. Prespecified subgroup analyses included negative binomial regression of community-level mortality rates according to country, age group, and intercensal period (details are provided in the statistical analysis plan in the protocol). A sample of 250 verbal autopsies were randomly selected from each country site and were compared with the use of the chi-square statistic, with clustering taken into account by community-level permutation. All statistical analyses were conducted with R software.

Figure 1 (facing page). Enrollment, Randomization, and Treatment.

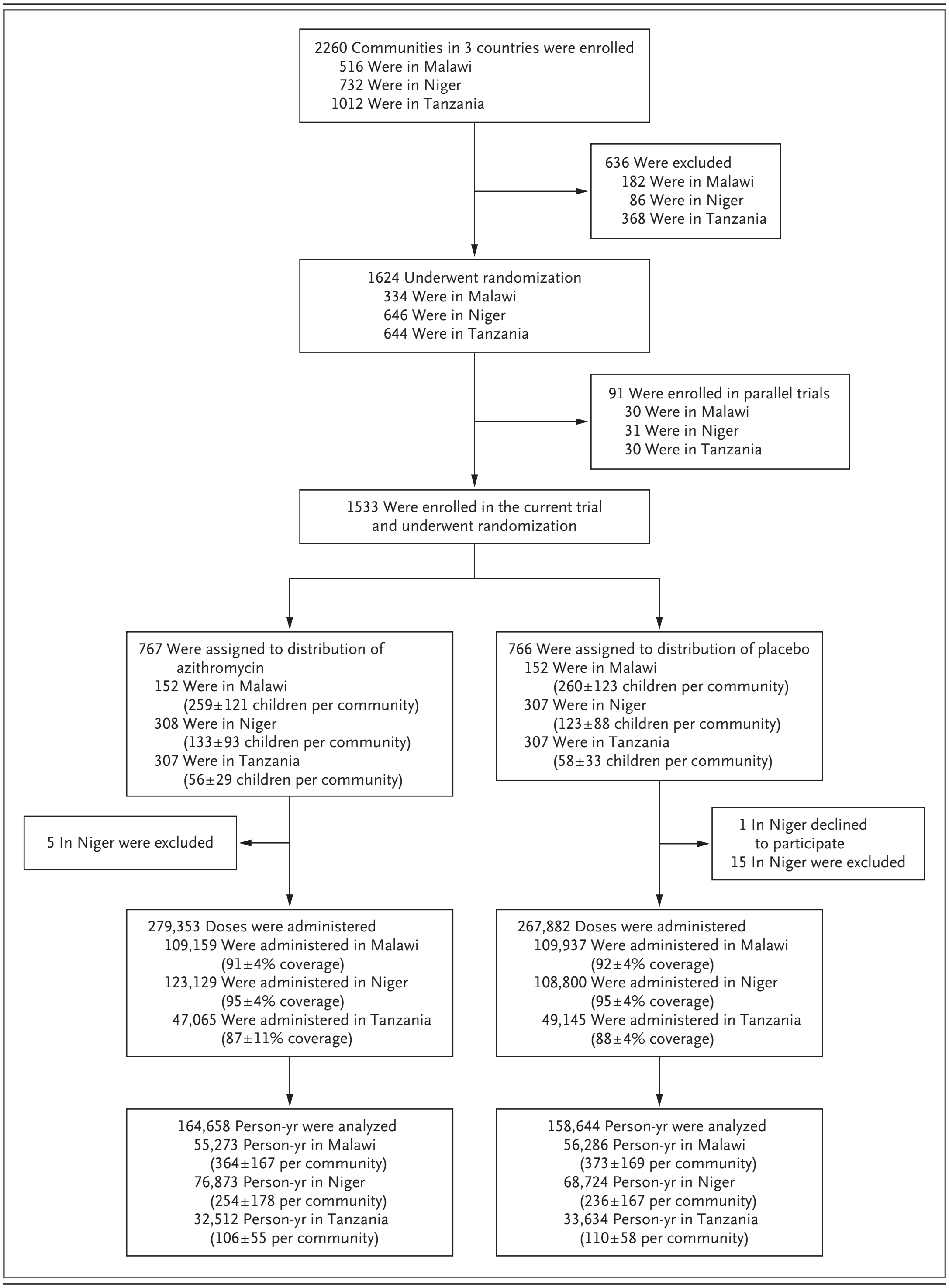
Communities in the three countries were enrolled and randomly assigned to distribution of azithromycin or placebo; censuses were carried out twice yearly for a total of five times over the course of the trial. Children 1 to 59 months of age at the time of a census were eligible to receive oral azithromycin or placebo, according to the randomization of their community. Enrollment criteria were identical for all three sites. Distribution by randomization unit is expressed as the estimated mean (±SD) for the population. Communities were excluded before randomization primarily because they had a population on the most recent census of fewer than 200 or more than 2000 persons or because the communities were not required for the target sample size. Communities were excluded after randomization because of errors on the most recent census, including duplicate communities with different spellings, nonexistent communities, or satellite communities that had become indistinguishable from larger neighboring communities.

RESULTS

PARTICIPATING COMMUNITIES

A total of 1624 communities were eligible for inclusion in the trial on the basis of the most recent census (Fig. 1). A random selection of 1533 communities were included in the current trial, and the remaining 91 were enrolled in smaller parallel trials at each site, in which additional microbiologic, anthropometric, and adverse-event data were collected. In Niger, 1 community declined to participate and 20 were excluded because of census inaccuracies. No randomization units were lost to follow-up after the initial census.

Census periods started in December 2014, August 2015, February 2016, August 2016, and February 2017. At the baseline census, 97,047 children were enrolled in the azithromycin group and 93,191 in the placebo group (Table 1). Over the five census visits, 323,302 person-years were monitored, including 111,559 person-years in Malawi, 145,597 person-years in Niger, and 66,146 person-years in Tanzania. To validate data collection, another census of a random subset of at least 200 households was conducted later during the same census period by an independent field team; most children who were counted in these later censuses had been counted in the earlier census: 95% (257 of 271) in Malawi, 92% (286 of



310) in Niger, and 95% (4544 of 4791) in Tanzania. Azithromycin was administered to a mean (±SD) of 90.3±10.6% of the targeted population, and placebo was administered to 90.4±10.1% (see the Supplementary Appendix). The main reason that a child did not receive azithromycin or placebo was that the child was away from the household at the time of the trial visit.

Table 1. Baseline Characteristics of the Communities and Participants in the Azithromycin and Placebo Groups.*

Characteristic	All Countries		Malawi		Niger		Tanzania	
	Azithromycin	Placebo	Azithromycin	Placebo	Azithromycin	Placebo	Azithromycin	Placebo
No. of communities	762	750	152	152	303	291	307	307
No. of children	97,047	93,191	39,386	39,534	40,345	35,747	17,316	17,910
No. of children per community	171±126	169±128	259±121	260±123	133±93	123±88	56±29	58±33
Male sex (%)	50.7	50.6	50.2	50.0	51.2	51.4	50.5	50.6
Age group (%)								
1–5 mo	7.4	7.4	7.0	6.9	6.8	6.9	9.4	9.2
6–11 mo	13.2	13.2	12.3	12.3	13.5	13.6	14.5	14.5
12–23 mo	19.1	19.2	20.5	20.2	17.0	16.8	21.0	21.8
24–59 mo	60.4	60.2	60.2	60.6	62.8	62.7	55.1	54.5

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding.

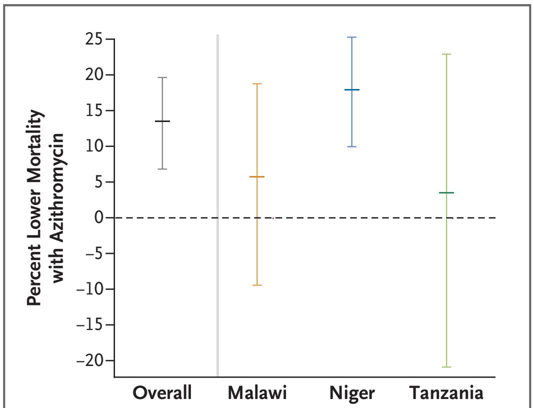


Figure 2. Efficacy of Azithromycin Overall and by Country.
Shown is the estimated percent lower mortality with twice-yearly distributions of oral azithromycin than with placebo. I bars indicate 95% confidence intervals.

PRIMARY RESULTS

The results of a 12-month interim analysis for efficacy did not meet the prespecified criterion for early stopping, which was a P value of less than 0.001 for the difference between groups. At the end of the trial, the annual mortality rate for eligible children in the three countries combined was 14.6 deaths per 1000 person-years in communities that received azithromycin (9.1 per 1000 person-years in Malawi, 22.5 in Niger, and 5.4 in Tanzania) and 16.5 deaths per 1000 person-years in communities that received placebo (9.6 per 1000 person-years in Malawi, 27.5 in Niger, and 5.5 in Tanzania). Community-level, intention-to-treat analysis showed that over all four intercensal periods, mortality was 13.5% lower overall (95% confidence interval [CI], 6.7 to 19.8) in the azithromycin group than in the placebo group (P<0.001). The proportion of children whose census status was recorded as moved or unknown did not differ significantly between the groups (P=0.71 and P=0.36, respectively).

SUBGROUP RESULTS

Mortality rates were 5.7% lower (95% CI, −9.7 to 18.9) in the azithromycin group than in the placebo group in Malawi (P=0.45), 18.1% lower (95% CI, 10.0 to 25.5) in Niger (P<0.001), and 3.4% lower (95% CI, −21.2 to 23.0) in Tanzania (P=0.77) (Fig. 2). Children in the youngest age group (1 to 5 months of age) had the highest overall mortality and the largest observed difference in mortality with azithromycin as compared with placebo (24.9% lower with azithromycin; 95% CI, 10.6 to 37.0; P=0.001) (Fig. 3). In the first period, mortality was 17.3 per 1000 person-years in the communities assigned to placebo and 16.1 per 1000 person-years in the communities assigned to azithromycin (an estimated 7.3% lower mortality with azithromycin; 95% CI, −5.9 to 18.8; P=0.26). In the last period, mortality was 16.1 per 1000 person-years in the communities assigned to placebo and 13.1 per 1000 person-years in the communities assigned to azithromy-

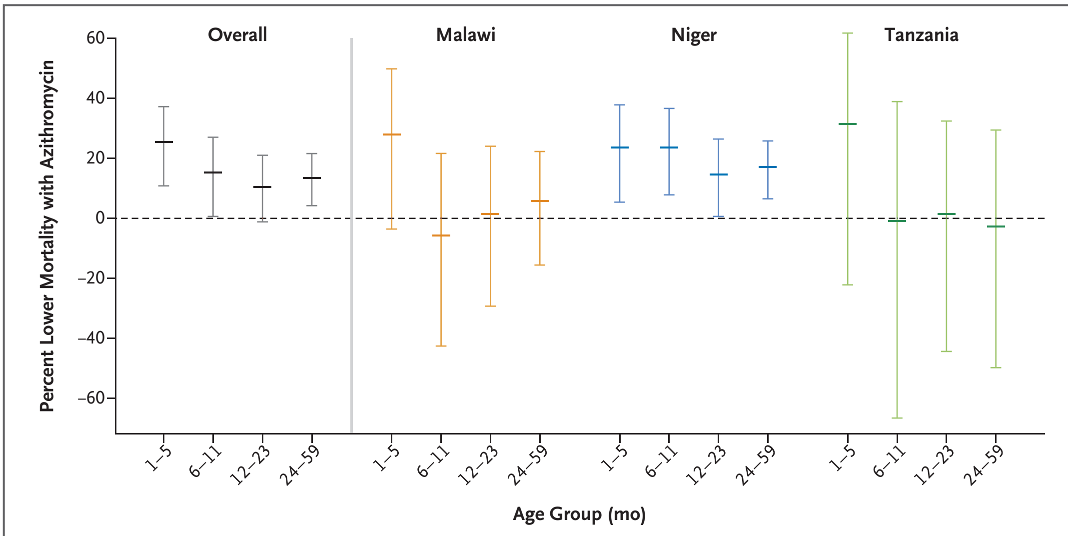


Figure 3. Efficacy of Azithromycin by Age Group.

Shown is the estimated percent lower mortality with twice-yearly distributions of oral azithromycin than with placebo, according to age group at the time of treatment. Younger children had the greatest benefit in all three countries. I bars indicate 95% confidence intervals.

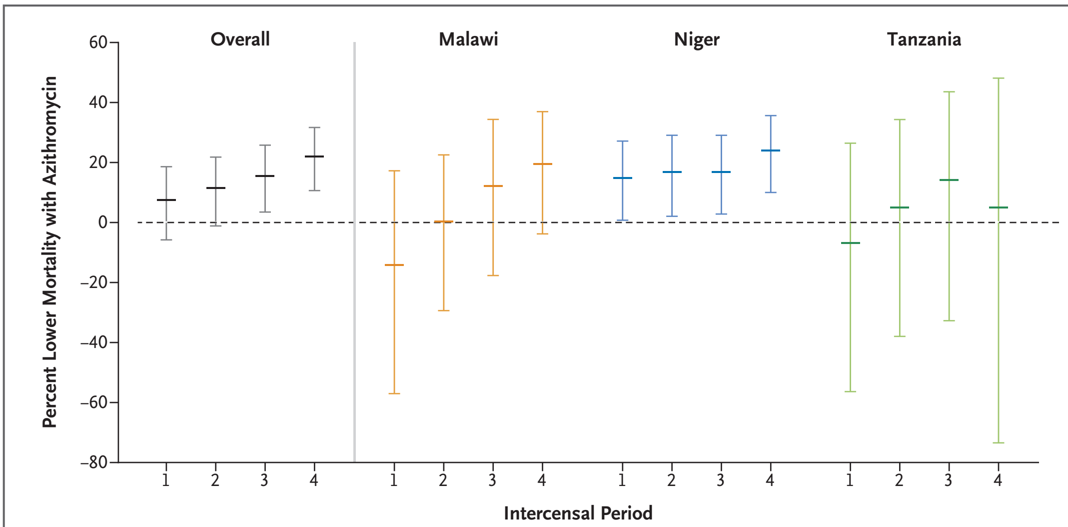


Figure 4. Efficacy of Azithromycin over Time.

Shown is the estimated percent lower mortality with twice-yearly distributions of oral azithromycin than with placebo over each of the four 6-month time periods. The aggregate efficacy of azithromycin as compared with placebo increased in each progressive time period. I bars indicate 95% confidence intervals.

cin (22.0% lower mortality; 95% CI, 10.6 to 31.9; P<0.001) (Fig. 4). Efficacy did not differ significantly between the two groups by country (P=0.17), age group (P=0.20), treatment period (P=0.09), or treatment coverage (P=0.34).

Causes of Death

In a random sample of 250 verbal autopsies from each of the three sites, we estimated that 41% of the deaths were due to malaria, 18% to diarrhea or dysentery, and 12% to pneumonia (see the

Supplementary Appendix). Causes of death differed significantly among the countries (P<0.001), with relatively more deaths attributed to malaria in Niger and more to pneumonia in Tanzania.

Adverse Events

Trial personnel were notified of 20 hospitalizations and life-threatening illnesses (see the Supplementary Appendix). Medical review was unable to determine whether any serious adverse event was caused by azithromycin. Nonserious adverse events were difficult to detect in the context of this trial, and they were reported less frequently than serious adverse events. No assessment of antimicrobial resistance was made in the communities that participated in the trial.

Discussion

In a trial involving postneonatal, preschool children in sub-Saharan Africa, all-cause mortality was significantly lower, by approximately 14%, among children who received a twice-yearly dose of oral azithromycin than among children who received placebo. The highest number of deaths and the largest observed effect was seen in Niger, in which mortality was 18% lower with azithromycin than with placebo. In subgroup analyses, significantly lower mortality with azithromycin than with placebo was observed only in Niger. The overall 14% effect was less than that seen in a previous case–control study and in a cluster-randomized trial in Ethiopia, but it was in line with the 18% effect that a group of experts had anticipated in a poll conducted before this trial.[15-17]

Azithromycin was most effective among children 1 to 5 months of age, preventing 1 of 4 deaths expected among children in this age group. The Food and Drug Administration has not approved azithromycin for children in this age group, and the WHO does not currently recommend including them in distributions to control trachoma.[21] However, the Centers for Disease Control and Prevention does recommend oral azithromycin for all ages for the treatment and prophylaxis of pertussis.[22] Any plan for mass distribution to children 1 month of age or younger would need to consider the risk of inducing infantile hypertrophic pyloric stenosis.[23-25]

This trial did not investigate the mechanism by which azithromycin reduced mortality. Before the trial, experts thought that a protective effect would most likely be due to reductions in respiratory infections, diarrhea, and malaria (in that order).[17] Such a hypothesis seems reasonable, given the activity of azithromycin against bacterial pathogens of the lungs and gastrointestinal tract and against the *Plasmodium falciparum* apicoplast. Further study will be necessary to identify the mechanism by which azithromycin prevents death. Investigation is already under way. Smaller parallel trials at each trial site collected additional data from detailed microbiologic, anthropometric, and adverse-event assessments. Inferences from these smaller trials will be directly applicable to the mortality result because the communities were chosen at random from the same pool as the parent trial. Azithromycin has been linked to death from cardiac causes in adults, although results of studies are mixed and may not be relevant to children in sub-Saharan Africa.[26-30] In this community-based trial, and even the more detailed parallel studies, QT intervals could not be monitored, as would be possible in a hospital-based setting.[28]

Nonspecific use of antibiotics is discouraged because of concern about antibiotic resistance. Repeated mass distributions of azithromycin for trachoma control select for macrolide resistance in nasopharyngeal *S. pneumoniae* and rectal *E. coli*.[6-8,31,32] Resistance emerging during mass azithromycin distributions could curb or even reverse any potential benefit with respect to mortality. We did not observe such a waning effect on mortality in this trial — in fact, the observed effect increased from 7% to 22% over the four twice-yearly intercensal periods. Nonetheless, longer follow-up is warranted to determine whether the mortality effect observed in the current trial changes with subsequent rounds of treatment.

The trial had several limitations. First, given the design, little information was collected on each individual child and community. Second, deaths were determined by consecutive censuses. Children who were born after one census and died before the next census did not contribute to either the number of deaths or the person-time at risk for the primary outcome. Secondary analyses may reveal whether these children benefited from living in a community treated with azithromycin even if they were not born in time to be included in community treatment. Third, no effort was made to follow children after they moved. Death rates may have differed among children who moved or had an unknown census status. Fourth, with twice-yearly distributions, a child's first treatment might not have been administered until 7 months of age. Supplementary treatments given to infants during a scheduled vaccination visit to a health clinic could potentially add benefit. Fifth, although mortality is seasonal, for logistic reasons communities were treated in a rolling fashion over each 6-month period. Secondary analyses may reveal whether the drug was particularly effective in certain seasons. Finally, although the trial was performed in three geographically diverse sites, the results may not be generalizable outside these districts. Subgroup analyses confirmed a significantly lower rate with azithromycin than with placebo in only one of the three sites.

Across three sites in sub-Saharan Africa, childhood mortality was significantly lower among children who received two doses of oral azithromycin per year than among those who received placebo. The largest effect was found in Niger, which has one of the highest child mortality rates in the world. Further investigation is required to identify specific mechanisms by which azithromycin reduced mortality. Any policy that recommends mass distribution of oral azithromycin to address childhood mortality would need to consider not only cost but also the risk of side effects, especially the potential for the induction or amplification of antibiotic resistance.[33]

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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