ORIGINAL ARTICLE

Azithromycin during Routine Well-Infant Visits to Prevent Death

Ali Sié, M.D., Ph.D., Mamadou Ouattara, M.D., Mamadou Bountogo, M.D., Valentin Boudo, M.S., Thierry Ouedraogo, Ph.D., Guillaume Compaoré, M.D., Clarisse Dah, M.D., Cheik Bagagnan, M.S., Elodie Lebas, R.N., Huiyu Hu, M.S.P.H., Jessica Rice, M.P.H., Travis C. Porco, Ph.D., M.P.H., Benjamin F. Arnold, Ph.D., M.P.H., Thomas M. Lietman, M.D., and Catherine E. Oldenburg, Sc.D., M.P.H.

ABSTRACT

BACKGROUND

Mass distribution of azithromycin to children 1 to 59 months of age has been shown to reduce childhood all-cause mortality in some sub-Saharan African regions, with the largest reduction seen among infants younger than 12 months of age. Whether the administration of azithromycin at routine health care visits for infants would be effective in preventing death is unclear.

METHODS

We conducted a randomized, placebo-controlled trial of a single dose of azithromycin (20 mg per kilogram of body weight) as compared with placebo, administered during infancy (5 to 12 weeks of age). The primary end point was death before 6 months of age. Infants were recruited at routine vaccination or other well-child visits in clinics and through community outreach in three regions of Burkina Faso. Vital status was assessed at 6 months of age.

RESULTS

Of the 32,877 infants enrolled from September 2019 through October 2022, a total of 16,416 infants were randomly assigned to azithromycin and 16,461 to placebo. Eighty-two infants in the azithromycin group and 75 infants in the placebo group died before 6 months of age (hazard ratio, 1.09; 95% confidence interval [CI], 0.80 to 1.49; P=0.58); the absolute difference in mortality was 0.04 percentage points (95% CI, −0.10 to 0.21). There was no evidence of an effect of azithromycin on mortality in any of the prespecified subgroups, including subgroups defined according to age, sex, and baseline weight, and no evidence of a difference between the two trial groups in the incidence of adverse events.

CONCLUSIONS

In this trial conducted in Burkina Faso, we found that administration of azithromycin to infants through the existing health care system did not prevent death. (Funded by the Bill and Melinda Gates Foundation; CHAT ClinicalTrials.gov number, NCT03676764.)

From Centre de Recherche en Santé de Nouna, Nouna, Burkina Faso (A.S., M.O., M.B., V.B., T.O., G.C., C.D., C.B.); and the Francis I. Proctor Foundation (E.L., H.H., T.C.P., B.F.A., T.M.L., C.E.O., J.R.), the Department of Epidemiology and Biostatistics (T.C.P., T.M.L., C.E.O.), the Department of Ophthalmology (T.C.P., B.F.A., T.M.L., C.E.O.), and the Institute for Global Health Sciences (T.M.L., C.E.O.), University of California, San Francisco, San Francisco. Dr. Oldenburg can be contacted at catherine.oldenburg@ucsf.edu or at the Francis I. Proctor Foundation, University of California, San Francisco, 490 Illinois St., Fl. 2, San Francisco, CA 94143.

Drs. Lietman and Oldenburg contributed equally to this article.

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Mass distribution of azithromycin was shown in one trial to reduce childhood all-cause mortality in high-mortality regions.[1] The Macrolides Oraux pour Réduire les Décès avec un Oeil sur la Résistance (MORDOR) trial showed 14% lower mortality in communities that received four twice-yearly mass distributions of azithromycin to children 1 to 59 months of age than in communities that received placebo.[1] The largest effects were seen among infants 1 to 11 months of age, with nearly 25% lower mortality. The World Health Organization (WHO) subsequently issued a conditional guideline recommending twice-yearly mass distribution of azithromycin to infants 1 to 11 months of age in regions with more than 60 deaths of infants per 1000 live births or more than 80 deaths among children younger than 5 years of age per 1000 live births.[2] Targeting azithromycin distribution to infants, who have the highest mortality, may be a strategy that reduces mortality in the most vulnerable groups while limiting selection for antimicrobial resistance by reducing the number of children receiving azithromycin.

Evidence supporting the use of azithromycin to prevent childhood death is based on periodic mass distribution to all children in a community. Simultaneous treatment provides greater indirect protection than the same amount of treatment given sporadically throughout the year.[3,4] However, mass drug administration requires substantial logistic coordination and resources, including travel to communities and large-scale, often door-to-door, distribution. Integration of azithromycin into existing health care system contact points is an alternative option for implementation, since many existing health care systems are already in contact with children for routine care. If the mechanism of the effect of mass distribution of azithromycin is the direct treatment of individual infections, providing azithromycin to children at clinic visits may be far more cost-effective than mass distribution.

Childhood vaccination coverage is reportedly high in Burkina Faso, with national estimates of 98% coverage for the bacille Calmette–Guérin (BCG) vaccine and 95% for the first dose of the diphtheria–pertussis–tetanus (DPT) vaccine. Children are vaccinated routinely in primary health care facilities and in their communities during monthly community vaccination days. Integration of azithromycin administration into routine visits is not mass distribution,[5] and effects may differ from community-based mass distribution. In the current trial, we evaluated the effect of the provision of azithromycin during routine contact with the health care system to prevent infant death.

METHODS

TRIAL DESIGN AND OVERSIGHT

In this randomized, placebo-controlled trial, we evaluated the efficacy of a single dose of azithromycin administered during routine early infancy vaccination visits to prevent infant death in rural Burkina Faso. Full details of the trial protocol, which is available with the full text of this article at NEJM.org, have been reported previously.[6] The trial was reviewed and approved by the institutional review boards at the University of California, San Francisco, and the Centre de Recherche en Santé de Nouna (Nouna Health Research Center) in Burkina Faso, as well as the Comité Technique d'Examen des Demandes d'Autorisation d'Essais Cliniques (Technical Committee for Review of Applications for Clinical Trials) and the Comité d'Ethique pour la Recherche en Santé (Ethics Committee for Health Research) in Ouagadougou, Burkina Faso. Written informed consent was obtained from the caregiver of each infant. Azithromycin and placebo were donated by Pfizer (New York). Neither Pfizer nor the sponsor (the Bill and Melinda Gates Foundation) had any role in the design and conduct of the trial, the interpretation of the results, or the decision to submit the manuscript for publication. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

The trial was overseen by a data and safety monitoring committee consisting of experts in randomized, controlled trials; pediatrics; pediatric infectious diseases; mass administration of azithromycin; and bioethics. The committee met annually during the trial and reviewed quarterly data reports in aggregate. A medical monitor reviewed all reports of serious adverse events. Any serious adverse events that were judged to be possibly related to trial participation were to be reported to the data and safety monitoring committee within 24 hours after the trial team became aware of them.

TRIAL SETTING

Infants were recruited in three areas of Burkina Faso: the province of Kossi, in the northwest; and Banfora and Karankasso-Vigué departments (municipalities), in the southwest. Communities in Kossi were concomitantly enrolled in Child Health with Azithromycin Trial (CHAT), a trial that randomly assigned communities to twice-yearly mass distribution of azithromycin or placebo to prevent death among children 1 to 59 months of age.[6] The current trial was designed as part of the CHAT trial to evaluate the efficacy of individual administration of azithromycin to infants during well-child visits both in the presence and absence of mass azithromycin distribution, which is being evaluated as part of the ongoing development of WHO guidelines regarding routine mass distribution of azithromycin for the reduction of child mortality.[2] Infants enrolled in the present trial in Kossi could reside in communities that were receiving azithromycin twice-yearly and could have been eligible for mass azithromycin distribution as part of community-wide treatment. Additional details related to the trial setting are provided in the Supplementary Appendix, available at NEJM.org.

PARTICIPANTS

Infants were eligible for the trial if they were 5 to 12 weeks of age and had no documented allergies to macrolides and if their family was planning to stay in the trial area for the 6-month trial period. The age range was chosen to cover the 8-week vaccination visit according to the Essential Programme on Immunization schedule in Burkina Faso and reflects the fact that infants are vaccinated at variable ages around the 8-week target. For example, BCG vaccination is indicated at birth, but in practice, infants receive it at up to 6 weeks of age. Participants were recruited through community outreach and during routine clinic-based vaccination visits. In the trial area, vaccine outreach teams visit communities each month.

RANDOMIZATION

Infants were randomly assigned, in a 1:1 ratio, to a single dose of azithromycin, administered orally at a dose of 20 mg per kilogram of body weight, or placebo. The placebo was identical to the azithromycin except for the active ingredient. Azithromycin and placebo were reconstituted with bottled water, and administration of all doses was directly observed.

Participants, caregivers, trial staff, and investigators were unaware of the group assignments; this concealment was achieved with the use of a placebo that was identical to the trial drug in appearance, smell, and taste. Azithromycin and placebo bottles were labeled identically with one of eight letters (L, M, N, etc.), four of which were assigned to azithromycin and four to placebo. The trial letters were randomly assigned to each participant-identification number; caregivers and trial staff did not know which letters were assigned to azithromycin and which to placebo. The trial biostatistician and data team were aware of the group assignments. We used a mobile phone application for data collection that did not show the assigned letter until after a participant was enrolled.

PRIMARY END POINT

The primary end point was death from any cause before 6 months of age. Caregivers were requested to bring their child to the primary health care facility for assessment of vital status. If the caregiver did not return to the clinic, attempts were made to conduct a home visit or to confirm the child's vital status by means of a telephone call. The child's vital status was recorded as alive, died, moved, or unknown. A child was considered to have had a primary end-point event if the child was recorded as having died between enrollment and the 6-month visit. The ascertainment occurred within 8 weeks before 6 months of age to 12 weeks after 6 months of age (infant age, 120 to 270 days [4 to 9 months]).

PRESPECIFIED SECONDARY END POINTS

Prespecified secondary end points included caregiver-reported hospitalization and sick-child clinic visits. At the 6-month visit, all caregivers were asked whether their child had been hospitalized or whether they had sought medical care for their child in a primary health care facility. If the child had been hospitalized or had received medical care, the caregivers were asked to specify the reasons (including malaria, pneumonia, and diarrhea).

ADVERSE EVENTS

Fourteen days after administration of azithromycin or placebo, caregivers from a random sample

of 10% of the enrolled trial population were asked (either at a clinic visit or by means of a telephone call) about hospitalization, sick-child clinic visits, and nonserious adverse events. The nonserious adverse-event survey assessed the following events: vomiting, diarrhea, fever, abdominal pain, rash, and constipation. We chose to use a sample size of 10% because extensive evidence of nonserious adverse events among infants receiving azithromycin as compared with placebo had already been reported, so it was not necessary to assess this in the full sample.[7,8]

STATISTICAL ANALYSIS

The sample size for the trial was based on the primary end point, death from any cause before 6 months of age. On the basis of estimates from the Institute for Health Metrics and Evaluation,[9] we assumed a probability of 40 deaths per 1000 infants. Assuming a 5% loss to follow-up, a sample size of 32,700 infants would give the trial approximately 80% power to detect 15% lower mortality among infants randomly assigned to azithromycin than among those assigned to placebo. In Boucle du Mouhoun region (where the province of Kossi is located), mortality of children younger than 5 years of age was estimated to be 110.8 deaths per 1000 live births in 2015.[9] Neonatal mortality was estimated to be 29.2 deaths per 1000 live births in Kossi in 2015. We assumed that half the post-neonatal deaths would occur during infancy.

A single, prespecified interim analysis was completed after full data related to the end points were available for the first third of enrolled infants. The interim analysis included prespecified stopping guidance for efficacy (at an alpha error of 0.001 with the use of a Haybittle–Peto approach) and futility (conditional power by simulation below 10% to detect a 30% reduction in mortality).

For the primary prespecified analysis, we used a binomial regression model that included vital status before 6 months of age, with a complementary log–log link to estimate the hazard ratio for death among infants in the azithromycin group as compared with those in the placebo group. The analysis was two-sided with an alpha error of 0.05. All inferences were based on a Monte Carlo permutation test with 10,000 replications. A similar approach was used for the prespecified binary end points. We analyzed the primary end point in five prespecified subgroups (defined according to age, sex, vaccination visit, weight at enrollment, and community azithromycin treatment) on additive and multiplicative scales with binomial regression that included terms for subgroups and their interaction with group assignment using linear or complementary log–log links. For the subgroup analysis of community azithromycin treatment, infants residing in a community that was randomly assigned to twice-yearly mass distribution of azithromycin to children 1 to 59 months of age were considered to be in an "azithromycin treatment" community. Infants residing in a community that was randomly assigned to placebo distribution or that was outside the Nouna district (and thus in a community not receiving azithromycin or placebo in the community-randomized trial) were considered to be in a "no azithromycin treatment" community. In the community-randomized trial, large communities were split into multiple clusters that were randomly assigned to azithromycin or placebo. In the split communities, the specific cluster in which infants in the current trial were residing was not available, and thus these infants were not included in the subgroup analysis.

RESULTS

PARTICIPANTS

Among the 32,877 infants who were enrolled in the trial and underwent randomization, 16,416 were assigned to azithromycin and 16,461 were assigned to placebo (Fig. 1). The infants in the azithromycin group were a median of 6.6 weeks of age (interquartile range, 5.0 to 8.7), and the infants in the placebo group were a median of 6.7 weeks of age (interquartile range, 5.1 to 8.9); in the azithromycin group, 49.0% of the infants were female, and in the placebo group, 49.4% were female (Table 1). The age and sex distributions of the infants in the trial were similar to those of infants 5 to 12 weeks of age in the general population (Table S1 in the Supplementary Appendix). Among the infants enrolled in the trial, 99.9% received azithromycin or placebo as assigned. In total, 15,734 infants (95.8%) in the azithromycin group and 15,701 (95.4%) in the placebo group had a 6-month measurement in the prespecified window and were not lost to

follow-up and thus were included in the primary analysis. Of the infants who were not included in the primary analysis, 364 infants in the azithromycin group and 367 in the placebo group were lost to follow-up, and 318 infants in the azithromycin group and 393 in the placebo group had measurements performed at a time other than the prespecified window (Table S2).

PRIMARY END POINT

A total of 82 infants (0.52%) in the azithromycin group and 75 infants (0.48%) in the placebo group died before 6 months of age (absolute difference, 0.04 percentage points; 95% CI, −0.10 to 0.21). This corresponded to a hazard ratio of 1.09 (95% confidence interval [CI], 0.80 to 1.49; P=0.58). We found no evidence of an effect of azithromycin on mortality in any of the prespecified subgroups (Table 2).

Information regarding participants' community of residence was available for 27,147 infants (83%), which allowed for a comparison of the efficacy of individual treatment with azithromycin between infants who were living in communities receiving mass azithromycin distribution and those who were living in communities that were not receiving mass azithromycin distribution. We found no evidence of interaction between community distribution of azithromycin and individual treatment with azithromycin in infancy

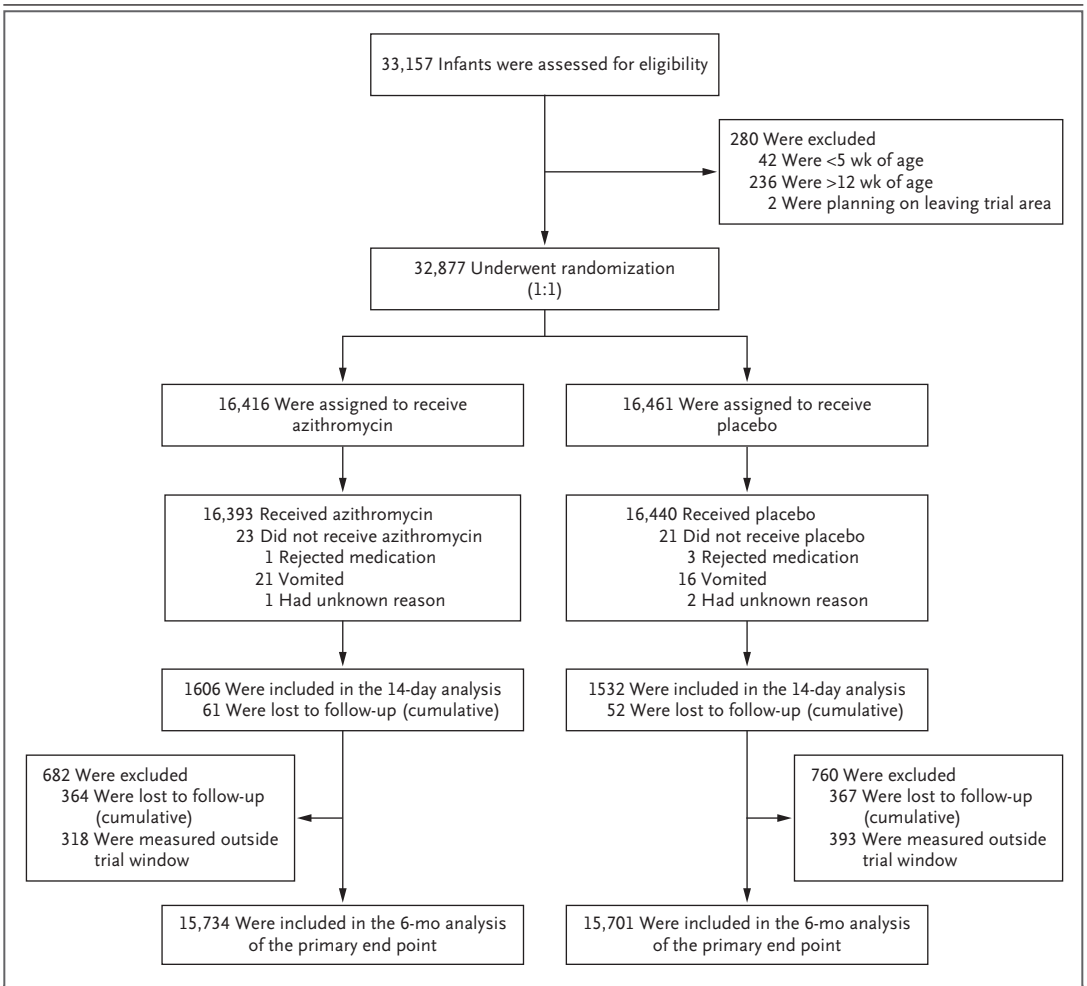

Figure 1. Screening, Randomization, and Follow-up of Participants.

Infants received either azithromycin or placebo during routine early infancy vaccination visits. At the 14-day visit, caregivers from a random sample of 10% of the enrolled trial population (1606 in the azithromycin group and 1532 in the placebo group) were asked about hospitalization, sick-child visits, and nonserious adverse events.

Table 1. Baseline Characteristics of the Participants.*

Characteristic	Azithromycin N=16,416	Placebo N=16,461
Median age (IQR) — wk	6.6 (5.0 to 8.7)	6.7 (5.1 to 8.9)
Female sex — no. (%)	8045 (49.0)	8136 (49.4)
Weight at enrollment <3800 g — no. (%)	2581 (15.7)	2557 (15.5)
Enrollment location — no. (%)		
Nouna, Kossi Province	14231 (86.7)	14271 (86.7)
Banfora	1298 (7.9)	1305 (7.9)
Karankasso-Vigué	887 (5.4)	885 (5.4)
Type of visit — no. (%)		
BCG vaccination	4731 (28.8)	4736 (28.8)
Pentavalent 1 vaccination†	4533 (27.6)	4618 (28.1)
Pentavalent 2 vaccination†	102 (0.6)	92 (0.6)
42-day follow-up‡	452 (2.8)	424 (2.6)
Community enrollment day	6272 (38.2)	6285 (38.2)
Other	325 (2.0)	304 (1.8)

* BCG denotes Bacille Calmette–Guérin, and IQR interquartile range.
† The pentavalent vaccine includes diphtheria, pertussis, tetanus, hepatitis B, and *Haemophilus influenzae* type b.
‡ The 42-day follow-up is a well-child visit conducted 42 days after birth.

(Table 2). The percentage of infants who died among those randomly assigned to azithromycin in azithromycin-treatment communities was 0.63%, as compared with 0.56% among infants randomly assigned to placebo in azithromycin-treatment communities (hazard ratio, 1.12; 95% CI, 0.67 to 1.89). The percentage of infants who died among those randomly assigned to azithromycin in no-azithromycin-treatment communities (no mass distribution of azithromycin) was 0.51%, as compared with 0.42% among the infants randomly assigned to placebo in placebo communities (hazard ratio, 1.20; 95% CI, 0.76 to 1.89).

ADVERSE EVENTS

Six serious adverse events were recorded over the course of the trial, including five hospitalizations in the azithromycin group within 14 days after treatment and one death in the placebo group within 14 days after receipt of the placebo (Table 3). No cases of cardiac arrhythmia or pyloric stenosis were identified. In a survey of caregivers in a random 10% sample of enrolled infants, the most common nonserious adverse events reported were vomiting and diarrhea (Table 3). No serious adverse event that was reported in the trial was considered by the site investigator to be possibly related to participation in the trial.

SECONDARY END POINTS

We found no evidence of a difference between the two groups with respect to caregiver-reported hospitalizations or sick-child visits before 6 months of age. The percentage of infants who were hospitalized was 1.2% in both the azithromycin and placebo groups (relative risk, 0.97; 95% CI, 0.79 to 1.19; Table 4). Approximately one third of infants attended a primary health care facility for a sick-child visit before 6 months of age: 36.9% in the azithromycin group and 36.4% in the placebo group (relative risk, 1.02; 95% CI, 0.98 to 1.06).

DISCUSSION

We found no evidence of a difference with respect to death before 6 months of age between infants randomly assigned to a single dose of azithromycin and those assigned to placebo when the active drug and placebo were administered through routine health systems channels (e.g., vaccination visits and community outreach). This finding is consistent with the results of the NAITRE trial (Nouveux-nés et Azithromycine: une Innovation dans le Traitement des Enfants), which showed no survival benefit from azithromycin distributed during the neonatal period,[8,10] and a trial that randomly assigned households to receive azithromycin or placebo as part of seasonal malaria chemoprevention campaigns for children 3 to 59 months of age.[11] In contrast, the MORDOR trial showed that community-wide distribution of azithromycin reduced childhood all-cause mortality by 13.5% among children 1 to 59 months of age.[1] Overall, the evidence from our trial does not support individual treatment of infants with azithromycin as an intervention to reduce childhood mortality.[9,12]

This trial may provide insight into the mechanism of azithromycin for the prevention of childhood death at the community level.[11] One hypothesis is that previous trials that randomly assigned individual children, as opposed to communities, to trial groups have relied on clinic-based recruitment, and these children may have health status and access to health care that are substantively different from those of children in

Table 2. Subgroup Analyses of the Primary End Point.

Subgroup	Azithromycin		Placebo		Hazard Ratio (95% CI)
	no. of infants	*no. of deaths (%)*	*no. of infants*	*no. of deaths (%)*	
All subgroups*	15,734	82 (0.52)	15,701	75 (0.48)	1.09 (0.80 to 1.49)
Age at enrollment					
5–8 wk	12,194	65 (0.53)	12,126	64 (0.53)	1.01 (0.71 to 1.43)
9–12 wk	3540	17 (0.48)	3575	11 (0.31)	1.56 (0.73 to 3.33)
Sex					
Female	7704	38 (0.49)	7769	40 (0.51)	0.96 (0.61 to 1.49)
Male	8030	44 (0.55)	7932	35 (0.44)	1.24 (0.80 to 1.94)
Vaccination visit					
Vaccine	8904	41 (0.46)	8946	37 (0.41)	1.11 (0.71 to 1.74)
Non-vaccine	6830	41 (0.60)	6755	38 (0.56)	1.07 (0.69 to 1.66)
Weight at enrollment					
<3800 g	2490	44 (1.77)	2461	33 (1.34)	1.32 (0.84 to 2.07)
≥3800 g	13,229	38 (0.29)	13,224	42 (0.32)	0.90 (0.58 to 1.40)
Community treatment†					
Azithromycin	4766	30 (0.63)	4807	27 (0.56)	1.12 (0.67 to 1.89)
No azithromycin	8089	41 (0.51)	8043	34 (0.42)	1.20 (0.76 to 1.89)

* P=0.58. The permutation P value is based on 10,000 Monte Carlo replications.
† Subgroup analyses for community treatment included 9573 infants in the azithromycin group of a community-randomized trial of azithromycin as compared with placebo and 16,132 infants who were in the placebo group or in a community not enrolled in the trial; information on the randomization group in the community trial was not available for 5730 infants.

Table 3. Adverse Events.*

Adverse Event	Azithromycin (N=1606)	Placebo (N=1532)	Risk Difference (95% CI)
	number (percent)		*percentage points*
Any serious adverse event	5 (0.3)	1 (0.1)	0.3 (0.0 to 0.6)
Hospitalization†	5 (0.3)	0 (0.0)	0.3 (0.1 to 0.6)
Death‡	0 (0.0)	1 (0.1)	–0.1 (–0.2 to 0.0)
Any nonserious adverse event	62 (3.9)	79 (5.2)	–1.4 (–2.9 to 0.1)
Vomiting	24 (1.5)	38 (2.5)	–1.0 (–2.0 to 0.0)
Diarrhea	36 (2.2)	45 (2.9)	–0.7 (–1.9 to 0.4)
Constipation	9 (0.6)	14 (0.9)	–0.4 (–1.0 to 0.2)
Hemorrhoids	6 (0.4)	8 (0.5)	–0.2 (–0.6 to 0.3)
Rash	9 (0.6)	12 (0.8)	–0.2 (–0.8% to 0.4)

* Active surveillance for adverse events was performed in a random sample of 10% of enrolled infants and recorded at 14 days after administration of azithromycin or placebo.
† Reasons for hospitalization included pneumonia in two infants, fever in one infant, malaria in one infant, and diarrhea in one infant.
‡ The cause of death is unknown for this infant.

Table 4. Caregiver-Reported Secondary End Points at 6 Months.

End Point	Azithromycin		Placebo		Risk Ratio (95% CI)
	no. of infants	*no. of infants reported (%)*	*no. of infants*	*no. of infants reported (%)*	
Any hospitalization	15,023	176 (1.2)	15,003	182 (1.2)	0.97 (0.79 to 1.19)
Any sick-child clinic visit	14,993	5530 (36.9)	14,980	5449 (36.4)	1.02 (0.98 to 1.06)
Reason for sick-child clinic visit					
Malaria	14,993	1578 (10.5)	14,980	1564 (10.4)	1.01 (0.94 to 1.08)
Pneumonia	14,993	2197 (14.7)	14,980	2175 (14.5)	1.01 (0.95 to 1.07)
Diarrhea	14,993	983 (6.6)	14,980	943 (6.3)	1.04 (0.95 to 1.14)

the general community.[8,13-15] In an analysis of baseline data from the present trial, the percentage of infants that were underweight was higher among those enrolled directly in their communities than among those enrolled in clinics; underweight is a strong predictor of death among infants and children.[14,16] Community-based delivery strategies could include more children who have reduced access to health care and are more vulnerable. We found no evidence of heterogeneity in effects between children recruited in the clinic and those in the community.

The Niger site of the MORDOR trial showed 18% lower mortality in the azithromycin-treated communities than in the placebo communities.[1] In studies of mass distribution of azithromycin for trachoma control, a spillover effect of azithromycin has been documented through the reduction of ocular *Chlamydia trachomatis* among untreated adults when children in the community are treated.[17] Similarly, water, sanitation, and hygiene interventions are probably more effective when they are implemented at a community level than when they are implemented at an individual level, because these interventions can reduce transmission of pathogens. Thus, the mechanism of azithromycin for preventing death in children is probably tied to mass distribution — for example, through spillover effects or reduction of pathogens when azithromycin is distributed to an entire community at the same time.

This trial has limitations. We observed substantially lower mortality than projected (40 infants per 1000 live births were expected to die, and 5 deaths per 1000 live births occurred), resulting in low statistical power. Although the point estimate for the effect of azithromycin on mortality was greater than 1 but close to 1, the confidence interval was consistent with a range from a 20% decreased risk of death with azithromycin to a 49% increased risk, and thus does not exclude the effect size assumed in the calculation for sample size (15% decrease). Although there was no evidence of a difference in effects in any subgroups, statistical power was very limited for subgroup analyses, because of the low number of infant deaths. Infants were recruited both in clinics and through community outreach, but community-based strategies may have missed the most vulnerable children, whose families were unable to attend outreach events. These results may be generalizable only to populations with similar mortality and similar distribution of causes of childhood death.

The results of this trial do not provide evidence to support distribution of azithromycin to infants during routine well-child visits to prevent death in Burkina Faso. If mass community-wide distributions of azithromycin for the prevention of death continue to show a benefit, the mechanism may be a reduction in transmission of pathogens. Individual-level treatment may not result in the same effects for prevention of death as have been observed with community-wide treatment, although the wide confidence interval was consistent with a range of effects and precludes a negative conclusion.

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

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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