ORIGINAL ARTICLE

Mass Administration of Azithromycin to Infants in Mali to Reduce Mortality

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ABSTRACT

BACKGROUND

Mass administration of azithromycin to children 1 to 59 months of age has been shown to reduce mortality among infants and children in this age group in some areas of sub-Saharan Africa. The largest effects have appeared to be among infants younger than 12 months of age, within 3 months after treatment; this observation motivated the design of the current trial.

METHODS

In this trial, we randomly assigned villages in Mali, West Africa, in a 3:4:2 ratio to receive distributions of placebo, azithromycin two times a year, or azithromycin four times a year. Infants 1 to 11 months of age received, in doses of 20 mg per kilogram of body weight, placebo every 3 months (control group); azithromycin at two quarterly visits from January through June and placebo at two quarterly visits from July through December (twice-yearly azithromycin group); or azithromycin every 3 months (quarterly azithromycin group). The primary outcome was death within 3 months after eligibility had been confirmed, analyzed in the intention-to-treat population.

RESULTS

From December 2020 through December 2022, a total of 1151 villages were enrolled in the trial; 386 villages were randomly assigned to the control group, 511 to the twice-yearly azithromycin group, and 254 to the quarterly azithromycin group. Among all the villages, 149,090 infants received at least one dose of placebo or azithromycin, with a total of 82,600 person-years of follow-up; 968 deaths were recorded. Mortality was 11.9 deaths per 1000 person-years at risk in the control group, 11.8 deaths per 1000 person-years in the twice-yearly azithromycin group (incidence rate ratio, 1.00; 95% confidence interval [CI], 0.83 to 1.19), and 11.3 deaths per 1000 person-years in the quarterly azithromycin group (incidence rate ratio, 0.93; 95% CI, 0.75 to 1.15). Adverse events were rare, and the percentages of infants with adverse events were similar in the three groups. Mortality among untreated children 12 to 59 months of age was similar across groups.

CONCLUSIONS

Mass administration of azithromycin in Mali, limited to infants 1 to 11 months of age, did not result in lower infant or child mortality than placebo, regardless of whether azithromycin was delivered twice yearly or quarterly. (Funded by the Gates Foundation; LAKANA ClinicalTrials.gov number, NCT04424511.)

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N Engl J Med 2025;393:1498-508.
DOI: 10.1056/NEJMoa2504644

Since 2000, global efforts have halved mortality among infants and children younger than 5 years of age, and the number of deaths among children was at a record low of 4.9 million in 2022. However, preventable diseases still claim millions of young lives, particularly during infancy and in high-mortality regions such as the Sahel, a semiarid region of western and north-central Africa.[1] With 59 countries unlikely to reach the 2030 target of 25 or fewer deaths per 1000 live births,[1,2] the 77th World Health Assembly called for urgent action to scale up evidence-based, cost-effective interventions that would accelerate progress in reducing the number of preventable deaths among children.[3]

One promising intervention is mass administration of azithromycin, a broad-spectrum antibiotic that was initially used for trachoma control.[4,5] Mass administration of azithromycin has shown potential in decreasing the prevalence of infections such as malaria, diarrhea, and pneumonia — leading causes of death among children in high-burden settings.[6-12] Reductions in mortality were also observed in trachoma trials.[13-15] The MORDOR (Macrolides Oraux pour Réduire les Décès avec un Oeil sur la Résistance) trial, which was conducted in Niger, Malawi, and Tanzania, specifically examined the effect of twice-yearly mass administration of azithromycin on mortality in children 1 to 59 months of age.[4] Results of that trial showed a significant 13.5% lower incidence of death from any cause among children who received azithromycin than among those who received placebo, with 6.6 fewer deaths per 1000 person-years. The largest reductions were among infants 1 to 5 months of age (24.9% lower mortality with azithromycin than with placebo) and in Niger (18.1% lower mortality with azithromycin). A secondary analysis suggested that much of the protective effect was observed in the first 3 months after treatment,[16] which has important implications for dosing frequency.

As a result of these findings, the World Health Organization (WHO) issued conditional guidelines in 2020 that recommend consideration of mass administration of azithromycin to infants 1 to 11 months of age in high-mortality settings.[17] This age restriction was designed to maximize benefits while minimizing the risks of antimicrobial resistance.[17-19]

In the LAKANA (Large-Scale Assessment of the Key Health-Promoting Activities of Two New Mass Drug Administration Regimens with Azithromycin) trial, we evaluated the effects of mass administration of azithromycin in Mali, West Africa, targeting infants 1 to 11 months of age, with administration either two times a year or four times a year. Here, we report the results of this trial regarding the effect of the intervention on infant and child mortality and safety.

A Quick Take is available at NEJM.org

METHODS

TRIAL DESIGN AND OVERSIGHT

In this double-blind, cluster-randomized, placebo-controlled trial with an adaptive design, we examined the effects of azithromycin (Zithromax, Pfizer) as compared with placebo on infant and child mortality, when administered to infants 1 to 11 months (29 to 364 days) of age in Mali. We assessed all-cause mortality over the course of 2 years in villages that were randomly assigned in a 3:4:2 ratio to receive distributions of placebo (control group), azithromycin two times a year (twice-yearly azithromycin group), or azithromycin four times a year (quarterly azithromycin group). Every 3 months, infants in the control group received placebo, and those in the quarterly azithromycin group received azithromycin. In the twice-yearly azithromycin group, infants received azithromycin at two quarterly visits from January through June — avoiding overlap with the national seasonal malaria chemoprevention program, which runs from July through December — and placebo at two quarterly visits from July through December. Details of the methods were reported previously[20] and can be found in the protocol, available with the full text of this article at NEJM.org.

The principal investigators designed the trial, vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, and made the decision to submit the results for publication. Pfizer produced, packaged, and donated the bottles of azithromycin and placebo but had no access to the trial data or group assignments.

Independent expert committees advised the investigators on trial design and implementation, and a data and safety monitoring board monitored the progress and safety of the trial. The Mali institutional review board — Comité

d'Éthique de l'Université des Sciences, des Techniques et des Technologies de Bamako — provided ethics approval for the trial. The researchers also received approval for the trial from the ethics committee of the Pirkanmaa Hospital District.

Village leaders gave permission for the trial to be conducted in their villages, and oral consent — recorded as "yes" or "no" and confirmed with a digital signature on tablets — was obtained from the heads of the households or authorized proxies before trial activities began. Oral consent was obtained from at least one caregiver for treatment of infants.

TRIAL SETTING, PARTICIPANTS, AND ELIGIBILITY CRITERIA

This trial involved villages located in the Kayes, Kita, and Koulikoro regions, which are considered to be nonurban, accessible, and safe according to the local health authorities and research team. Eligibility criteria for administration of azithromycin or placebo included an age of 1 to 11 months (29 to 364 days), residence in a trial village, a body weight of at least 3 kg, and caregiver consent. Infants with a known allergy to macrolides or a severe illness requiring referral to a health facility were excluded from the trial.

RANDOMIZATION AND MASKING

The randomization unit (cluster) was the village, with all the infants in a given village assigned to the same regimen. Randomization was stratified according to cluster size (<100 infants or ≥100 infants) on the basis of national population estimates. Eighteen letters of the alphabet were randomly assigned to bottles containing an oral suspension of azithromycin or placebo and were used in combinations to randomly assign villages to the control group, the twice-yearly azithromycin group, or the quarterly azithromycin group. Randomization occurred at public events in which village representatives selected two-letter coded lottery tickets in a blinded fashion (i.e., without knowledge of the group assignments). Additional details are provided in the Supplementary Appendix, available at NEJM.org, and at https://lakana.org.

Personnel who were aware of the group assignments included staff from Research Triangle Institute International, Pfizer, an external statistician, and the chair of the data and safety monitoring board. Participants, trial staff, investigators, and the statistician who led the analysis were unaware of the group assignments. Blinding was possible because azithromycin and placebo tablets were similar in appearance, smell, and packaging.

CENSUS AND FOLLOW-UP

Over the course of 2 years, a house-to-house census was performed every 3 months (±4 weeks) in each village to enumerate the population and to provide azithromycin or placebo to eligible infants. At the first household visit, a baseline assessment was conducted in which the trial team obtained global positioning system coordinates; data on access to clean water, sanitation, and hygiene (WASH); and socioeconomic and demographic information. At subsequent visits, vital status (alive, deceased, moved, or status unknown) of all household members was updated, and new members and households were added. Data collectors also recorded infants' exposure to seasonal malaria chemoprevention and immunizations. All data were obtained with the use of a mobile application (CommCare, Dimagi).

INTERVENTIONS

At each visit, infants were weighed on an electronic hanging scale (ADE M111600-01, ADE Germany), and the mobile application was used to calculate the dose in milliliters to be administered. Data collectors used syringes to administer an oral suspension of azithromycin or placebo, under direct observation and at a single dose of 20 mg per kilogram of body weight, in line with current WHO guidelines.[17] Each infant could receive a total of one to four doses of azithromycin or placebo, depending on their age at enrollment. If vomiting occurred within 15 minutes after ingestion of azithromycin or placebo, administration was repeated at the same dose.

OUTCOMES

The prespecified primary outcome was death from any cause among infants 1 to 11 months of age. The unit of primary-outcome measurement was a 3-month time period, which was the inter-

val between successive study visits. The dates of the consecutive visits were used to calculate person-years at risk. Any child could contribute data from one to four 3-month time intervals to the primary outcome analysis.

The secondary outcomes involved the indirect effects of mass administration of azithromycin on all-cause mortality among children 12 to 59 months of age at the time of the most recent mass administration in each village. We also assessed effect modification according to the infant's age at the time of mass drug administration, sex, weight-for-age z score, season (rainy or not rainy), seasonal malaria chemoprevention exposure, order of mass administration, district of residence, distance from the nearest health facility in kilometers, household asset index, WASH index, and national outreach strategy (Table S1 in the Supplementary Appendix). The WASH index was developed with the use of a principal component analysis (details are provided in the statistical analysis plan, included with the protocol); component scores were standardized to a mean of 0 (range, –1.3 to 1.78, with lower scores indicating worse WASH conditions).

ADVERSE EVENTS

Adverse events were defined as any new illness or symptom occurring within 14 days after mass administration. Serious adverse events were defined as any adverse events resulting in death, life-threatening condition, hospitalization or prolongation of existing hospitalization, substantial disability or incapacity, or any condition deemed by a trial physician to be medically important.

Serious adverse events were monitored through passive surveillance at all trial sites. Caregivers were advised to report major symptoms occurring within 14 days after administration of the azithromycin or placebo. Health center agents were advised to report deaths and hospitalizations. Deaths occurring more than 14 days after administration or those identified at subsequent trial visits were reported as primary-outcome events. In a subgroup of 59 villages selected to assess other trial objectives, adverse events were monitored through active surveillance with the use of interviews that were conducted 14 days after mass administration with the caregivers of infants 4 to 11 months of age.

STATISTICAL ANALYSIS

All enrolled households and infants who received at least one dose of the azithromycin or placebo were included in the trial database. We analyzed mortality outcomes in accordance with the intention-to-treat principle.[21] Simulations were conducted to evaluate power, determine the required sample size for the primary-outcome analyses, and confirm that interim analysis-related procedures did not compromise the type I error rates.[22] We calculated that a sample size of 1151 clusters with an average of 31 infants with analyzable data per cluster per time interval would provide the trial with approximately 89% power to test the hypothesis that twice-yearly mass administration of azithromycin would result in lower mortality than that with placebo, greater than 99% power to test the hypothesis that quarterly mass administration of azithromycin would result in lower mortality than that with placebo, and 80% power to test the hypothesis that quarterly mass administration of azithromycin would result in lower mortality than a twice-yearly distribution. A prespecified interim analysis was conducted by an independent statistician and reviewed by the data and safety monitoring board when approximately 60% of the estimated total person-years had accrued.[20,23]

We hypothesized that, first, infant mortality would be lower in the villages receiving twice-yearly mass administration of azithromycin than in those receiving placebo, and second, that infant mortality would be lower in the villages receiving quarterly mass administration of azithromycin than in those receiving twice-yearly azithromycin. We conducted one-sided hypothesis testing for the primary outcome and estimated incidence rate ratios and 95% confidence intervals to compare the regimens. We used mixed-effect Poisson models to estimate the between-group differences with respect to the intervention effects, with the use of random intercepts for clusters and log-link function with person-years as an offset variable. Models were adjusted for the randomization stratification factor (cluster size) as a fixed effect. In accordance with the close-testing method for controlling for multiple group comparisons, we tested, at a 5% significance level, the global null hypothesis that mortality in all three groups would be

the same. A pairwise null hypothesis was to be rejected at a one-sided P value of less than 0.025 only if the global null hypothesis was rejected. Analyses of the secondary outcomes were conducted with the use of two-sided tests, with two-sided P values and 95% confidence intervals.

We assessed effect modification using mixed-effect Poisson models with an interaction term for the assigned intervention and each modifier. Stratified comparisons were to be tested only if the interaction was significant (P<0.1). All analyses were conducted with the use of Stata software, version 18.0 (Stata Corp), and R software, version 4.3.2 (R Foundation for Statistical Computing).

RESULTS

ENROLLMENT AND BASELINE CHARACTERISTICS

From November 2020 through December 2022, a total of 1170 villages in 11 administrative districts were screened for eligibility; 19 were ineligible or declined to participate in the trial. The remaining 1151 villages were randomly assigned to the control group (386 villages), the twice-yearly azithromycin group (511 villages), or the quarterly azithromycin group (254 villages) (Fig. 1, and Figs. S1 and S2). At the first mass distribution of azithromycin and placebo, the baseline characteristics of the villages were similar in the three groups, including the number of eligible infants per village and the distribution of infants according to age, sex, and weight-for-age distributions (Table 1).

DELIVERY OF AZITHROMYCIN AND PLACEBO

Of the 9085 planned visits for the mass administration of azithromycin or placebo, 86.2% were completed on time, 1.0% were completed early, 9.9% were completed late, and 2.9% were missed. The proportion of completed visits was similar in the three trial groups and varied slightly according to visit. In 128 villages, the last round of mass administration was not completed owing to expiration of azithromycin or placebo; in 10 additional villages, the follow-up period was truncated for other reasons.

Over the course of the trial period, 285,227 households were registered; 27 households declined to participate in the trial. A total of 149,090 infants received at least one dose of azithromycin or placebo; 274,896 administrations and 82,600 person-years of follow-up were recorded (Fig. 1). Vital status was unknown for 2.7% of the infants (4080 infants) who received azithromycin or placebo owing to migration or

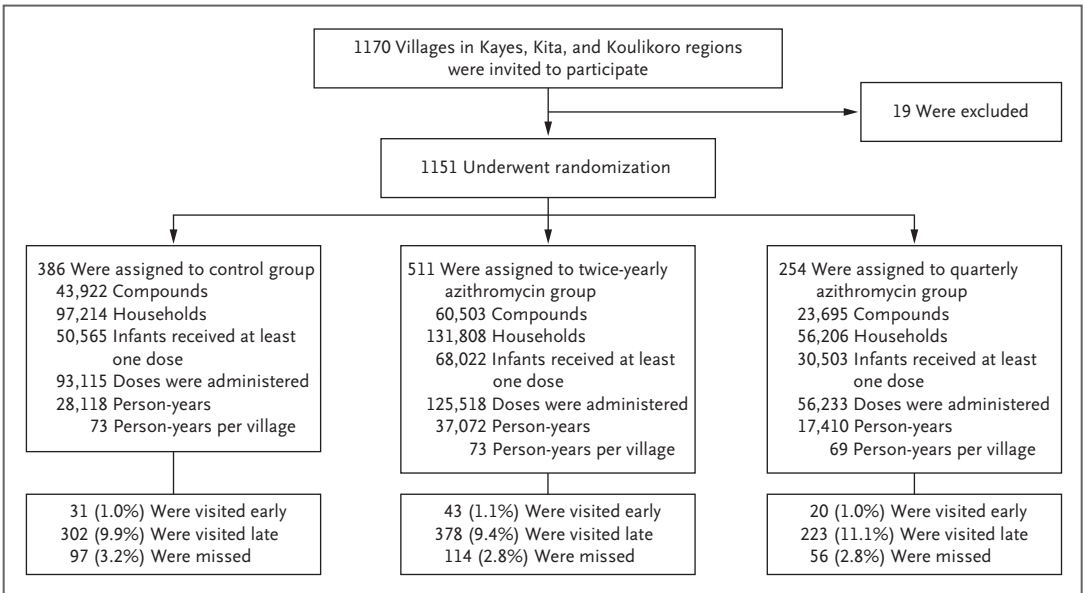

Figure 1. Screening, Randomization, and Administration.
The term "compounds" refers to local residential groupings that consist of multiple households in the trial setting.

Table 1. Characteristics of the Trial Villages and Infants 1 to 11 Months of Age at Baseline.*

Characteristic	Control	Twice-Yearly Azithromycin	Quarterly Azithromycin
Village Characteristics			
No. of villages	386	511	254
No. of large villages (%)†	70 (18)	88 (17)	44 (17)
Infant Characteristics			
Median no. of infants 1–11 mo of age per village	17	18	19
Total no. of infants 1–11 mo of age	13,187	18,040	8,201
Female sex (%)	49.3	49.0	49.4
Weight-for-age z score	−0.89±1.35	−0.89±1.38	−0.92±1.36
Age — mo	6.0±3.0	6.0±3.1	6.1±3.1
Age group (%)			
1–2 mo	18.7	19.0	18.4
3–5 mo	29.8	29.6	29.3
6–8 mo	29.8	28.8	29.5
9–11 mo	21.7	22.6	22.8

* Plus–minus values are means ±SD.
† Large villages were defined as those that had a population of at least 100 infants.

other reasons that resulted in loss to follow-up — 2.8% in the control group, 2.7% in the twice-yearly azithromycin group, and 2.6% in the quarterly azithromycin group.

Azithromycin or placebo could not be administered as planned at 10,094 of the administration visits (3.7%), in most cases because of temporary absence, a body weight of less than 3 kg, illness, allergy concerns, or caregiver refusal. In 273 administrations (0.1%), the infant erroneously received an incorrect preparation (wrong letter code). In 41 of these events, the error affected the actual agent that was received. At 1930 administration visits (0.7%), infants received a second dose of azithromycin or placebo because of vomiting within 15 minutes after the first dose. The percentages of missed administrations, incorrect administrations, and administrations that required a second dose were similar in the three groups (Table S2).

PRIMARY OUTCOME

Among infants 1 to 11 months of age at the time of the mass administration visit, 968 deaths were recorded over the course of the trial (Table 2, and Tables S3 and S4). The overall mortality was 11.7 deaths per 1000 person-years at risk; mortality was 11.9 deaths per 1000 person-years at risk in the control group, 11.8 deaths per 1000 person-years in the twice-yearly azithromycin group, and 11.3 deaths per 1000 person-years in the quarterly azithromycin group ($P=0.76$ for the comparison among the three groups). Among infants 1 to 11 months of age at the time of mass administration, the incidence rate ratio for mortality was 1.00 (95% confidence interval [95% CI], 0.83 to 1.19) in the twice-yearly azithromycin group as compared with the control group and 0.93 (0.75 to 1.15) in the quarterly azithromycin group as compared with the control group. The incidence rate ratio in the quarterly azithromycin group as compared with the twice-yearly azithromycin group was 0.93 (95% CI, 0.76 to 1.15). Absolute between-group differences in mortality were minimal.

SECONDARY OUTCOMES

The incidence rate ratio for mortality for either of the azithromycin groups as compared with the control group among infants 1 to 11 months of

Table 2. All-Cause Mortality (Deaths per 1000 Person-Years at Risk) among Infants 1 to 11 Months of Age at the Time of Mass Administration.

Variable	Control	Twice-Yearly Azithromycin	Quarterly Azithromycin
Deaths	335	437	196
Person-yr at risk	28,117.9	37,072.0	17,409.5
Deaths per 1000 person-yr at risk	11.9	11.8	11.3
Incidence rate ratio vs. control*	Reference	1.00 (0.83 to 1.19)	0.93 (0.75 to 1.15)
P value		0.48	0.25
Incidence rate difference vs. control	Reference	–0.05 (–2.31 to 2.21)	–0.91 (–3.55 to 1.73)
P value		0.96	0.50
Incidence rate ratio vs. twice-yearly azithromycin*			0.93 (0.76 to 1.15)
P value			0.25
Incidence rate difference vs. twice-yearly azithromycin			–0.85 (–3.34 to 1.64)
P value			0.50

* The incidence rate ratios were adjusted for the randomization stratification factor (cluster size).

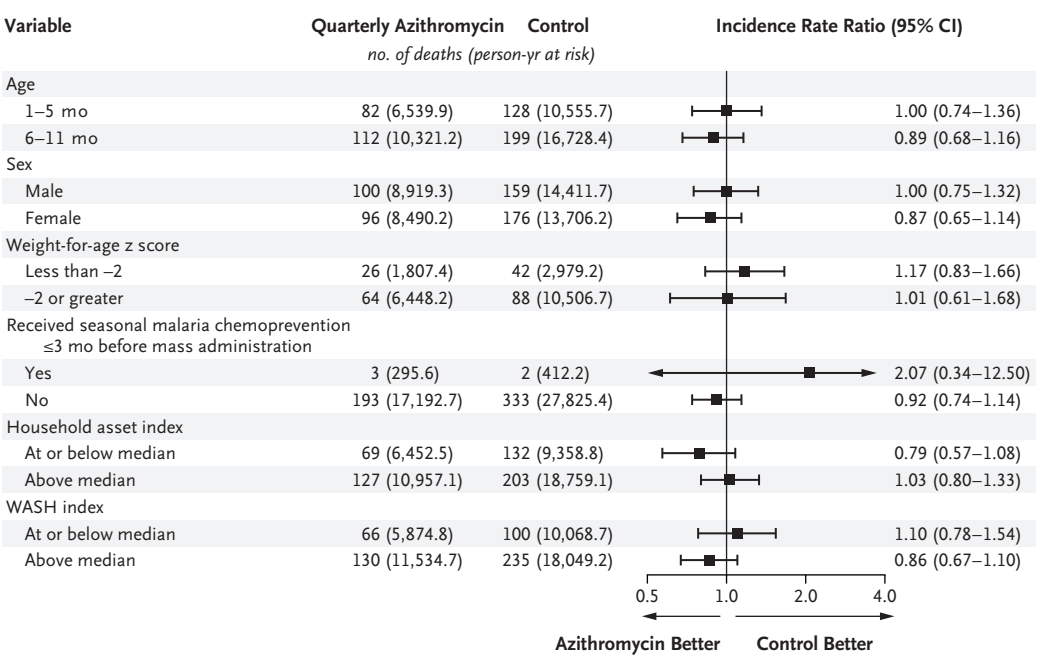

Figure 2. Subgroup Analysis of All-Cause Mortality among Infants 1 to 11 Months of Age at the Time of Mass Administration.

Shown is the difference between the control and quarterly azithromycin groups in all-cause mortality among infants 1 to 11 months of age at the time of mass administration. The incidence rate ratio was not modified according to infant age, sex, weight-for-age z score, recent treatment with seasonal malaria chemoprevention, household asset index, or WASH (access to clean water, sanitation, and hygiene) index. The x axis of this figure uses a logarithmic scale for visual clarity and symmetry. However, the numerical values shown in the far-right column represent incidence rate ratios, not log-transformed coefficients.

age at the time of mass administration appeared generally similar in analyses performed in subgroups defined according to infant age, sex, weight-for-age z score, recent treatment with seasonal malaria chemoprevention, household asset index, or WASH index (Fig. 2 and Fig. S3). Similarly, no apparent effect modification was observed according to seasonality, order of mass administration, distance to the nearest health facility, or national outreach strategy. Some apparent variation according to district was observed (Figs. S4 and S5).

A total of 967 deaths occurred among untreated children 12 to 59 months of age at the time of mass administration. After adjustments for follow-up time, the overall mortality was 10.6 deaths per 1000 person-years at risk among children 12 to 23 months of age, 3.4 deaths per 1000 person-years among those 24 to 35 months of age, 2.2 deaths per 1000 person-years among those 36 to 47 months of age, and 1.5 deaths per 1000 person-years among those 48 to 59 months of age. Among children 12 to 59 months of age at the time of mass administration, the incidence rate ratio for mortality was 1.03 (95% CI, 0.85 to 1.24) in villages assigned to the twice-yearly azithromycin group as compared with those assigned to the control group and 0.97 (95% CI, 0.77 to 1.22) in villages assigned to the quarterly azithromycin group as compared with those assigned to the control group (Table S5).

ADVERSE EVENTS

No suspected serious adverse events were reported. Among 1408 infants with active monitoring for adverse events, caregivers reported 22 episodes of diarrhea, loose stools, or vomiting; 12 episodes of crying more than usual; and 31 episodes of other adverse events. Adverse events occurred in 3.2% of infants in the control group, in 1.0% of infants in the twice-yearly azithromycin group, and in 1.9% of infants in the quarterly azithromycin group.

DISCUSSION

We evaluated the effect on infant and child mortality of twice-yearly and quarterly mass administration of azithromycin to infants 1 to 11 months of age in a high-mortality, holoendemic malaria setting with a national seasonal malaria chemoprevention program. In a sample of 1151 villages in Mali, with 82,600 person-years of observation and 968 recorded deaths, mortality was not lower in the twice-yearly azithromycin group than in the control group. Mass administration of azithromycin, limited to infants 1 to 11 months of age, did not result in lower infant or child mortality than placebo, regardless of whether azithromycin was delivered twice yearly or quarterly. Although the trial was large, mortality was lower than anticipated, and the evidence does not support the hypothesized level of mortality reduction.[23] Mortality among untreated infants 12 to 59 months of age was similar across groups.

The results of our trial align with those of the AVENIR (Azithromycine pour la Vie des Enfants au Niger: Implementation et Recherche) trial in Niger, which also showed no significant reduction in mortality when twice-yearly mass administration of azithromycin was limited to infants 1 to 11 months of age.[24] Furthermore, the CHAT (Child Health with Azithromycin Trial) and NAITRE (Nouveux-nés et Azithromycine: une Innovation dans le Traitement des Enfants) trials in Burkina Faso, which provided azithromycin to healthy infants at routine well-child visits during the first 3 months of life, showed no mortality benefit.[25,26] In contrast, the MORDOR and AVENIR trials in Niger both showed a reduction in mortality of 14 to 18% when azithromycin was delivered by mass administration two times a year to all infants and children 1 to 59 months of age.[4,24] In the CHAT trial, in which azithromycin was distributed two times a year to the same wider age group as that in the MORDOR and AVENIR trials, mortality was 18% lower in clusters that received azithromycin than in those that received placebo, although the difference was not significant ($P=0.07$).[26]

Taken together, the current evidence suggests that mass administration of azithromycin reduces mortality among children in West Africa if it is distributed to all infants and children 1 to 59 months of age but not when administration is limited to infants. Although the mechanism remains uncertain, containment of infectious diseases is one likely pathway.[27-29] Azithromycin has both antibacterial and antimalarial activity,[6-11,30,31] and malaria accounts for a higher proportion of deaths among older children than among infants.[32] Older children also harbor potentially pathogenic

Gram-negative bacteria in the gut, which may contribute to sepsis, more often than breast-fed infants[33,34]; the antibacterial and antiinflammatory properties of azithromycin may lead to a decreased number of these bacteria.[35-37] Individual-level elimination of potential pathogens would also reduce the community burden of malaria and other infections, which would explain the herd protection observed among infants when older children have been included in the mass administration of azithromycin.[24]

The lower-than-expected mortality observed in this trial resulted in limited power to detect modest differences among the groups and may limit the generalizability of the results to higher-mortality settings. In the control group, mortality was 12 deaths per 1000 person-years at risk, a rate that corresponds to infant mortality of approximately 36 deaths per 1000 live births, which is markedly lower than the initial assumption of 70 deaths per 1000 live births that was based on 2018 data[38] and lower even after adjustment of the assumption to 60 deaths per 1000 live births and an increase in the sample size.[20,23] A separate trial conducted in Mali showed a major decrease in mortality among infants and children younger than 5 years of age in a control group receiving no intervention — from 148 deaths per 1000 live births in 2017 to 55 deaths per 1000 live births in 2020.[39] These results suggest a possible Hawthorne effect (i.e., changes in behavior because of being observed) on mortality[40] but may also reflect a national reduction in mortality among infants and children younger than 5 years of age,[41] which could partially explain the lack of effect observed in our trial.[42] The representativeness of the trial population is further addressed in Table S6.

WHO guidelines currently recommend targeting infants 1 to 11 months of age if mass administration of azithromycin is considered for child survival.[17] Although this focused approach will certainly limit the risk of antimicrobial resistance, the latest evidence suggests that a mortality benefit may require targeting a wider age group.[43] However, the age range of the target group is still unknown, owing to limited data and lack of clarity on the mechanism of action of the intervention.[17] In any case, monitoring the prevalence of antimicrobial resistance will be important if mass administration of azithromycin is scaled up,[44] which is currently happening in Nigeria, Niger, and Mali.[45-47] Tracking mortality trends will also be essential, since the efficacy of the intervention may wane with declining baseline mortality.[42]

In this trial, mass administration of azithromycin in Mali, limited to infants 1 to 11 months of age, did not reduce infant or child mortality, regardless of whether azithromycin was delivered two times a year or four times a year.

Supported by grants (OPP1210821, INV-003354, and INV-005877) from the Gates Foundation.

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.

We thank Awa Traore, Uma Onwuchekwa, Fatoumata Diallo, Mamoudou Kodio, Djouma Keita, Moussa Traore, and Kevin Wilson for technical support; Elisabeth Diallo, Béatrice Abossolo, and Modibo Diarra for external monitoring; Karen Kotloff, Anthony Solomon, and Thomas Lietman for scientific advice; Robert Black, Paul Milligan, Julia Bielicki, Queen Dube, and Alassane Dicko for serving on the data and safety monitoring board; and the trial communities and the staff at the Malian Ministry of Health and Social Development for their constant support.

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