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RESEARCH ARTICLE

Mass administration of azithromycin to infants does not promote their survival in Mali

[version 1]

Fadima Cheick Haidara[1*], Laura Adubra[2*], Mahamadou Abdou[3], Dagmar Alber[4], Ulla Ashorn[2], Yin Bun Cheung[2], Elaine Cloutman-Green[5], Mamadou Diallo[1], Camilla Ducker[6], Yue-Mei Fan[2], Gwydion Gruffudd[6], Lotta Hallamaa[2], Tiia Haapaniemi[2], Rikhard Ihamuotila[2], Jane Juma[1], Nigel Klein[4+], Juho Luoma[2], Owen Martell[6], Akshaya Murugesan[2], Collins Okello[1], Oumar Samaké[1], Cheick Amadou Tidiane Traore[3], Taru Vehmasto[2], Kaisa Ylikruuvi[2], Samba Sow[1*], Per Ashorn[2*]

[1]Center for Vaccine Development–Mali, Bamako, 251 Bamako, Mali
[2]Center for Child, Adolescent and Maternal Health Research, Tampere University Faculty of Medicine and Health Technology, Tampere University and Tampere University Hospital, Tampere, Pirkanmaa, FIN-33014, Finland
[3]Ministère de la Santé et du Développement Social du Mali, Bamako, Mali
[4]Great Ormond Street Institute of Child Health, University College London Institute of Child Health, London, England, UK
[5]Great Ormond Street Hospital, London, UK
[6]Tro Da Ltd, Caerphilly,Wales, UK

[*] Equal contributors [+] Deceased author

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Abstract

Background

Mass drug administration (MDA) of azithromycin to children aged 1–59 months has reduced under-five mortality in some Sub-Saharan African settings, with possibly stronger effects in infants and within three months of treatment. We evaluated the impact of azithromycin MDA restricted to 1–11-month-old infants on infant and child mortality in Mali.

Methods

LAKANA was a cluster-randomized, double-blind, parallel-group trial in

Central and Western Mali. Villages were randomly assigned in a 3:4:2 ratio to receive placebo, biannual azithromycin, or quarterly azithromycin. Vital status was assessed quarterly over two years. At each visit, 1–11-month-old infants were weighed and received a single dose of study drug. The primary outcome was mortality within 90 days of treatment eligibility, deaths per 1,000 person-years at risk (PYR), analyzed using an intention-to-treat approach.

Results

Between December 2020 and December 2022, 1,151 villages were enrolled to placebo (n=386), biannual azithromycin (n=511), or quarterly azithromycin (n=254) groups. A total of 149,201 infants received at least one dose of study drug, with 82,600 PYRs of follow-up time and 968 recorded deaths: 335 in placebo, 437 in biannual, and 196 in quarterly groups, with mortality rates of 11.9, 11.8 (IRR 1.00; 95% CI, 0.83–1.19), and 11.3 (IRR 0.93; 95% CI, 0.75–1.15), respectively. No effect modification by background factors was observed. Mortality among untreated 12–59-month-olds was similar across groups.

Conclusion

Azithromycin MDA limited to 1–11-month-old infants, whether biannual or quarterly, did not reduce infant or child mortality in Mali.
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Keywords
Randomized, Infant, Antibiotic, Azithromycin, Mortality, Morbidity, Growth, Infection, Inflammation, Antimicrobial resistance

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Corresponding author: Per Ashorn (per.ashorn@tuni.fi)

Author roles: Haidara FC: Methodology, Project Administration, Writing – Review & Editing; **Adubra L**: Methodology, Project Administration, Writing – Review & Editing; **Abdou M**: Resources, Writing – Review & Editing; **Alber D**: Methodology, Resources, Supervision, Writing – Review & Editing; **Ashorn U**: Conceptualization, Funding Acquisition, Methodology, Project Administration, Resources, Supervision, Validation, Writing – Review & Editing; **Cheung YB**: Conceptualization, Funding Acquisition, Methodology, Supervision, Validation, Writing – Review & Editing; **Cloutman-Green E**: Resources, Supervision, Writing – Review & Editing; **Diallo M**: Project Administration, Writing – Review & Editing; **Ducker C**: Conceptualization, Funding Acquisition, Project Administration, Supervision, Writing – Review & Editing; **Fan YM**: Methodology, Project Administration, Resources, Supervision, Writing – Review & Editing; **Gruffudd G**: Software, Writing – Review & Editing; **Hallamaa L**: Data Curation, Formal Analysis, Visualization, Writing – Review & Editing; **Haapaniemi T**: Project Administration, Writing – Review & Editing; **Ihamuotila R**: Methodology, Project Administration, Writing – Review & Editing; **Juma J**: Investigation, Writing – Review & Editing; **Klein N**: Conceptualization, Funding Acquisition, Methodology, Project Administration, Resources, Supervision, Writing – Review & Editing; **Luoma J**: Data Curation, Formal Analysis, Methodology, Project Administration, Software, Visualization, Writing – Review & Editing; **Martell O**: Project Administration, Writing – Review & Editing; **Murugesan A**: Project Administration, Writing – Review & Editing; **Okello C**: Project Administration, Writing – Review & Editing; **Samaké O**: Investigation, Supervision, Writing – Review & Editing; **Traore CAT**: Resources, Writing – Review & Editing; **Vehmasto T**: Project Administration, Writing – Review & Editing; **Ylikruuvi K**: Data Curation, Project Administration, Writing – Review & Editing; **Sow S**: Conceptualization, Funding Acquisition, Methodology, Project Administration, Resources, Supervision, Writing – Review & Editing; **Ashorn P**: Conceptualization, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Supervision, Validation, Writing – Original Draft Preparation, Writing – Review & Editing

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Introduction

Global efforts have halved the under-five mortality rate (U5MR) since 2000, reducing child deaths to a record low of 4.9 million in 2022. Yet, preventable diseases still claim millions of young lives, particularly during infancy and in high-mortality regions like the Sahel.[1] With 59 countries unlikely to achieve the target U5MR of 25 or fewer deaths per 1,000 live births by 2030,[1,2] the 77th World Health Assembly has called for urgent, decisive actions, including scaling up evidence-based, cost-effective interventions to accelerate progress in reducing child mortality.[3]

One promising intervention is mass drug administration (MDA) of azithromycin, a broad-spectrum antibiotic initially used for trachoma control.[4,5] Beyond trachoma, azithromycin MDA has shown potential in reducing the prevalence of infections such as malaria, diarrhea, and pneumonia — leading causes of child mortality in high-burden settings.[6–12] Mortality reductions were also observed in trachoma trials.[13–15] The Macrolides Oraux pour Réduire les Décès avec un Oeil sur la Résistance (MORDOR) trial, conducted in Niger, Malawi, and Tanzania, specifically examined the impact of azithromycin MDA on mortality in children aged 1-59 months.[4] The results suggested a 13.5% reduction in all-cause mortality, 6.6 fewer deaths per 1,000 person-years, among children receiving biannual treatment than among infants receiving placebo. The largest reductions were observed among infants aged 1-5 months (24.9% lower mortality) and in Niger (18.1% lower mortality). A secondary analysis suggested that much of the protective effect was in the first three months post-treatment,[16] raising important considerations for optimal dosing frequency.

Considering these findings, the World Health Organization (WHO) issued conditional guidelines in 2020, recommending consideration of azithromycin MDA for 1-11-month-old infants in high-mortality settings.[17] This age restriction was designed to maximize benefits while minimizing the risks of antimicrobial resistance (AMR), a growing global concern.[17–19]

In the Large-scale Assessment of the Key health-promoting Activities of two New mass drug administration regimens with Azithromycin (LAKANA) trial, we aimed to study the effects of azithromycin MDA in Mali, West Africa, in a program where the MDA was limited to 1-11-month-old infants and provided either twice or four times a year. In this article, we report the trial's results on infant and child mortality, as well as on intervention safety.

Methods

Trial design and oversight

The LAKANA trial was a cluster-randomized, placebo-controlled, double-blinded, parallel-group, three-arm clinical trial, with an adaptive design comparing the effects of azithromycin (Zithromax, Pfizer) to placebo, administered to 1-11-month-old infants (29-364 days), on infant and child mortality in Mali. We assessed all-cause mortality over the course of two years in participating villages randomly assigned in a ratio of 3:4:2 to one of three groups: control; biannual azithromycin (twice a year), and quarterly azithromycin (every three months). In the control group, infants received placebo and in the quarterly azithromycin group they received azithromycin every three months. In the biannual azithromycin group, infants received azithromycin twice at 3-month intervals between January and June, and placebo twice at 3-month intervals between July and December. The period from July to December corresponds with a season when seasonal malaria chemoprevention is offered by the national malaria control program. To address other study objectives, 59 villages located closer to health facilities was selected as a subsample. These villages were visited at additional time points for data and sample collection. Details of the methods can be found in the protocol and standard operating procedures (SOP), with the full text available at the project website https://lakana.org, and as previously reported.[20]

The Project Steering Group (PSG) was responsible for the overall supervision of the trial and was composed of the principal investigator and four co-principal investigators from the participating research institutions. Two committees of independent experts, a National Advisory Committee (NAC) and a Technical Advisory Group (TAG) advised on general design issues, implementation strategy, and conduct throughout the life of the trial. A data and safety monitoring committee (DSMB) independently oversaw trial progress and patient safety through annual meetings and quarterly progress reports. Pfizer Inc. (New York City, NY, USA) donated the azithromycin and placebo, and manufactured, packaged, and shipped the study drugs directly to Mali.

The trial was conducted in accordance with Good Clinical Practice (ICH-GCP) guidelines, the principles of the Declaration of Helsinki, and all applicable regulatory requirements in Mali. Ethics approval was obtained from the Mali Institutional Review Board (IRB), namely the *Comité d'Éthique de l'Université des Sciences, des Techniques et des Technologies de Bamako* (IRB approval number: N2019/181/CE/FMPOS/FAPH). The study was originally approved on December 27, 2019, with the most recent annual reapproval (IRB approval number: N2023/252/USTBB) on October 15, 2024. Ethics committees in Finland have no legal mandate to authorize trials abroad, but the LAKANA trial received a

favorable opinion from the Ethics Committee of the Pirkanmaa Hospital District for Tampere University researchers to participate in the project. The LAKANA trial was registered at ClinicalTrials.gov (NCT04424511) on June 11, 2020.

Permissions were granted by village leaders, and verbal consent documented with a digital signature, was obtained from household heads or authorized proxies before activities began. Additionally, verbal consent was obtained from at least one caregiver for treatment of infants. The process for capturing digital signatures is detailed in the study's SOPs. The Mali IRB approved the overall consent procedures, including the use of electronically documented verbal consent within the context of tablet-based field data collection.

Trial setting, participants, and eligibility criteria

The LAKANA trial included all villages located in the Kayes, Kita, and Koulikoro regions considered non-urban, accessible, and safe by the local health authorities and research team. Eligibility criteria for receiving the study drug included: age between 1 and 11 months (29 to 364 days), residence in a village enrolled in the trial, weight of at least 3.0 kg, and parental consent. Infants with known allergies to macrolide antibiotics, or severe illness that warranted referral to a health facility were excluded from treatment at the MDAs.

Randomization and masking

The randomization unit (cluster) was the village: in any one village, all infants received the same treatment at each MDA visit. Randomization was stratified by cluster size, below or above 100 infants per cluster (categorization based on national population estimates). Villages were randomly allocated into the three trial arms at public allocation events where village representatives blindly pulled lottery tickets out of a container. Each ticket was marked with a two-letter code.

A total of 18 letters (A, B, C, E, F, G, H, J, K, N, P, R, S, T, U, X, Y, Z) were randomly assigned to represent azithromycin or placebo: eight letters were allocated to azithromycin and 10 letters to placebo. Each village received two letters: one for visits between January and June and one for visits between July and December. There were nine possible letter combinations to ensure that treatments were allocated to villages in a ratio of 3:4:2. Of the nine two-letter combinations, three were allocated to control (both letter codes for placebo), four to the biannual azithromycin regimen (one letter code for placebo, the other for azithromycin), and two to the quarterly azithromycin regimen (both letter codes for azithromycin).

Unmasked personnel (i.e., holders of the trial code) included key members of Research Triangle Institute (RTI) International, the external partner responsible for data support services at the beginning of the trial, who randomly assigned the treatments to the letters and transmitted the code to Pfizer; key members of Pfizer staff; a statistician external to the trial team; and the Chair of the DSMB. Study arm allocation was masked for participants, trial investigators including principal investigators, and site staff, including personnel administering treatment and collecting data.

Azithromycin and placebo were similar in appearance, smell, and packaging to ensure that investigators, participants, treatment administrators, and outcome assessors remained unaware of the villages' group assignments. A statistician, blinded to the villages' assignments, led the data analyses.

Census and follow-up

A house-to-house census was performed in each village every three months, for a total of two years, to enumerate the population and provide study drug to eligible infants. To accommodate unavoidable delays or advances in timelines, a flexible MDA scheduling window was implemented, allowing for a $\pm$ 4-week adjustment within the 3-month intervals. All households and infants who were enrolled or treated with study drugs during any MDA visit were included in the study.

At the first visit to each household, the trial team conducted a baseline assessment and collected data on household location (GPS coordinates), socio-economic and Water, Sanitation, and Hygiene (WASH) information, as well as demographic data for household members.

At subsequent visits (MDA2-MDA8), the vital status of all household members was recorded. New members, including newborns, and new households were added. Valid vital status information for infants was obtained from a caregiver residing in the household. Infant age was calculated based on visit date and date of birth, primarily obtained from health cards and, secondarily, from caregiver-reported information (if the exact date was known), and tertiarily using a time-bound event calendar. The data collectors also recorded treated infants' exposure to SMC and Expanded Programme on Immunization (EPI) vaccinations, verified from health cards.

At the close-out visit (visit 9), the vital status of household members and infants' exposure to SMC and vaccinations were again recorded.

All data were collected electronically using a custom-designed mobile application (CommCare by Dimagi, Cambridge, MA, USA).

Interventions

Azithromycin and placebo were administered, in an oral suspension, by data collectors using syringes as a single dose of 20 mg per kilogram of body weight. At each MDA visit, infants were weighed on an electronic baby hanging scale (ADE Model M111600-01, Hamburg, Germany) as part of the eligibility screening procedure, and the study mobile application automatically calculated the dose in milliliters based on the infant's weight. All study drugs were administered under direct observation. If an infant vomited within 15 minutes of ingesting the study drug, a new dose of the same size was given.

Outcomes

The prespecified primary outcome was the all-cause mortality rate: deaths per 1000 person-years at risk (PYR) among 1-11-month-old (29-364 days) infants at MDA. The unit of primary outcome measurement was a 3-month time interval, between successive study visits. The exact dates of the consecutive visits were used to calculate PYR. Any one child could contribute 1–4-time intervals to the primary outcome analysis.

The secondary outcomes focused on indirect effects. We assessed the all-cause mortality rate PYR among children who were 12-59 months old when the latest azithromycin MDA took place in their village of residence. We also assessed effect modification by the child's age at the time of MDA, along with sex and weight-for-age z-score (WAZ); seasonality (rainy season versus non-rainy season at the time of MDA); SMC given to the child within 3 months of an MDA; order of MDA in the village; district of residence; distance from the nearest health facility in km; household asset index; WASH index; and national outreach strategy (a categorization to guide the level of effort needed to provide health services to people, based on the distance between their home villages and the nearest health facility, categorized as "standard" or "advanced").

Children's vital status was evaluated at the quarterly visits and categorized as alive, deceased, moved, or unknown. If a child's death was reported, the date and cause of death, as reported by the caregiver, were recorded. The cause of death was classified as trauma, acute illness lasting less than or more than 2 weeks, or other; no verbal autopsy interview was conducted.

Adverse events

Serious adverse events (SAEs) were defined as any adverse events experienced by a participant that resulted in death, was life-threatening, required inpatient hospitalization or the prolongation of existing hospitalization, or that resulted in persistent or significant disability or incapacity, or was considered an important medical event by a study physician. Adverse events (AEs) were defined as any new illness or symptom during the 14 days following MDA, including but not limited to diarrhea, loose stools, vomiting, rash-itching, swelling of the lips, difficulty breathing, wheezing, and crying more than usual.

Participants were monitored for SAEs through passive surveillance at all study sites and AEs through active surveillance in the subset sample. The caregivers of all treated infants were instructed to seek medical care and inform the study team of any major symptoms experienced within the 14 days following drug administration. Health center agents were also instructed to report any major events (deaths, hospitalizations) among 1-11-month-old infants recorded within 14 days of an MDA. In addition, 14 days after an MDA in the subset sample, caregivers of 4-11-month-old infants were interviewed about the child's experience of AEs. Deaths that occurred more than 14 days after an MDA or that became known through interviews at subsequent study visits were not considered suspected SAEs. These deaths were reported as primary outcomes. Participants experiencing an SAE that was likely to be related to the trial intervention were withdrawn from further study drug provision.

Statistical analysis

We analyzed the mortality outcome data by the intention-to-treat (ITT) principle,[21] where the ITT population included all infants of the eligible age at the time of the MDA visit in all randomized villages according to the treatment the villages had been randomized to receive. Power-by-simulation was conducted to determine the appropriate sample size to achieve target levels of power for the main objectives as well as to confirm that the procedures related to an interim analysis did not compromise type I error rates.[22] A sample size of 1151 clusters (villages) with on average 31 analyzable infants per cluster

per time interval provided approximately 89% power for testing the hypothesis that biannual azithromycin MDA reduced mortality, >99% power for testing the hypothesis that quarterly azithromycin MDA reduced mortality, and 80% power for testing the hypothesis that quarterly azithromycin MDA reduced mortality more than biannual azithromycin MDA.

A prespecified interim analysis was conducted by an independent statistician and reviewed by the trial DSMB when approximately 60% of the study's estimated total person-years had been accumulated. The details of the interim analysis have been published in the trial protocol and statistical analysis plan.[20,23]

The trial hypotheses were that i) infants living in villages receiving biannual azithromycin MDA would have lower mortality than infants living in control villages, and that ii) infants living in villages receiving quarterly azithromycin MDA would have lower mortality than infants living in villages receiving biannual azithromycin MDA. We conducted the main hypothesis testing as one-sided. We estimated incidence rate ratio (IRR) and its 95% confidence interval (CI) to compare the treatment regimens. We used mixed-effects Poisson modelling to estimate intervention effects between treatment groups, with random intercepts for clusters (villages), using log link function with person-years as an offset variable. We adjusted the model for stratification factors in the randomization scheme (village size category) as a fixed effect. As per the close-testing method for controlling multiplicity arising from multiple group comparisons, the global null hypothesis of mortality in all three groups being the same was tested at a 5% significance level. A pairwise null hypothesis was rejected at $p < 0.025$ only if the global null hypothesis was rejected.

To examine the effect modification, we constructed mixed-effects Poisson models with interaction term between the study intervention and the potential effect modifier. Hypothesis testing of differences between groups within each stratum was performed only if the interaction test gave statistically significant results ($p < 0.1$).

Data analysis was performed by Juho Luoma, and Lotta Hallamaa. All analyses were conducted using Stata statistical software version 18.0 (StataCorp, College Station, TX) and the open-source R programming language version 4.3.2.

The analytical code used for the primary and secondary outcome analyses is openly available on GitHub.[24] De-identified individual-level trial data, along with accompanying documentation, are available on Zenodo.[25]

Results

Enrolment and baseline characteristics

Between November 2020 and December 2022, a total of 1,170 villages across 11 administrative districts were approached and screened for participation. Nineteen villages were ineligible or not willing to participate. The remaining 1151 villages were randomized to control (386 villages), biannual azithromycin (511), or quarterly azithromycin (254) MDA interventions. The ratio of villages allocated to the different trial arms was similar (3:4:2) in all the 11 administrative districts.

Table 1. Characteristics of the study communities and 1-11-month-old infants at the first mass drug administration, by trial arm.

	Control	Biannual azithromycin	Quarterly azithromycin
Number of villages	386	511	254
Number (%) of large villages	70 (18%)	88 (17%)	44 (17%)
Median number of 1-11 mo. infants/village	17	18	19
Total number of 1-11 mo. infants	13,187	18,040	8,201
Proportion of girls	49.3%	49.0%	49.4%
Mean (SD) WAZ	-0.89 (1.35)	-0.89 (1.38)	-0.92 (1.36)
Mean (SD) age, months	6.0 (3.0)	6.0 (3.1)	6.1 (3.1)
Proportion in different age groups			
1-2 months	18.7%	19.0%	18.4%
3-5 months	29.8%	29.6%	29.3%
6-8 months	29.8%	28.8%	29.5%
9-11 months	21.7%	22.6%	22.8%

SD = Standard deviation, WAZ = weight for age Z-score.

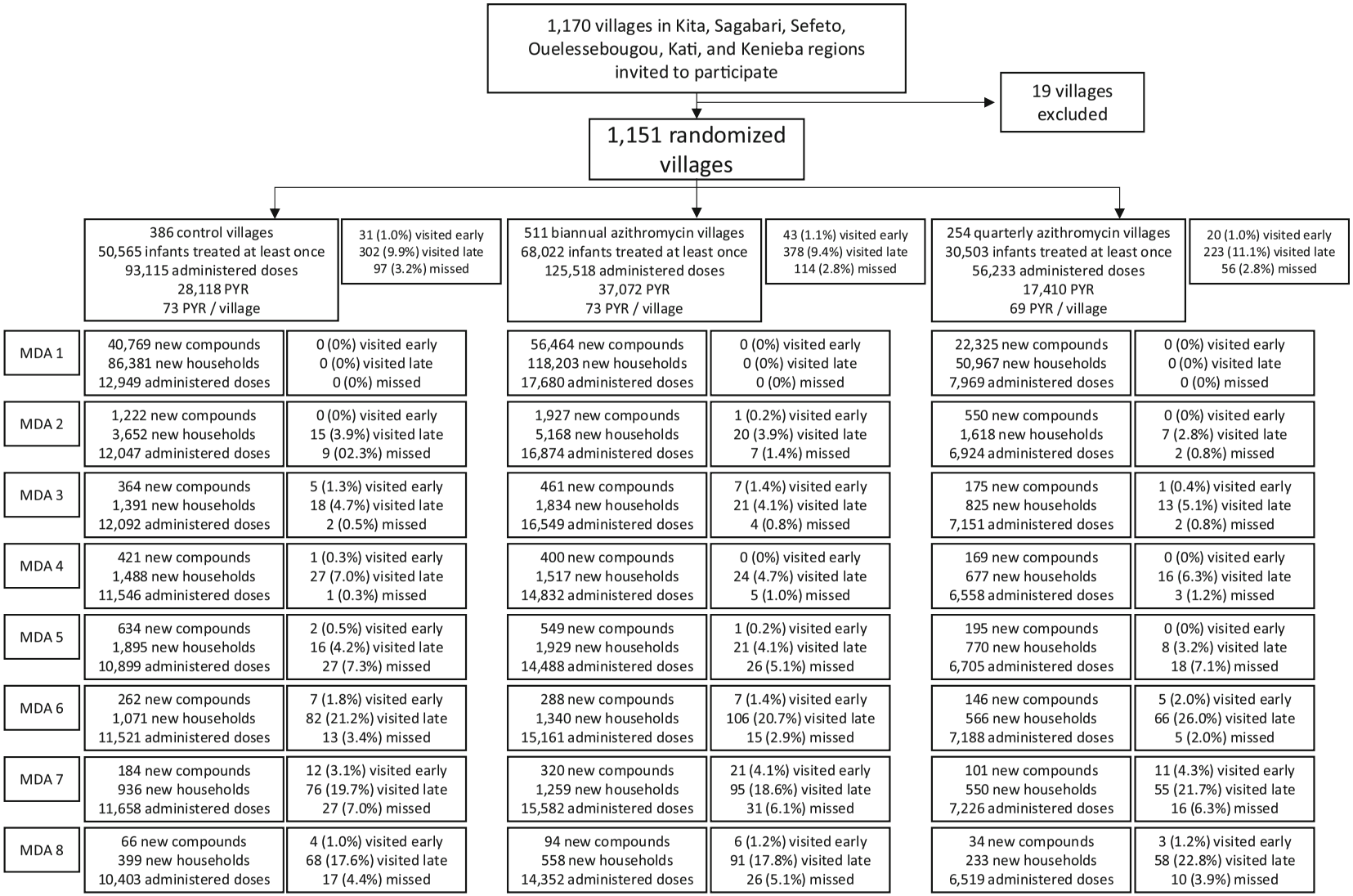

Figure 1. **LAKANA Trial flow chart according to CONSORT guidelines.**

In each of the trial arms, a similar proportion (17-18%) of the villages were considered "large". At the first MDA, the groups were also similar in terms of the number of eligible infants per village and the age-, sex-, and weight-for age distribution among the 1-11-month-old infants (Table 1).

Delivery of the study drug

Of the 9,085 planned MDA visits to the study villages, 86.2% were completed within the planned time window, 1.0% were completed early, 9.9% were completed late, and 2.9% were missed. The completion proportions were similar between trial arms and varied slightly between the different MDA visits (Figure 1). For 128 villages, the last MDA round could not be completed due to expiry of the study drug, for 10 additional villages, the follow-up was truncated for other reasons.

Over the trial period, the study team enumerated 128,120 compounds, in which there were a total of 285,227 households. Of these households, 27 declined to participate, the others were included in the trial. The number of infants who received at least one dose of the study drug was 149,201, the total number of recorded treatments was 274,896 and the follow-up time among the included infants was 82,600 PYR (Figure 1). For 4,080 (2.7%) of the treated infants, there was no information on their subsequent vital status, due to migration or other loss to follow-up. This proportion was 2.8% in the control group, 2.7% in the biannual azithromycin group, and 2.6% in the quarterly azithromycin group.

The study drug could not be administered as planned (usually because the child was temporarily absent, ill or considered allergic to the study drug, or the parent refused the treatment) in 9,609 (3.5%) of the planned treatment visits. In 273 (0.1%) of the treatments, the infant erroneously received a study preparation with an incorrect letter code. In 41 of these events, the error led to the infant receiving incorrect preparation (placebo instead of azithromycin or vice versa), while in the others, the letter code error did not change the actual preparation. In 1,930 (0.7%) of the treatment events, the infant received a second dose of the study drug, because of vomiting within 15 minutes of the first dose. All the proportions were similar in the three trial arms.

Primary outcomes

During the study period, the team recorded 968 deaths among infants who were 1-11 months old at the time of MDA. The overall mortality was 11.7 deaths/1,000 PYR; 11.9 in the control, 11.8 in the biannual azithromycin and 11.3 in the quarterly azithromycin group ($p = 0.765$). Compared to the control group, the incidence rate ratio (95% CI) for mortality among infants who were 1-11 months old at the time of MDA was 1.00 (0.83 to 1.19) in the biannual azithromycin group and 0.93 (0.75 to 1.15) in the quarterly azithromycin group. Compared to the biannual azithromycin group, the respective incidence rate ratio in the quarterly azithromycin group was 0.93 (0.76 to 1.15). The absolute mortality differences were minimal between the three groups (Table 2).

Secondary outcomes

The mortality ratio between the control and the quarterly azithromycin groups (Figure 2) or between the control and the biannual azithromycin groups (data not shown), among infants who were 1-11 months old at the time of MDA, was not

Table 2. All-cause mortality among participants who were 1-11-months old at the time of mass-drug administration.

	Control	Biannual azithromycin	Quarterly azithromycin	Quarterly vs Biannual
Number of deaths	335	437	196	
Number of PYR	28,117.9	37,072.0	17,409.5	
Number of deaths/1000 PYR	11.9	11.8	11.3	
Incidence rate ratio[a] (95% CI) p-value	REF	1.00 (0.83 to 1.19) 0.481	0.93 (0.75 to 1.15) 0.252	0.93 (0.76 to 1.15) 0.253
Incidence rate difference (95% CI) p-value	REF	-0.05 (-2.31 to 2.21) 0.963	-0.91 (-3.55 to 1.73) 0.500	-0.85 (-3.34 to 1.64) 0.501

[a]Adjusted for stratified randomization factor (village size category).

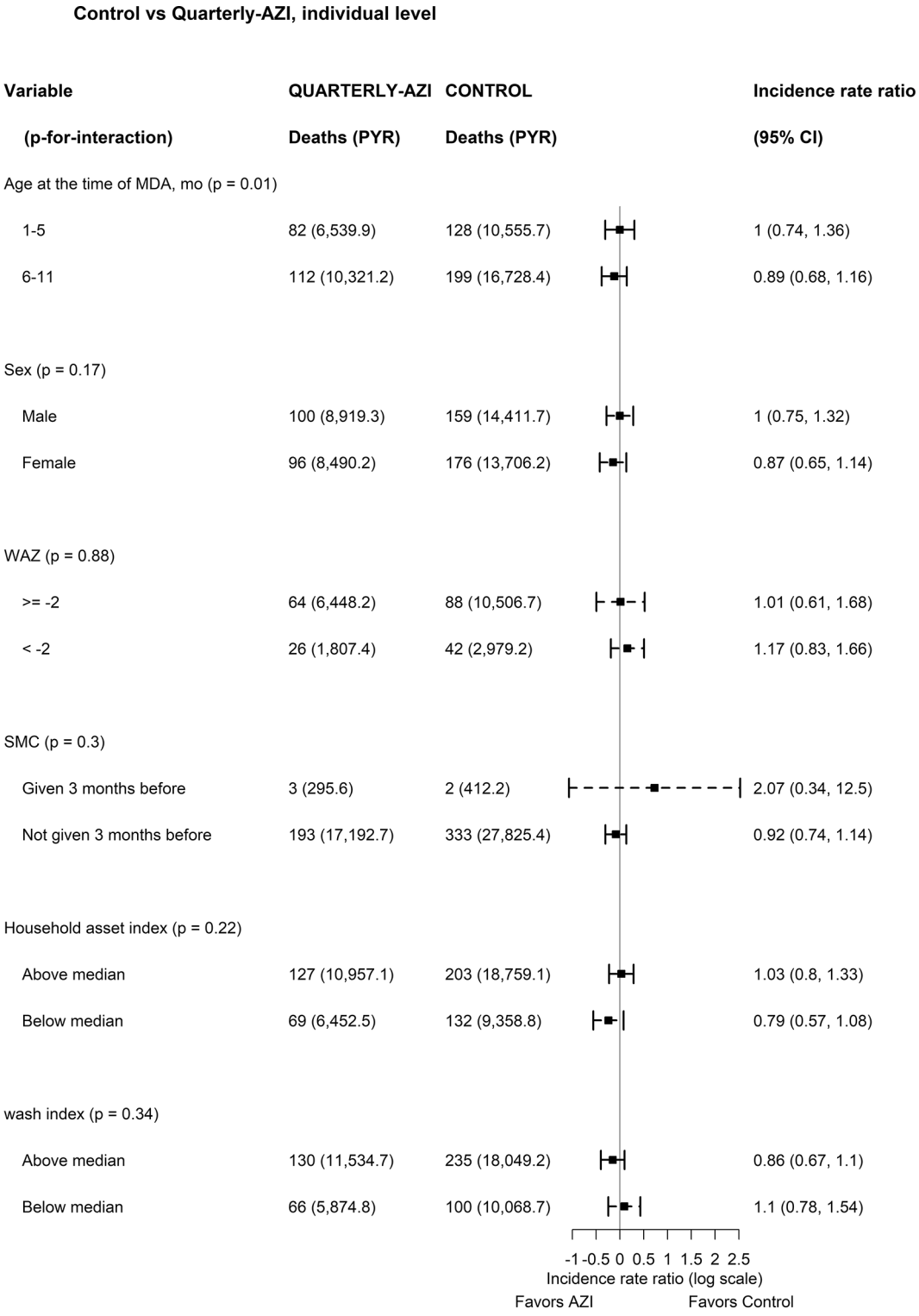

Figure 2. Mortality difference between the control and quarterly azithromycin (AZI) groups, among predefined sub-groups of infants, who were 1-11-months old at the time of mass-drug administration, according to individual and household characteristics.

modified by the infant age, sex, WAZ, recent SMC dosing, household asset or WASH index, or MDA season. Similarly, there was no modification of the association by seasonality, MDA order, distance to the nearest health facility or national outreach strategy. There was some variation in mortality by the administrative district, with a few statistically significant

differences between the groups in some of the smaller districts (Figure 3). The differences were, however, in both directions, and the pattern was not identical when comparing the control group to the quarterly azithromycin (Figure 3) or to the biannual azithromycin groups (data not shown).

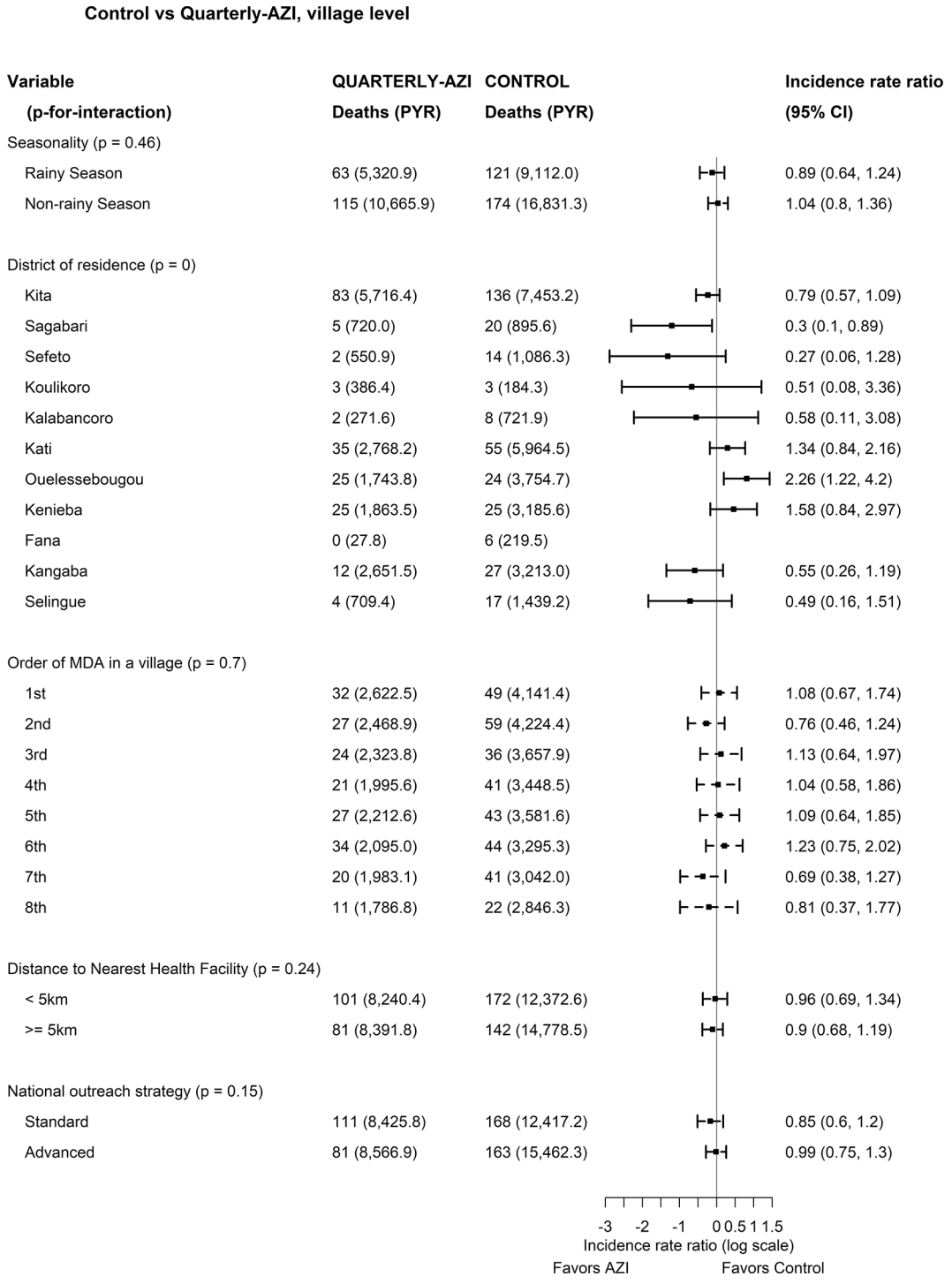

Figure 3. Mortality difference between predefined sub-groups in the control and quarterly azithromycin (AZI) groups, among infants, who were 1-11-months old at the time of mass-drug administration, according to ecological characteristics.

Among children who were 12-59 months old at the time of MDA (and who were not treated with the study drug), the team recorded a total of 967 deaths. Adjusted for follow-up time, the overall mortality was 10.6 deaths/1000 PYR among 12-23-month-olds, 3.4 among 24-35-month-olds, 2.2 among 36-47-month-olds, and 1.5 among 48-59-month-olds. Compared to the control group, the incidence rate ratio (95% CI) for mortality among children who were 12-59 months old at the time of MDA was 1.03 (0.85 to 1.24) in the biannual azithromycin group and 0.97 (0.77 to 1.22) in the quarterly azithromycin group.

Adverse events

There were no reports of suspected serious adverse events. In a subsample of 1,408 infants, among whom there was an active interview of all adverse events, guardians reported 22 episodes of diarrhea, loose stools or vomiting, 12 episodes of crying more than usual and 31 other episodes. The proportion of infants with any adverse event was 3.2% in the control, 1.0% in the biannual azithromycin group, and 1.9% in the quarterly azithromycin group.

Discussion

The LAKANA trial was designed to assess whether biannual or quarterly MDA with azithromycin would reduce infant or child mortality, when given to 1-11-month-old infants in a high-mortality setting with holoendemic malaria and a seasonal malaria chemoprevention program. In a Malian sample of 1151 villages, 82,600 person-years of observation and 968 recorded deaths, mortality was not lower in the biannual azithromycin group than the control group. Mortality was 7% lower in the quarterly azithromycin group, but the confidence interval around the point-estimate was wide and included the null value. There were no between-group differences in mortality among 12-59-month-old children residing in the same villages.

Internal validity of the findings could theoretically have been compromised by the lack of survival information on infants who had migrated or been otherwise lost to follow-up. Another potential source of bias was the non-treatment of infants who were temporarily absent, ill, considered allergic or for whom parents refused treatment. These events were, however, rare and balanced across trial groups. Given this and the large sample size, as well as the similarity of the groups at baseline and the rigorous quality assurance of trial conduct,[20,23] we consider the results valid and reliable. Thus, the findings do not support a hypothesis that azithromycin MDA, when limited to 1-11-month-old infants and given either quarterly or biannually, would reduce infant or child mortality in Mali. For some subgroups, data are consistent with an effect, but the possibility of random error cannot be excluded.

The LAKANA results are consistent with those from the AVENIR trial in Niger, which also found no significant mortality reduction when biannual azithromycin MDA was targeted at 1-11-month-old infants alone.[26] Furthermore, the CHAT and NAITRE trials in Burkina Faso, providing azithromycin to healthy infants at routine well-child visits in their first three months of life, did not document any protective effect with regard to mortality.[27,28] In contrast, there was evidence of a mortality reduction (point-estimate 14-18%) in both the MORDOR and AVENIR trials in Niger, which provided biannual azithromycin MDA to all 1-59-month-old infants and children.[4,26] Also in the CHAT trial in Burkina Faso, targeting the same wider age group biannually, 18% lower mortality was observed in clusters receiving azithromycin compared to clusters receiving placebo, although the difference was not statistically significant ($p = 0.07$).[29]

The current evidence thus suggests that azithromycin MDA reduces mortality among West African children if distributed to all 1-59-month-olds, but not if the intervention is limited to infants only. Whereas the mechanism of azithromycin MDA's mortality reduction is still uncertain, these results suggest containment of infectious diseases as one likely pathway.[30] Azithromycin has both antibacterial and anti-malarial activity,[31] and the attributable fraction of malaria and bacterial infections as a cause of death is higher among older children than among infants.[32,33] Older children also harbor more often potentially pathogenic Gram-negative bacteria in the gut than breast-fed infants,[34,35] and contribution of these bacteria to septic infections could be reduced in older children both by azithromycin's anti-inflammatory properties[36] as well as by its antibacterial effect.[37] Individual-level elimination of potential pathogens would also reduce the community burden of malaria and other infections, explaining the observed herd-protection among infants when older children were received included in the azithromycin MDA.[26]

One striking result in the LAKANA trial was the markedly lower than expected baseline mortality. When the trial was initially planned, the sample size was based on an assumed infant mortality rate (IMR) of approximately 70 deaths/1000 live births/year, documented for the Kayes region in the most recent (2018) demographic and health survey.[38] Based on observed mortality, the estimate was later downgraded to 60/1000 and the sample size increased accordingly.[20,23] The actual mortality in the control group was, however, only 12 deaths /1000 PYR, corresponding to an IMR of approximately 36 deaths/1000 live births. Another cluster-randomized trial in Mali documented a major under-five mortality decrease in a control group receiving no intervention, from 148 deaths/1,000 live births in 2017 to 55 in 2020.[39] These results suggest

a possible Hawthorne-effect on mortality, by other trial activities besides the specific intervention.[40] There is, however, also evidence of a national mortality reduction among under-five-year old children in Mali.[41] This lower-than-expected baseline mortality may partially explain lack of effect in the LAKANA trial, as there is evidence of an inverse relationship between baseline mortality and azithromycin MDA's effect on mortality.[42]

In its current guideline, WHO recommends limiting the target group to 1-11-month-old infants, if health professionals consider azithromycin MDA as a tool to promote child survival.[17] Whereas such a focused approach will certainly limit the risk of antimicrobial resistance (AMR), mortality results from the LAKANA, AVENIR, NAITRE and CHAT trials do not support this practice. For a mortality benefit, it seems critical to target a wider age group. Two countries in West Africa – Niger and Mali – are actually adopting this approach and scaling up biannual azithromycin MDA to 1-59-month-old children, in areas with the highest baseline mortality.[43,44] Because of the wider age-group and the known risk of AMR in population-wide azithromycin MDA,[19,45] it will be critical to monitor AMR prevalence in such scale-up projects. Monitoring mortality trends will be equally important, because the intervention's efficacy will likely wane with decreasing baseline mortality, and there is already evidence of rapid mortality declines among under-five-year-old children, both in Mali[39,41] as well as in the MORDOR and AVENIR trial sites in Niger.[4,26]

Data availability statement

Underlying data

The underlying data from the LAKANA Trial, *Mass administration of azithromycin to infants does not promote their survival in Mali*, have been deposited in Zenodo. Because open data sharing was not included in the study information sheet at the time of data collection, access to these datasets is restricted. Data will be made available to users who submit a written request outlining their proposed use and providing a justification and data use plan. Access requests should be submitted to the LAKANA Trial Project Steering Group, as listed on the trial registration record (ClinicalTrials.gov identifier: NCT04424511).

Zenodo: LAKANA analysis data. https://doi.org/10.5281/zenodo.15155036.[25]

This project includes the following datasets:

- **LAKANA Primary outcome data_de-ident_HIPAA.csv** – De-identified individual-level mortality and follow-up data for infants enrolled in the trial.
- **LAKANA Primary outcome data_older.csv** – De-identified individual-level mortality and follow-up data for older children in the trial.

Extended data

The original and latest versions of the LAKANA trial protocol, the CONSORT Checklist, as well as the underlying codebook and data dictionary are available at GitHub: https://github.com/LAKANA-Trial-team/Main-outcome.

The repository is archived on Zenodo: https://doi.org/10.5281/zenodo.15166981[24]

This component of the project includes:

- **LAKANA Protocol version 1.0_2019-11-27** – original protocol
- **LAKANA Protocol version 7.0_2024-11-13** – latest protocol
- LAKANA CONSORT 2010 Checklist
- **LAKANA data dictionary for main outcome analysis.xlsx** – Variable descriptions and coding information.
- **Analytical scripts** – Code used for data analysis.

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