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Azithromycin for the prevention of rehospitalisation and death among Kenyan children being discharged from hospital: a double-blind, placebo-controlled, randomised controlled trial

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Summary

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Contributors

JLW, PBP, BOS, RN, LM, BAR, JBB, and GCJ-S were responsible for the trial conceptualisation and funding acquisition. Data were obtained by a clinical research team supervised by BOS, MA, JO, and EA. Training and standardisation were managed by CJM and BOS. Laboratory analyses were overseen by DR, SNT-B, and SK. Clinical oversight and decision making were overseen by BOS, LM, and GB. Data cleaning and analysis were done by RLB, PBP, KDT, JDC, and BAR. KDT and JDC verified the data. PBP and JLW wrote the first draft of the manuscript and all authors edited and approved the content of the final manuscript. The final manuscript was also reviewed by all members of the Data and Safety Monitoring Board.

Declaration of interests

BAR reports participation on Data Safety and Monitoring Boards for HIV PrEP clinical trials funded by Gilead and COVID-19 treatment trials funded by the US National Institute of Allergy and Infectious Diseases, outside the submitted work. All other authors declare no competing interests.

Data sharing

The complete de-identified dataset, data dictionary, and analytical code are publicly available. Study protocol, informed consent forms, statistical analysis plan, and case report forms can be found in the appendix (pp 9–128).

See Online for appendix

For the dataset, data dictionary, and analytical code see https://dataverse.harvard.edu/dataset.xhtml?persistentId=doi:10.7910/DVN/YTMFOJ

Background—Mass drug administration of azithromycin to children in sub-Saharan Africa has been shown to improve survival in high-mortality settings. The period after hospital discharge is a time of elevated risk unaddressed by current interventions and might provide an opportunity for targeting empirical azithromycin administration. We aimed to assess the efficacy of azithromycin administered at hospital discharge on risk of death and rehospitalisation in Kenyan children younger than 5 years.

Methods—In this double-blind, placebo-controlled randomised trial, children were randomly assigned (1:1) to receive a 5-day course of azithromycin (oral suspension 10 mg/kg on day 1, followed by 5mg/kg per day on days 2–5) or identically appearing and tasting placebo at discharge from four hospitals in western Kenya. Children were eligible if they were aged 1–59 months at hospital discharge, weighed at least 2 kg, and had been admitted to hospital for any medical reason other than trauma, poisoning, or congenital anomaly. The primary outcome was death or rehospitalisation in the subsequent 6-month period in a modified intention-to-treat population, compared by randomisation group with Cox proportional hazards regression and Kaplan-Meier. Azithromycin resistance in *Escherichia coli* isolates from a random subset of children was compared by randomisation group with generalised estimating equations. This trial is registered with ClinicalTrials.gov, NCT02414399.

Findings—Between June 28, 2016, and Nov 4, 2019, 1400 children were enrolled in the trial at discharge from hospital, with 703 (50·2%) randomly assigned to azithromycin and 697 (49·8%) to placebo. Among the 1398 children included in the modified intention-to-treat analysis (702 in the azithromycin group and 696 in the placebo group), the incidence of death or rehospitalisation was 20·4 per 100 child-years in the azithromycin group and 22·5 per 100 child-years in the placebo group (adjusted hazard ratio 0·91, 95·5% CI 0·64–1·29, p=0–58). Azithromycin resistance was common in commensal *E coli* isolates from enrolled children before randomisation (37·7% of 406 isolates) despite only 3·7% of children having received a macrolide antibiotic during the hospitalisation. Azithromycin resistance was slightly higher at 3 months after randomisation in the azithromycin group (26·9%) than in the placebo group (19·1%; adjusted prevalence ratio 1·41, 95% CI 0·95–2·09, p=0·088), with no difference observed at 6 months (1·17, 0·78–1·76, p=0·44).

Interpretation—We did not observe a significant benefit of a 5-day course of azithromycin delivered to children younger than 5 years at hospital discharge despite the overall high risk of mortality and rehospitalisation. These findings highlight the need for more research into mechanisms and interventions for prevention of morbidity and mortality in the post-discharge period.

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Introduction

Over 5 million children younger than 5 years die annually in sub-Saharan Africa, primarily from infectious diseases.[1] A large trial of biannual mass drug administration of azithromycin delivered to children younger than 5 years living in Niger, Tanzania, and Malawi—the MORDOR trial—reported a 13·5% reduction in child mortality during the 24-month follow-up period.[2] These findings have prompted interest in the empirical use of azithromycin to prevent under-5 mortality in sub-Saharan Africa, including the issuance of a policy statement by WHO.[3]

Despite evidence of benefit in reducing death in specific populations and settings, mass drug administration with azithromycin can lead to community-wide azithromycin resistance in the intestinal resistome (the collection of all antibiotic resistance genes in intestinal microbiota) and in nasal *Streptococcus pneumoniae* isolates.[4–9] Although the individual-level implications of azithromycin resistance in the absence of disease are unclear, the potential for reduced clinical efficacy of macrolide antibiotics is of global public health concern.[10–12] Alternative azithromycin delivery strategies that reduce mortality while limiting antibiotic pressure are urgently needed.

Targeting the delivery of azithromycin to children at high risk of death might optimise benefit while minimising antibiotic exposure.[13] In sub-Saharan Africa, children recently discharged from hospital are an accessible population at high risk of mortality and rehospitalisation in the months after discharge.[14,15] Although the mechanisms underpinning this elevated risk are incompletely understood, factors such as untreated ongoing infections, nosocomial or community-acquired infections, and alterations in the gut microbiota as a result of health-care exposure all likely contribute to this elevated risk.

We hypothesised that targeted azithromycin delivered to children at hospital discharge would reduce severe morbidity and mortality while minimising population-level exposure to this broad-spectrum macrolide antibiotic. To test this hypothesis, we did a randomised clinical trial testing the effect of azithromycin administered at hospital discharge on risk of death and rehospitalisation in Kenyan children younger than 5 years.

Methods

Study design and participants

The Toto Bora trial was a multi-site, double-blind, placebo-controlled randomised controlled trial done at four hospitals in Kenya. The trial protocol and statistical analysis plan are described elsewhere (appendix pp 9–44).[16] Briefly, children were recruited from the inpatient wards of Kisii Teaching and Referral Hospital, Homa Bay Teaching and Referral Hospital, St Paul Mission Hospital, and Kendu Adventist Mission Hospital (Kenya) between June 28, 2016, and Nov 4, 2019. All children discharged during study working hours (Monday to Friday 0800 h to 1600 h) were screened for eligibility. Children aged 1–59 months were eligible at hospital discharge if they weighed at least 2 kg and had been admitted to hospital for any medical reason other than trauma, poisoning, or congenital anomaly. Children were excluded if they had been prescribed a macrolide antibiotic (ie, azithromycin, erythromycin, or clarithromycin) at discharge, were taking a protease inhibitor (eg, lopinavir) for HIV infection, or if they had a documented allergy to macrolide antibiotics. Additionally, children were excluded if their caregiver did not plan for them to remain in the study area for 6 months, if a twin sibling of the same sex was enrolled contemporaneously, or if the accompanying caregiver was not the legal guardian.

The trial was approved by the institutional review boards at the Kenya Medical Research Institute (KEMRI; SERU 3086, Sept 8, 2015, to present), the Kenya Pharmacy and Poisons Board (ECCT/15/10/04, Dec 3, 2015, to present), and the University of Washington (IRB 49120, June 2, 2015, to present). Caregivers gave informed written consent in their preferred

local language (English, Kiswahili, Kisii, or Luo). If a caregiver was not literate, information was read to the caregiver in the language of their choice, and consent was obtained using a witnessed thumbprint.

Randomisation and masking

Participants were randomly assigned (1:1) in blocks of ten, stratified by site, to receive either azithromycin or identically appearing and tasting placebo at discharge. By use of a random number generator in Microsoft Excel, each participant was assigned a unique identifier, and the randomisation code linking each identifier to the allocated treatment was maintained by staff not otherwise involved in the study. Identically appearing bottles were labelled with the unique identifier, masking study staff and participants to randomisation group. Study participants, investigators, the study staff, hospital clinicians, and individuals involved in data management or analysis were masked to the allocation group during all data collection and management phases of the study.

Procedures

Consenting caregivers were interviewed to assess demographic information and medical history, and clinical data of the child were abstracted from hospital records, including presenting diagnosis, medical management, length of stay, procedures done, relevant medical history, physical examination, and laboratory data. Case report forms can be found in the appendix (pp 53–128). These interviews ranged from 30 min to 60 min in length. A physical examination was done by a study clinician, including measurement of height or length, weight, and mid-upper arm circumference.

After discharge, enrolled children received either a 5-day course of oral suspension formulation azithromycin (10 mg/kg on day 1, followed by 5 mg/kg per day on days 2–5) or identically appearing and tasting placebo. The first dose was directly observed. Doses on days 2–5 were administered by caregivers at home. Caregivers were asked to record each administered dose and to return bottles at the 3-month follow-up visit.

During scheduled follow-up visits at 3 months and 6 months post-discharge, history of recent illness or morbidity, post-discharge medication use, and current condition of the child were collected by use of a standardised questionnaire. If the child could not return to the facility, a member of the study staff visited the child’s home. If the child was not found at their home after two attempts, a telephone interview was done, lasting 20–45 min. If hospitalisations were reported during the interview, their date, length of stay, and medications administered were ascertained from both caregivers and medical records (when accessible). Caregivers were encouraged to bring the child to the study health facility when seeking care for illness (unscheduled visits) and the study team triaged the child’s care.

When a death occurred, a verbal autopsy was done with use of a validated questionnaire.[11] Final causes of death were determined by consensus among masked clinical investigators (BOS, KDT, and JLW) on the basis of available death certificates, medical records, and verbal autopsies.

We collected whole stool or flocked rectal swabs (Pediatric FLOQswab, Copan Diagnostics, Murrieta, CA, USA) before study medication administration at enrolment and at the 3-month and 6-month follow-up visits. A portion of stool or swab was placed in Cary-Blair media (Copan Diagnostics) within 1 h of collection. Samples were maintained between 2°C and 8°C and shipped to the KEMRI Center for Microbiology laboratory in Nairobi for processing within 24 h of collection. *Escherichia coli* colonies were grown and identified by use of selective and differential agar plating, Gram staining, and oxidase testing and further confirmed using API-20E testing kits (bioMerieux, Marcy-l'Étoile, France). Three colonies per sample were pooled into 15% glycerol and frozen at −80°C for potential antibiotic susceptibility testing.

E coli isolates from a randomly selected subset of children enrolled in the trial underwent antibiotic resistance testing with the disc diffusion method. Frozen stocks were thawed, quadrant-streaked onto MacConkey agar, and incubated at 37°C in ambient air. If more than one morphologically distinct colony was present upon restoration, each was individually subjected to antibiotic susceptibility testing. Isolates from up to three morphologies were placed separately in 5 mL of normal saline standardised to a 0·5 MacFarland turbidity standard and plated on Mueller Hinton agar with antibiotic discs placed on the agar surface. Plates were inoculated for 18–24 h at 37°C before the measurement of zones of inhibition. Zone sizes had not been established for resistance to azithromycin in *E coli* at the time of writing; therefore we considered 13 mm or more to be susceptible and 12 mm or less to be resistant on the basis of epidemiological breakpoints for *Salmonella enterica* serotype Typhi.[17] If a child had more than one morphologically distinct *E coli* isolate at a given timepoint, the *E coli* was considered resistant to azithromycin if one or more of the colonies was resistant.

Outcomes

The primary outcome was death or rehospitalisation in the 6 months after hospital discharge. Secondary outcomes included cause-specific death and proportion of children with azithromycin-resistant *E coli*. Mild, moderate, and severe adverse events were identified by the study clinicians during clinical examinations at scheduled and unscheduled follow-up or reported by caregivers during interviews at scheduled visits. Event severity was defined according to the 2014 Division of AIDS table for grading the severity of adult and paediatric adverse events. Adverse events were captured throughout the entire follow-up period, and plausible relatedness was determined by the clinical team after full review of the case. Non-serious adverse events were considered to be possibly related to the study drug if a recognised side-effect of azithromycin (diarrhoea, vomiting, rash, facial or airway swelling, difficulty breathing, jaundice, and abdominal swelling) occurred within 72 h of a scheduled drug administration (ie, within 7 days of study enrolment).

Statistical analysis

A sample size of 1400 children was calculated for the primary endpoint, assuming an α level of 0·05, power of 0·80, 1:1 randomisation, 20% loss to follow-up, a cumulative incidence of 22·5% for the combined outcome among children treated with placebo,[14,15,18] and a hazard ratio of 0·70. At the time of study planning (2013–14), the best evidence of the effect of

empirical azithromycin on childhood mortality was an observed 49% reduction in mortality after azithromycin mass drug administration in Ethiopia;[19] thus a 30% reduction was chosen as a more conservative effect size.

We used Cox proportional hazards regression to compare the rates of death or first rehospitalisation after discharge on the basis of randomisation allocation, excluding any children deemed ineligible after randomisation (modified intention-to-treat [mITT]). All analyses were adjusted for site as an indicator variable. In secondary analyses, we adjusted for breastfeeding status and a discharge diagnosis of "other", modelled as indicator variables, to account for a possible imbalance in these two variables between the randomisation groups. In per-protocol analyses, we compared treatment effects in groups defined by self-reported adherence to the 5-day course of azithromycin (five doses *vs* fewer than five doses). The primary adherence measure was self-reporting at follow-up visits and the secondary adherence measure was the number of bottle tick marks on returned bottles collected at follow-up visits. Additionally, we did Cox regression for time to mortality and time to rehospitalisation as separate endpoints. In prespecified subgroup analyses, we compared treatment effects in children whose caregivers reported no additional antibiotic use during follow-up and among subsets of children defined by age, site, HIV status, malnutrition status, and discharge diagnosis. An α of 0·045 was used as the statistical significance boundary for the final primary analysis due to α spending at a predefined interim analysis, as specified in the statistical analysis plan (appendix pp 31–44).

We modelled azithromycin resistance in *E coli* at baseline, 3 months, and 6 months of follow-up by randomisation group using generalised estimating equations with a Poisson link and exchangeable correlation structure, including site in the model. Models included an interaction term between randomisation group and follow-up timepoint (month 3 or month 6) to test whether an effect on resistance waned with time. Prevalence ratios (PRs) were reported for two-way comparisons between randomisation groups and within randomisation groups, by follow-up visit. *E coli* isolated from stool collected at follow-up visits outside of a 60–120-day window for 3-month visits and outside of a 150–210-day window for 6-month visits were excluded from the primary analysis but included in sensitivity analyses. Models were done in the mITT population among those with antimicrobial resistance testing done and in whom *E coli* was isolated. All analyses were done in STATA, version 16.0, and R.

A data safety and monitoring committee reviewed monthly adverse event summaries and details of severe adverse events. A single interim analysis was done in Dec 20, 2018, when 50% of expected person-time (350 child-years) was accrued. O'Brien-Fleming boundaries with a two-sided Z score critical value of 2·797 or −2·797 (p value <0·005) were used to compare the interim analysis p value from a Kaplan-Meier log-rank test. This trial is registered with ClinicalTrials.gov, NCT02414399.

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, decision to publish, or preparation of the manuscript.

Results

Between June 28, 2016, and Nov 4, 2019, 3283 children discharged from study hospitals were screened for eligibility and 1400 of those were enrolled in the trial, with 703 (50·2%) randomly assigned to azithromycin and 697 (49·8%) to placebo (figure 1). One child in each group was deemed ineligible after randomisation: one child in the azithromycin group had been admitted for poisoning and one in the placebo group had a twin sibling of the same sex enrolled in the trial on the same day.

Among the 1398 children included in the mITT analysis, 465 (33·3%) were younger than 12 months, 570 (40·8%) were girls, and 874 (62·5%) were from households living on less than US$1·90 per day (table 1). At enrolment, 315 (22·6%) children were stunted, 132 (9·4%) had acute malnutrition, 147 (10·5%) were exposed to HIV, and 18 (1·3%) were confirmed to be infected with HIV. Common diagnoses at discharge included lower respiratory tract infection, malaria, and gastroenteritis or diarrhoea (table 1). Participant characteristics were balanced across the randomisation groups, except for slightly fewer children in the azithromycin group with a diagnosis of “other” (driven largely by more urinary tract infection diagnoses in the placebo group than in the azithromycin group) and slightly more children in the azithromycin group being partly (rather than exclusively) breastfed during the first 6 months of life.

Most children (1253 [89·6%]) received an antibiotic during hospitalisation, most commonly penicillin (839 [60·0%] of 1398 in the mITT), gentamicin (757 [54·2%]), and ceftriaxone (538 [38·5%]). Macrolides (azithromycin, clarithromycin, or erythromycin) were infrequently given in hospital (52 [3·7%]), with azithromycin prescribed to only 24 (1·7%) children. Many children (867 [62·0%]) were also prescribed an antibiotic at discharge, most commonly amoxicillin (600 [42·9%]), penicillin (87 [6·2%]), and cefuroxime (82 [5·9%]). Antimalarials were also frequently administered in hospital, with 509 (36·4%) children receiving an antimalarial during hospitalisation, most commonly artemether lumefantrine (161 [11·5%]), paludrine (49 [3·5%]), artesunate (447 [32·0%]), and quinine (two [0·1%]). Additionally, nearly a third (379 [27·1%]) of children were prescribed an antimalarial at discharge (281 [20·1%] artemether lumefantrine, 106 [7·6%] paludrine, and three [0·2%] artesunate).

34 (2·4%) children died during the 6-month follow-up and 115 (8·2%) children were rehospitalised at least once (table 2). Ten children (0·7%) were hospitalised twice. The incidence of the combined outcome of death or first rehospitalisation was 20·4 per 100 child-years in children randomly assigned to azithromycin and 22·5 per 100 child-years in the placebo group (adjusted hazard ratio [HR] 0·91, 95·5% CI 0·64-1·29, p=0·58; table 2, figure 2). The incidence of rehospitalisation alone was similar in the azithromycin and placebo groups (table 2). Approximately a quarter of the 115 first rehospitalisations occurred in the first 30 days after initial discharge (13 [22·4%] of 58 in the azithromycin group and 15 [26·3%] of 57 in the placebo group). The incidence of death was 4·7 per 100 child-years in the azithromycin group and 6·0 per 100 child-years in the placebo group (adjusted HR 0·79, 95·5% CI 0·39-1·58). Approximately a third of deaths in each group occurred in the first 30 days of follow-up (four [26·7%] of 15 in the azithromycin group and seven [36·8%] of 19

in the placebo group), two of which in each group occurred within the first 7 days. Another third of deaths occurred in the 31–90-day post-discharge period (six [40·0%] of 15 in the azithromycin group and six [31·6%] of 19 in the placebo group) and the remaining third occurred 91–180 days after discharge (five [33·3%] of 15 in the azithromycin group and six [31·6%] of 19 in the placebo group). Causes of death are reported in table 3. Subgroup analyses did not identify subgroups more or less likely to benefit from azithromycin's effect on risk of rehospitalisation or death in the 6-month post-discharge period (appendix p 6).

All children were directly observed receiving the first dose of study drug, and more than 90% received all five doses according to caregiver report by questionnaire (appendix p 3). Roughly 70% of caregivers returned bottles for the secondary adherence assessment (702 [73·3%] in the azithromycin group and 696 [71·7%] in the placebo group), and 265 (51·5%) in the azithromycin group and 266 (53·3%) in the placebo group indicated by tick mark that all five doses were administered to the child. In per-protocol analyses—excluding children who did not receive the full course (by caregiver report in questionnaire or by bottle tick marks), who had consent withdrawn, or who were lost to follow-up—the effect of azithromycin on the risk of death or rehospitalisation (alone or in combination) did not meaningfully differ from the mITT analysis results (appendix pp 4–6).

E coli were isolated from faecal samples from 1219 (87·2%) of 1398 children at hospital discharge, from 1212 (96·1%) of 1261 with faecal samples at 3 months, and 1145 (94·6%) of 1210 with faecal samples at 6 months. 406 children enrolled with at least one baseline *E coli* isolate were randomly selected for antimicrobial resistance testing; of those, 350 had month 3 isolates and 330 had month 6 isolates also available from within the 1-month window for antimicrobial resistance testing. 153 (37·7%) baseline *E coli* isolates were resistant to azithromycin (38·4% in the azithromycin group and 36·9% in the placebo group). At the 3-month follow-up visit, these percentages decreased by almost half in both groups (PR 0·54, 95% CI 0·32–0·91, p=0·02 for month 3 *vs* month 0 visit in the azithromycin group, and 0·52, 0·35–0·75, p=0–001 for month 3 *vs* month 0 visit in the placebo group; figure 3). We observed a modestly higher prevalence of azithromycin resistance 3 months after randomisation in the azithromycin group (26·9%) than in the placebo group (19·1%; PR 1·41, 95% CI 0·95–2·09, p=0·088) with no difference at 6 months after randomisation between the intervention and placebo groups (1·17, 0·78–1·76, p=0·44, $p_{\text{time-interaction}}$ =0·45). When including *E coli* isolates that occurred outside of visit windows, results did not meaningfully differ (appendix p 8).

Discussion

In this randomised, double-blind, placebo-controlled trial of 1400 children in Kenya, a 5-day course of azithromycin administered to children being discharged from hospital did not decrease the risk of the combined outcome of mortality or rehospitalisation in the subsequent 6-month period. We did not observe a significant benefit in this trial despite the overall high risk of mortality and rehospitalisation. Our findings differ from those found in other mass drug administration trials of azithromycin for mortality prevention.[20] The high rates of adverse outcomes observed underscore the importance of the post-discharge period to child health and the need to develop guidelines and interventions for this crucial period.

WHO guidelines recommend mass drug administration with azithromycin to promote survival in children aged 1–11 months in settings where the under-5 mortality is more than eight deaths per 100 child-years on the basis of several trials of azithromycin delivered through mass drug administration.[3,20] We did not detect an age effect in reducing the combined outcome of death or rehospitalisation, despite observing a mortality rate of 8·1 deaths per 100 child-years in children younger than 1 year. This study was designed to detect a primary outcome of death or rehospitalisation and was not designed or powered to evaluate mortality alone or to evaluate age-specific effects. As a result, we cannot exclude the possibility that azithromycin delivered at hospital discharge confers a mortality benefit at least as large as that observed in studies of mass drug administration to improve child survival.

Almost all children received antibiotics during their inpatient stay and most were prescribed antibiotics at discharge, although we do not know how many of those prescriptions were filled. It is possible that these antibiotics treated nosocomial or incompletely treated infections, reducing the additional benefit of azithromycin in the early discharge period. Alternative treatment schedules, such as intermittent antimicrobial administration, might be a more effective strategy for post-discharge treatment with azithromycin, as has been shown in trials of post-discharge malaria chemoprophylaxis.[21,22] High antibiotic usage during and immediately after hospital discharge might also have selected for antimicrobial resistance, which could have further reduced the benefit conferred by azithromycin. Importantly, mortality benefits observed in mass drug administration trials of azithromycin might be due to the indirect effects related to population-wide delivery, such as reducing pathogen load in communities and environments, which could explain the lack of effect in this targeted, individually randomised trial. Such indirect effects have been observed in trials of mass drug administration of azithromycin for trachoma control.[23,24]

Over a third of enrolled children had azithromycin resistance detected in commensal *E coli* at the time of randomisation, despite few receiving a macrolide antibiotic during their hospital stay. Although azithromycin resistance was common among children at hospital discharge, resistance declined substantially in the 3 months and 6 months after discharge in both study groups. This decline might be due to a fitness disadvantage of azithromycin-resistant *E coli* isolates such that once antibiotic pressure is removed, wild-type isolates become more predominant.[25] This occurrence could explain why individual-level antibiotic use tends to be a less important driver of antibiotic resistance than community use of antibiotics or a physical environment conducive to resistance-gene sharing, such as crowded settings with poor sanitation.[26–28] We observed a slightly higher azithromycin resistance prevalence in *E coli* isolates from children randomly assigned to the azithromycin group at 3 months but this difference of borderline significance was no longer present at 6 months, consistent with transient increases observed in some mass drug administration trials.[4–7,29]

Our study had high retention (>99%), a well characterised study population, complete adherence to the first dose of study medication, and high adherence to the full 5-day course reported by caregivers. However, our study also had important limitations. With the number of events observed (n=132), we were powered to detect an HR of 0·61 for the combined endpoint of death or rehospitalisation and, with 34 deaths, an HR of 0·35 for

the outcome of death alone. Powering our trial for the observed HR of 0·91 (or a 9% reduction in rehospitalisation or death) would have required 36 000 children to be enrolled. 22 000 children would have been required to detect the observed HR for death alone of 0·79. These sample sizes exceed what is feasible within individually randomised clinical trials, but community-randomised trials are powered to detect these more modest effect sizes.[2] We chose to evaluate a combined outcome of death and rehospitalisation because hospitalisation is strongly associated with mortality and represents a severe economic event to many families, even in settings where paediatric care is free.[14] However, hospitalisation might be a heterogeneous outcome, driven partly by financial resources and location.[30] A trial of azithromycin in conjunction with seasonal malaria prophylaxis in Mali and Burkina Faso also used a combined outcome of all-cause hospitalisation or death and observed no evidence of benefit, perhaps also due to hospitalisation being a heterogeneous outcome.[31] Additionally, the assessment of adherence to the study medication in this trial was limited to self-report, which might have overestimated the true adherence to the study medication.

As countries work towards achieving the sustainable development goal of reducing childhood mortality to fewer than 25 deaths per 1000 livebirths,[32] hospital discharge represents a practical timepoint for delivering life-saving interventions to children at high risk. Although several trials of azithromycin delivered through mass drug administration have shown mortality benefit, our trial did not show efficacy in reducing mortality or rehospitalisation with a 5-day course of azithromycin administered to children younger than 5 years at discharge from hospital. Novel interventions to reduce mortality and morbidity during the post-discharge period are urgently needed to address the substantial burden of illness during this crucial period.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2016 results. Seattle, WA: Institute for Health Metrics and Evaluation, 2017.

2. Keenan JD, Bailey RL, West SK, et al. Azithromycin to reduce childhood mortality in sub-Saharan Africa. N Engl J Med 2018; 378: 1583–92. [PubMed: 29694816]

3. WHO. WHO guideline on mass drug administration of azithromycin to children under five years of age to promote child survival. Geneva: World Health Organization, 2020.

4. Coles CL, Mabula K, Seidman JC, et al. Mass distribution of azithromycin for trachoma control is associated with increased risk of azithromycin-resistant *Streptococcus pneumoniae* carriage in young children 6 months after treatment. Clin Infect Dis 2013; 56: 1519–26. [PubMed: 23487375]

5. Haug S, Lakew T, Habtemariam G, et al. The decline of pneumococcal resistance after cessation of mass antibiotic distributions for trachoma. Clin Infect Dis 2010; 51: 571–74. [PubMed: 20649409]

6. Skalet AH, Cevallos V, Ayele B, et al. Antibiotic selection pressure and macrolide resistance in nasopharyngeal *Streptococcus pneumoniae*: a cluster-randomized clinical trial. PLoS Med 2010; 7: e1000377. [PubMed: 21179434]

7. Seidman JC, Coles CL, Silbergeld EK, et al. Increased carriage of macrolide-resistant fecal *E. coli* following mass distribution of azithromycin for trachoma control. Int J Epidemiol 2014; 43: 1105–13. [PubMed: 24659584]

8. Seidman JC, Johnson LB, Levens J, et al. Longitudinal comparison of antibiotic resistance in diarrheagenic and non-pathogenic *Escherichia coli* from young Tanzanian children. Front Microbiol 2016; 7: 1420. [PubMed: 27656179]

9. Doan T, Worden L, Hinterwirth A, et al. Macrolide and nonmacrolide resistance with mass azithromycin distribution. N Engl J Med 2020; 383: 1941–50. [PubMed: 33176084]

10. Hoffman SJ, Caleo GM, Daulaire N, et al. Strategies for achieving global collective action on antimicrobial resistance. Bull World Health Organ 2015; 93: 867–76. [PubMed: 26668439]

11. Serina P, Riley I, Stewart A, et al. A shortened verbal autopsy instrument for use in routine mortality surveillance systems. BMC Med 2015; 13: 302. [PubMed: 26670275]

12. Poddighe D Macrolide resistance and longer-term assessment of azithromycin in MORDOR I. N Engl J Med 2019; 381: 2184–85.

13. Oldenburg CE, Arzika AM, Maliki R, et al. Optimizing the number of child deaths averted with mass azithromycin distribution. Am J Trop Med Hyg 2020; 103: 1308–10. [PubMed: 32067626]

14. Moisi JC, Gatakaa H, Berkley JA, et al. Excess child mortality after discharge from hospital in Kilifi, Kenya: a retrospective cohort analysis. Bull World Health Organ 2011; 89: 725–32, 32A. [PubMed: 22084510]

15. Wiens MO, Pawluk S, Kissoon N, et al. Pediatric post-discharge mortality in resource poor countries: a systematic review. PLoS One 2013; 8: e66698. [PubMed: 23825556]

16. Pavlinac PB, Singa BO, John-Stewart GC, et al. Azithromycin to prevent post-discharge morbidity and mortality in Kenyan children: a protocol for a randomised, double-blind, placebo-controlled trial (the Toto Bora trial). BMJ Open 2017; 7: e019170.

17. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing, 30th edn. Wayne, PA: Clinincal and Laboratory Standards Institute, 2020.

18. Snow RW, Howard SC, Mung'Ala-Odera V, et al. Paediatric survival and re-admission risks following hospitalization on the Kenyan coast. Trop Med Int Health 2000; 5: 377–83. [PubMed: 10886803]

19. Porco TC, Gebre T, Ayele B, et al. Effect of mass distribution of azithromycin for trachoma control on overall mortality in Ethiopian children: a randomized trial. JAMA 2009; 302: 962–68. [PubMed: 19724043]

20. Oldenburg CE, Arzika AM, Amza A, et al. Mass azithromycin distribution to prevent childhood mortality: a pooled analysis of cluster-randomized trials. Am J Trop Med Hyg 2019; 100: 691–95. [PubMed: 30608051]

21. Kwambai TK, Dhabangi A, Idro R, et al. Malaria chemoprevention in the postdischarge management of severe anemia. N Engl J Med 2020; 383: 2242–54. [PubMed: 33264546]

22. Phiri K, Esan M, van Hensbroek MB, Khairallah C, Faragher B, ter Kuile FO. Intermittent preventive therapy for malaria with monthly artemether-lumefantrine for the post-discharge management of severe anaemia in children aged 4–59 months in southern Malawi: a multicentre, randomised, placebo-controlled trial. Lancet Infect Dis 2012; 12: 191–200. [PubMed: 22172305]

23. House JI, Ayele B, Porco TC, et al. Assessment of herd protection against trachoma due to repeated mass antibiotic distributions: a cluster-randomised trial. Lancet 2009; 373: 1111–18. [PubMed: 19329003]

24. Chidambaram JD, Melese M, Alemayehu W, et al. Mass antibiotic treatment and community protection in trachoma control programs. Clin Infect Dis 2004; 39: e95–97. [PubMed: 15494901]

25. Andersson DI, Hughes D. Antibiotic resistance and its cost: is it possible to reverse resistance? Nat Rev Microbiol 2010; 8: 260–71. [PubMed: 20208551]

26. Walson JL, Marshall B, Pokhrel BM, Kafle KK, Levy SB. Carriage of antibiotic-resistant fecal bacteria in Nepal reflects proximity to Kathmandu. J Infect Dis 2001; 184: 1163–69. [PubMed: 11598839]

27. Ramay BM, Caudell MA, Cordón-Rosales C, et al. Antibiotic use and hygiene interact to influence the distribution of antimicrobial-resistant bacteria in low-income communities in Guatemala. Sci Rep 2020; 10: 13767. [PubMed: 32792543]

28. Collignon P, Beggs JJ, Walsh TR, Gandra S, Laxminarayan R. Anthropological and socioeconomic factors contributing to global antimicrobial resistance: a univariate and multivariable analysis. Lancet Planet Health 2018; 2: e398–405. [PubMed: 30177008]

29. Doan T, Arzika AM, Hinterwirth A, et al. Macrolide resistance in MORDOR I—a cluster-randomized trial in Niger. N Engl J Med 2019; 380: 2271–73. [PubMed: 31167060]

30. Chuma J, Gilson L, Molyneux C. Treatment-seeking behaviour, cost burdens and coping strategies among rural and urban households in coastal Kenya: an equity analysis. Trop Med Int Health 2007; 12: 673–86. [PubMed: 17445135]

31. Chandramohan D, Dicko A, Zongo I, et al. Effect of adding azithromycin to seasonal malaria chemoprevention. N Engl J Med 2019; 380: 2197–206. [PubMed: 30699301]

32. UN General Assembly. Transforming our world: the 2030 agenda for sustainable development. 2015. https://sdgs.un.org/2030agenda (accessed Sept 1, 2020).

Research in context

Evidence before this study

We reviewed relevant clinical trials on the effect of azithromycin on morbidity and mortality identified by searching PubMed for articles in English from inception to Dec 25, 2020, using the following MeSH search terms: "("mortality" OR "morbidity") AND "azithromycin" AND "Africa, Sub Saharan"", with filters accepting only "(clinical trials OR systematic reviews)" and "children". These search criteria yielded 35 results, including a systematic review and meta-analysis of cluster-randomised clinical trials of the effect of mass azithromycin use for prevention of childhood mortality in sub-Saharan Africa. This meta-analysis reported pooled child mortality rates in azithromycin-treated and placebo-treated communities. We found only a single individually randomised trial of azithromycin that evaluated a combined outcome of hospitalisation or death (a trial of azithromycin in conjunction with seasonal malaria chemoprevention), which found no difference between randomisation groups.

Added value of this study

We did an individually randomised double-blind, placebo-controlled trial of a 5-day course of azithromycin given to 1400 Kenyan children who were discharged from hospital. Children discharged from hospital are an accessible population at high risk of morbidity and mortality, in whom the targeted use of azithromycin could reduce mortality while minimising risk of community-wide antibiotic resistance. Despite the high incidence of rehospitalisation and death in children treated with placebo, we found no evidence of an effect of azithromycin on the combined outcome of rehospitalisation or death and a modestly higher prevalence of azithromycin resistance at 3 months but not at 6 months after randomisation.

Implications of all the available evidence

As countries work towards achieving the Sustainable Development Goal of reducing childhood mortality to fewer than 25 deaths per 1000 livebirths, hospital discharge represents a practical timepoint for delivering life-saving interventions to children at high risk. We did not find evidence of benefit in reducing mortality or rehospitalisation from a 5-day course of azithromycin administered at discharge from hospital. In 2020, WHO released a series of evidence reviews and guidelines recommending against universal mass drug administration of azithromycin for preventing child mortality but included a consideration for its use among children aged 1–11 months living in sub-Saharan African settings with high child mortality rates. The lack of an observed effect in our trial highlights the need for further research into mechanisms of childhood mortality prevention from empirical azithromycin administration.

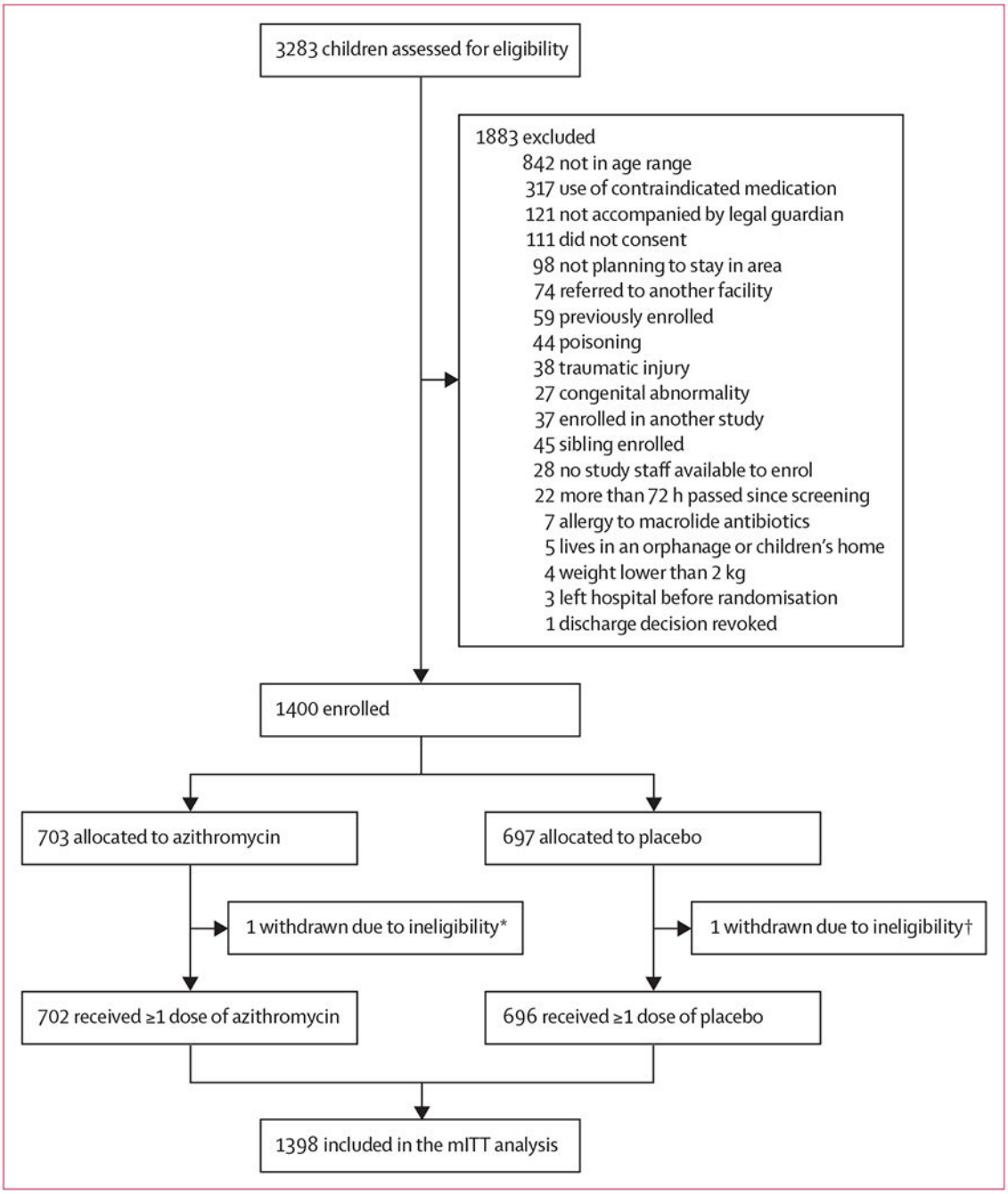

Figure 1: Trial profile

mITT=modified intention to treat. *Child was admitted for poisoning alone, which is an exclusion criterion. †Child was a twin whose sibling had already been enrolled.

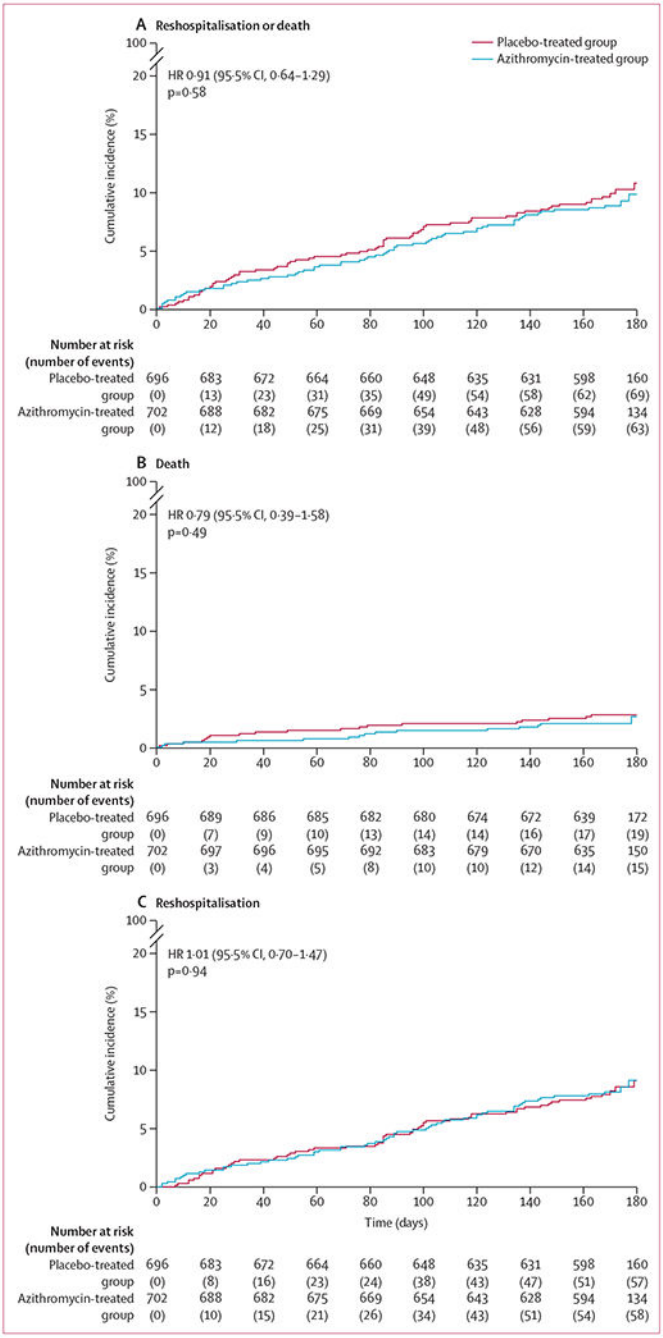

Figure 2: Kaplan-Meier curves of time to first rehospitalisation or death (A), death alone (B), and time to first rehospitalisation alone (C) by randomisation group

HR=hazard ratio.

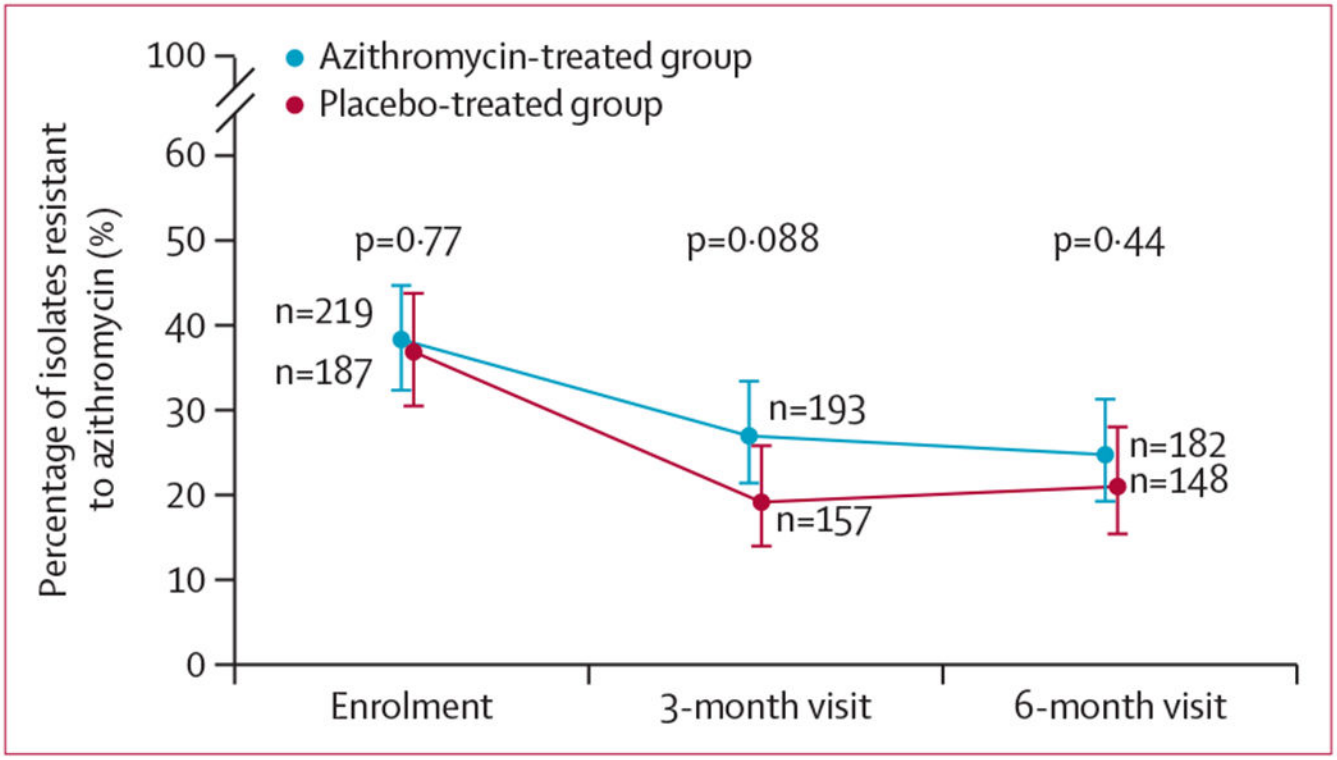

Figure 3: Percentage of *Escherichia coli* isolates resistant to azithromycin

Error bars are 95% CI. The p values are from a generalised estimating equation model containing all timepoints with Poisson link, exchangeable correlation structure, and time by resistance (yes or no) interaction.

Table 1:

Baseline characteristics overall and by randomisation group

	All (n=1398)	Azithromycin-treated group (n=702)	Placebo-treated group (n=696)
Site			
Kisii Teaching and Referral Hospital	822 (58·8%)	412 (58·7%)	410 (58·9%)
Homa Bay County Referral Hospital	521 (37·3%)	259 (36·9%)	262 (37·6%)
Kendu Adventist Hospital	36 (2·6%)	20 (2·8%)	16 (2·3%)
St Paul Mission Hospital	19 (1·4%)	11 (1·6%)	8 (1·1%)
Sociodemographic characteristics			
Age at enrolment, months			
1–5	188 (13·4%)	94 (13·4%)	94 (13·5%)
6–11	277 (19·8%)	141 (20·1%)	136 (19·5%)
12–23	406 (29·0%)	202 (28·8%)	204 (29·3%)
24–59	527 (37·7%)	265 (37·7%)	262 (37·6%)
Age at entry, months	18 (9–32)	18 (9–31)	18 (9–33)
Sex			
Female	570 (40·8%)	276 (39·3%)	294 (42·2%)
Male	828 (59·2%)	426 (60·7%)	402 (57·8%)
Extreme poverty *	874 (62·5%)	433 (61·7%)	441 (63·4%)
Caregiver schooling no higher than primary school †	644 (46·1%)	333 (47·5%)	311 (44·7%)
Household living conditions			
Crowding (≥2 people per room living in house)	629 (45·0%)	310 (44·2%)	319 (45·8%)
Unimproved water source (well, spring, or surface water) †	243 (17·4%)	125 (17·8%)	118 (17·0%)
Reported treating drinking water †‡	691 (50·5%)	348 (50·7%)	343 (50·4%)
Toilet type †			
Flush	135 (9·7%)	74 (10·6%)	61 (8·8%)
Pit latrine	1209 (86·5%)	599 (85·4%)	610 (87·6%)
Open defecation	53 (3·8%)	28 (4·0%)	25 (3·6%)
Admission history			
Discharge diagnoses §			
Anaemia	178 (13·4%)	102 (15·2%)	76 (11·5%)
Gastroenteritis or diarrhoea	251 (18·9%)	127 (19·0%)	124 (18·8%)
Lower respiratory tract infection	436 (32·8%)	211 (31·5%)	225 (34·1%)
Malaria	334 (25·1%)	174 (26·0%)	160 (24·2%)
Malnutrition	88 (6·6%)	44 (6·6%)	44 (6·7%)
Meningitis	68 (5·1%)	40 (6·0%)	28 (4·2%)
Sepsis	52 (3·9%)	28 (4·2%)	24 (3·6%)

	All (n=1398)	Azithromycin-treated group (n=702)	Placebo-treated group (n=696)
Sickle cell[¶]	108 (8·1%)	53 (7·9%)	55 (8·3%)
Tuberculosis	23 (1·7%)	13 (1·9%)	10 (1·5%)
Other[//]	201 (15·1%)	83 (12·4%)	118 (17·9%)
Duration of hospital admission, days	3 (2–5)	3 (2–5)	3 (2–5)
Left hospital against medical advice	2 (0·1%)	1 (0·1%)	1 (0·1%)
Received antibiotics in hospital	1253 (89·6%)	628 (89·5%)	625 (89·8%)
Prescribed antibiotics at discharge	867 (62·0%)	447 (63·7%)	420 (60·3%)
Nutritional, HIV, and vaccine status			
Breastfeeding status (in first 6 months of life)[**]			
Exclusively breastfed	663 (47·4%)	322 (45·9%)	341 (49·0%)
Partly breastfed	632 (45·2%)	334 (47·6%)	298 (42·8%)
Never breastfed	24 (1·7%)	14 (2·0%)	10 (1·4%)
Unknown	79 (5·7%)	32 (4·6%)	47 (6·8%)
Stunted (HAZ <−2)[††]	315 (22·6%)	156 (22·3%)	159 (22·9%)
Underweight (WAZ <−2)[††]	177 (12·7%)	89 (12·7%)	88 (12·7%)
Acute malnutrition[‡‡]			
Severe (WHZ <−3 or MUAC <11·5 cm or oedema)	57 (4·1%)	28 (4·0%)	29 (4·2%)
Moderate (WHZ ≥−3 to <−2 or MUAC ≥11·5 to <12·5 cm)	75 (5·4%)	36 (5·1%)	39 (5·6%)
HIV status			
Infected	18 (1·3%)	9 (1·3%)	9 (1·3%)
Exposed, uninfected[§§]	140 (10·0%)	70 (10·0%)	70 (10·1%)
Exposed, unknown infection status[¶¶]	7 (0·5%)	3 (0·4%)	4 (0·6%)
HIV status unknown	41 (2·9%)	23 (3·3%)	18 (2·6%)
Received all age-appropriate vaccines[†,////]	646 (46·4%)	333 (47·7%)	313 (45·1%)

Data are n (%) or median (IQR). HAZ=height-for-age Z score. WAZ=weight-for-age Z score. WHZ=weight-for-height Z score. MUAC=mid-upper arm circumference.

[*] Income <US$1·90 per day.

[†] Among those who had responses.

[‡] Among those who did not report using only bottled water for drinking.

[§] Diagnoses might not be mutually exclusive; percentages are among the 1330 children who had records available and diagnosis recorded.

[¶] Includes sickle cell crisis and sickle cell disease as comorbidity because these were not always distinguished in medical record.

[//] Urinary tract infection (n=11); fever of unknown origin (n=0); acutely unwell, unknown cause (n=4); poisoning or herbal intoxication (n=5); asthma (n=30); convulsions (n=82); blood dyscrasia (n=4); congenital or acquired heart disease (n=8); cerebral palsy (n=10); diabetic ketoacidosis (n=4); skin or soft tissue infection (n=16); skin disease (n=7); hernia (n=5); helminth infection (n=2); burn or trauma (n=3); liver disease (n=3); congenital malformation (n=2); neurological disease (n=6); kidney disease (n=2); intestinal obstruction (n=3); cerebrovascular accident (n=1); Down syndrome (n=2).

** For children younger than 6 months, defined as up until time of enrolment; exclusively breastfed defined as no other food or drink (including water) except for breastmilk in the first 6 months of life; partly breastfed defined as child received breastmilk in addition to other food (including formula) or drink in the first 6 months of life; never breastfed defined as no breastmilk in the first 6 months of life.

†† Among those with plausible values.

‡‡ MUAC only used in children aged 6 months or older.

§§ Among children known to be uninfected with HIV who were accompanied by their biological mother whose HIV status was known (by antibody test or self-report) or who were not accompanied by their biological mother but the HIV status of the biological mother was known to be positive.

¶¶ Children with a biological mother infected with HIV but whose HIV infection status was not known.

‖‖ According to the Kenya Ministry of Health vaccine schedule (allowing a 4-week window); malaria vaccine and measles vaccine at 6 months for children positive for HIV were not included in the definition of all age-appropriate vaccines despite being recommended in Kenyan guidelines.

Table 2:

Effect of azithromycin on time to death or first rehospitalisation

	Azithromycin-treated group (n=702)			Placebo-treated group (n=696)			Effect estimate*	
	Participants	Person-time, child-years	Incidence rate, per 100 child-years	Participants	Person-time, child-years	Incidence rate, per 100 child-years	Hazard ratio (95·5% CI)†	p value‡
Death or rehospitalisation	63	308·9	20·4	69	306·9	22·5	0·91 (0·64–1·29)	0·58§
Death¶	15	321·2	4·7	19	319·1	6·0	0·79 (0·39–1·58)	0·49‖
First rehospitalisation	58	308·9	18·8	57	306·9	18·6	1·01 (0·70–1·47)	0·94**

*Adjusted for site as an indicator variable.

†An α of 0·005 was used at the interim analysis; therefore we are reporting 95·5% CIs to account for the 0·5% α spending.

‡p values should be compared with an α of 0·045 rather than standard 0·05 cutoff for interpretation (based on α spending of 0·005 at the interim analysis).

§p=0·59 for log-rank test of survivor function equality from Kaplan-Meier stratified by site.

¶The combined outcome of death or rehospitalisation includes some children who had both outcomes; thus numbers for individual outcomes might exceed the value for combined outcome.

‖p=0·50 for log-rank test of survivor function equality from Kaplan-Meier stratified by site.

**p=0·9 for log-rank test of survivor function equality from Kaplan-Meier stratified by site.

Table 3:

Cause of death by clinical consensus by randomisation group

	Azithromycin-treated group (n=15)	Placebo-treated (n=19)
Primary cause		
LRTI or pneumonia	4	3
Diarrhoea	1	1
Malaria	1	1
Tuberculosis	0	1
Other infection *	1	10
Other non-infectious condition †	8	3
Predisposing conditions ‡		
HIV	2	2
Sickle-cell disease	3	2
SAM	2	2
Confirmed acquired condition §	1	1
Confirmed congenital condition ¶	1	3

Data are n. LRTI=lower respiratory tract infection. SAM=severe acute malnutrition.

* Includes unknown cause of death with signs of infection (fever, abnormal white cell count and differential; n=1) in the azithromycin group, and CNS infection (n=2) and unknown cause of death with signs of infection (n=8) in the placebo group.

† Includes unknown cause without signs of infection (n=4), anaemia (n=2), severe sickle-cell crisis (n=1), and congestive heart failure (n=1) in the azithromycin group; and anaemia (n=1), congestive heart failure (n=1), and unknown cause without signs of infection (n=1) in the placebo group.

‡ One child in the placebo group had both severe malnutrition and HIV.

§ Confirmed acquired conditions include congestive heart failure in the azithromycin group and rheumatic heart disease in the placebo group.

¶ Confirmed congenital conditions include congenital abdominal abnormality (n=1) in the azithromycin group and cerebral palsy (n=1), congenital heart disease (n=1), and tracheomalacia (n=1) in the placebo group.

Table 4:

Adverse events by randomisation group

	Azithromycin-treated group (n=702)			Placebo-treated group (n=696)		
	n (%)	Days since enrolment		n (%)*	Days since enrolment	
		0–7	8–180		0–7	8–180
Serious adverse events						
Death	15 (2%)	2	13	19 (3%)	2	17
Life-threatening	52 (7%)	5	47	54 (8%)	1	53
Non-serious adverse events						
Severe	0 (0%)	0	0	0 (0%)	0	0
Moderate	193 (27%)	5	188	195 (28%)	8	187
Mild	81 (12%)	3	78	81 (12%)	4	77

Data are n (%) or n. Adverse event grade is defined according to 2014 Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events.

Four serious adverse events were flagged as potentially related to the study drug during data collection, but all four were found to be in placebo-treated children after unblinding the study. An additional ten moderate or mild adverse events were considered potentially related before study unblinding: eight among placebo-treated children and two were in azithromycin-treated children.

* Does not include minor complaints (eg, runny nose and bee sting).