Azithromycin in Labor Lowers Clinical Infections in Mothers and Newborns: A Double-Blind Trial

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abstract

BACKGROUND AND OBJECTIVES: We have recently completed a proof-of-concept trial showing that bacterial colonization decreased in women and newborns after the administration of azithromycin during labor. Here, we aim to assess the effect of the intervention on maternal and neonatal clinical infections.

METHODS: This was a double-blind, placebo-controlled randomized trial. Gambian women in labor were given either an oral dose of azithromycin (2 g) or placebo. Follow-up was conducted for 8 weeks after delivery.

RESULTS: From April 2013 to April 2014, we recruited 829 mothers and their 830 newborns. Sixteen infants died during the follow-up period (8 per arm). No maternal deaths or serious adverse events related to the intervention were reported. Maternal infections were lower in the azithromycin group (3.6% vs 9.2%; relative risk [RR], 0.40; 95% confidence interval [CI], 0.22–0.71; $P = .002$), as was the prevalence of mastitis (1.4% vs 5.1%; RR, 0.29; 95% CI, 0.12–0.70; $P = .005$) and fever (1.9% vs 5.8%; RR, 0.33; 95% CI, 0.15–0.74; $P = .006$). Among newborns, the overall prevalence of infections was also lower in the azithromycin group (18.1% vs 23.8%; RR, 0.76; 95% CI, 0.58–0.99; $P = .052$) and there was a marked difference in prevalence of skin infections (3.1% vs 6.4%; RR, 0.49; 95% CI, 0.25–0.93; $P = .034$).

CONCLUSIONS: Azithromycin given to women in labor decreases infections in both women and newborns during the puerperal period. Larger studies designed to evaluate the effect of the intervention on severe morbidity and mortality are warranted.

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This trial has been registered at www.clinicaltrials.gov (identifier NCT01800942).

WHAT'S KNOWN ON THIS SUBJECT: We had previously showed in a double-blind trial that an oral dose (2 g) of azithromycin given to Gambian women in labor decreased bacterial colonization of the study bacteria (*Staphylococcus aureus*, *Streptococcus pneumoniae*, group B *Streptococcus*) in the women and the newborns during the neonatal period.

WHAT THIS STUDY ADDS: This post-hoc analysis shows that an oral dose of azithromycin given during labor decreased prevalence of clinical infections in women (occurrence of fever, mastitis, and overall infections) and newborns (skin and overall infections) during the 8 weeks following the intervention.

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Although maternal and neonatal health are identified high-priority areas for international development, maternal and neonatal mortality remain unacceptably high. Worldwide, there are ~1 million maternal deaths and 4 million neonatal deaths per year, half of them occurring in sub-Saharan Africa (SSA).[1] Puerperal sepsis is one of the leading causes of preventable maternal deaths in low-income countries, and neonatal sepsis causes 1 out of 3 neonatal deaths,[1] with 75% of deaths occurring during the first week of life.

In SSA, neonatal sepsis is caused by a wide range of bacterial pathogens,[2] with a predominance of gram-positive bacteria (eg, *Staphylococcus aureus*, group B *Streptococcus* [GBS] and *Streptococcus pneumoniae*). Early neonatal sepsis (first week of life) is predominantly due to the transmission of pathogenic bacteria during birth and early life from the mother to the offspring,[3] and might therefore be prevented by interventions targeting this route of transmission. In the United States, the incidence of early-onset GBS disease fell by 70% after the widespread use of targeted prophylaxis with intravenous intrapartum antibiotics (ampicillin or penicillin) among women in labor carrying GBS in the vaginal tract.[4] Unfortunately, prepartum screening and intrapartum treatment with intravenous antibiotics is not feasible in low-income countries. In addition, given that sepsis in SSA is caused by several bacterial species, any preventive measure should cover a wider spectrum of bacteria.[2,3,5]

Maternal infections, which include puerperal sepsis, mastitis, and other infections occurring during the postpartum period, remain an important cause of maternal morbidity and mortality, particularly in developing countries.[6] Although reliable population-based estimates of maternal sepsis in SSA are not available, a recent World Health Organization (WHO) systematic review showed that >1 out of 9 maternal deaths reported worldwide are due to puerperal sepsis.[7] For each death due to puerperal sepsis, ~20 severe episodes occur, with several bacterial pathogens being responsible for these episodes.[8,9] Mastitis, although generally less severe than puerperal sepsis, affects up to 20% of lactating women,[10,11] with *S aureus* playing a leading role.

Recent WHO guidelines on the prevention of maternal and neonatal peripartum infections state prophylactic antibiotics should only be used when the risk of maternal infections is high (eg, cesarean deliveries or severe perineal tears).[12] Additional research is needed to assess whether prophylactic antibiotics should be used for episiotomies, uncomplicated vaginal births, and prolonged rupture of membranes at term.

In The Gambia, the rate of maternal mortality (461 per 100 000 live births) is one of the highest among all developing countries,[13] and neonatal deaths represent ~40% of all deaths of children under 5 years of age.[14] Hence, interventions that target maternal and neonatal morbidity and mortality are urgently needed. We have recently concluded a proof-of-concept double-blind trial in a periurban health facility in Western Gambia where women in labor were randomized to receive either an oral dose of 2 g of azithromycin or placebo.[15] The study was designed to determine the effect of the intervention on bacterial carriage (*S aureus*, GBS, and *S pneumoniae*) in nasopharyngeal swabs, breast milk samples, and vaginal swabs collected up to 28 days after delivery.[16] Azithromycin substantially reduced bacterial carriage in both the mother and the newborn and also reduced the use of antibiotics during the puerperal period by 60%. In this article, we present a post hoc analysis of the effect of the intervention on the occurrence of maternal and neonatal fever, malaria and, clinical infections during the 8-week follow-up period. Clinical diagnoses were based on clinical judgement by study clinicians who were blinded to the intervention arm.

METHODS

Main Trial

The detailed study protocol[15] and the main results[16] have been published elsewhere. Briefly, this was a phase-III, double-blind, placebo-controlled, randomized trial in which pregnant women in labor were randomized to receive a single dose of 2 g of oral azithromycin or placebo (ratio 1:1). The primary endpoint was prevalence of *S aureus*, GBS, or *S pneumoniae* carriage in the nasopharyngeal swab sample of the newborn at day 6.

The packaging and labeling of the investigational medicinal product (IMP) was conducted by IDIFARMA. Azithromycin and placebo were provided as tablets packed in blisters. The randomization list was created by an independent data manager and IDIFARMA numbered the blisters according to the list.[15] One blister pack of IMP contained 4 tablets of 0.5 g (2 g total) of either azithromycin or placebo. The active drug and the placebo looked identical.

Study Site and Population

The study was based at the Jammeh Foundation for Peace (JFP), a government-run health center located in Western Gambia that manages 4500 deliveries per year. The population covers the main ethnic groups in The Gambia and illiteracy is high. The climate of the area is typical of SSA.

Between April 2013 and April 2014, women in labor aged 18 to 45 years were recruited when attending the

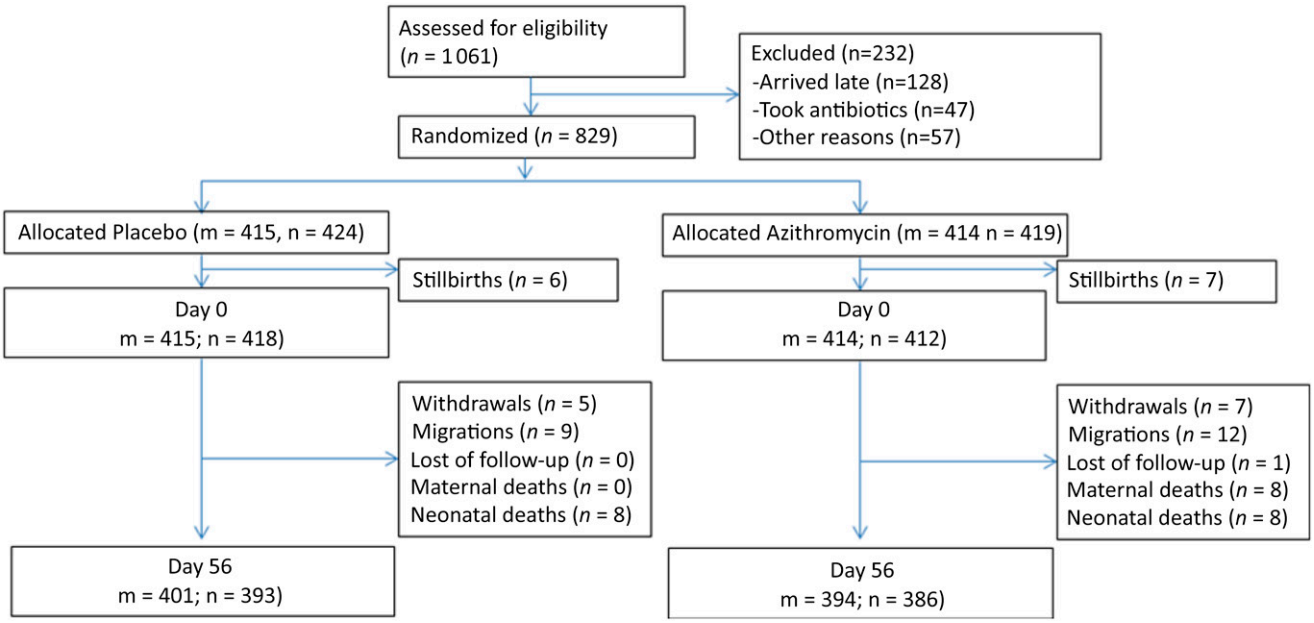

FIGURE 1
Trial profile. m, mothers; n, newborns.

TABLE 1 Mothers: Baseline Characteristics of Study Participants

Mothers	Azithromycin (*N* = 414), *n* (%)	Placebo (*N* = 415), *n* (%)
Characteristics		
Age, y, median (IQR)	26.0 (22.0–30.0)	25.0 (22.0–30.0)
Ethnicity		
Mandinka	161 (40.1)	187 (45.8)
Fula	77 (19.2)	64 (15.7)
Jola	68 (17.0)	56 (13.7)
Other	95 (23.7)	101 (24.8)
Season of delivery[a]		
Rainy	141 (34.1)	143 (34.5)
Mode of delivery		
Vaginal	404 (97.6)	410 (98.8)
Cesarean	10 (2.4)	5 (1.2)
Multiple pregnancy	5 (1.2)	9 (2.2)
Hours between treatment and delivery		
Median, IQR	3.2 (1.1–8.3)	2.9 (1.3–6.3)
Hours between rupture of membranes and delivery[b]		
Median, IQR	0.4 (0.1–1.8)	0.3 (0.1–1.3)
>18 h, %	35 (8.5)	32 (7.7)
Tears	53 (12.8)	33 (8.0)
Episiotomies	15 (3.6)	20 (4.8)

IQR, interquartile range.
[a] Rainy season: children born June to October.
[b] Time of rupture of membranes is missing in *n* = 441 (230 in the azithromycin and 211 in the placebo arm).

JFP labor ward. They had signed consent forms to participate in the study during their antenatal visits. Exclusion criteria were: (1) known HIV infection; (2) any chronic/acute conditions that could interfere with the study as judged by the research clinician; (3) planned travel out of the catchment area during the follow-up period; (4) planned caesarean delivery; (5) known required referral; (6) known multiple pregnancy; (7) known severe congenital malformation of the newborn; (8) intrauterine death confirmed before randomization; (9) known allergy to macrolides; and (10) consumption of any antibiotic within the previous week.

Eligibility for recruitment was reassessed in the labor ward, and those eligible were randomized and treated with the IMP. After delivery, mothers and infants were discharged and subsequently visited at home for 2 months: daily during the first week and weekly thereafter. JFP lacked the capacity to provide emergency obstetric care, most especially surgical care. As a result, women in labor who needed emergency caesarean delivery were referred to the teaching hospital in Banjul (~20 km from the study site).

To evaluate the safety of the intervention on mothers and newborns, adverse events (AE) were monitored and assessed throughout the follow-up period. Special attention was paid to hypertrophic pyloric stenosis in the newborn, usually reported as projectile vomiting, as a potential side effect of azithromycin.[17]

TABLE 2 Newborns: Baseline Characteristics of Study Participants

Newborns	Azithromycin ($N = 419$), n (%)	Placebo ($N = 424$), n (%)
Characteristics		
Sex		
Girl	207 (49.4)	198 (46.7)
Apgar score at birth		
0	6 (1.4)	6 (1.4)
1–6	8 (1.9)	5 (1.2)
7–10	402 (96.6)	408 (97.4)
Weight[a]		
Median, IQR	3.1 (2.8–3.5)	3.1 (2.9–3.4)
Gestational age (wk)[b]		
Median, IQR	36.0 (35.0–38.0)	36.0 (35.0–38.0)

IQR, interquartile range.

[a] Weight is missing in $n = 2$ (both in the placebo arm).

[b] Gestational age is missing in $n = 33$ (16 in the azithromycin and 17 in the placebo arm).

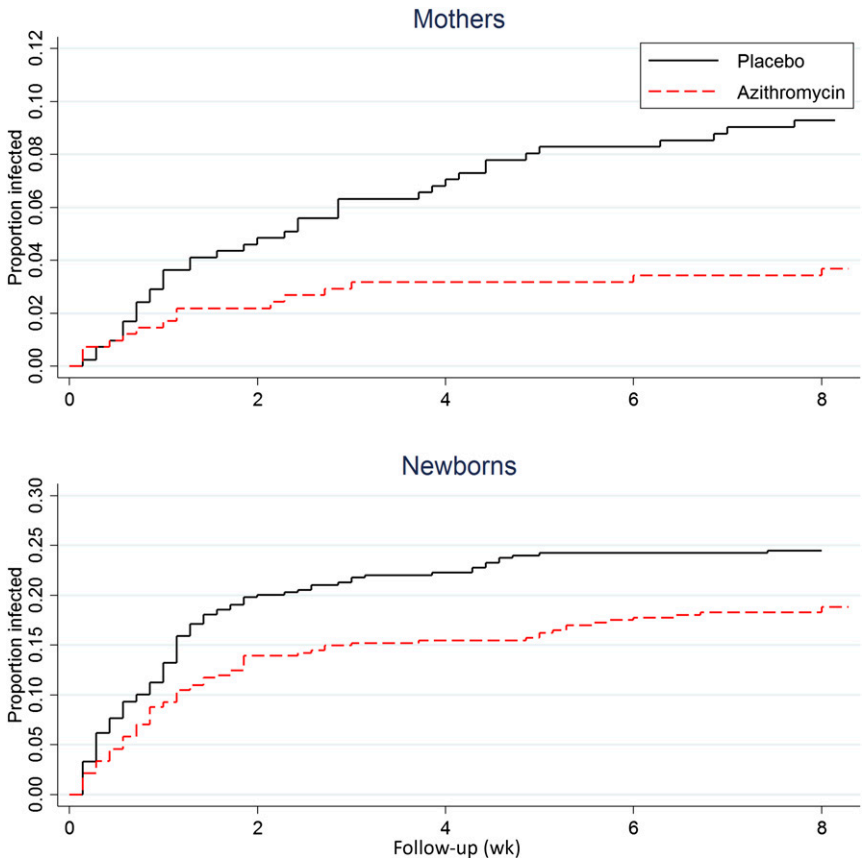

FIGURE 2
Proportion of mothers and newborns infected at different points during the follow-up period. P values were derived using the log-rank test (mothers, $P = .001$; newborns $P = .040$).

Ethical Approval

The study was approved by the joint Gambia Government/Medical Research Council ethics committees. An independent data safety and monitoring board (DSMB) monitored the data quality and treatment safety.

Procedures

Screening was done in the labor ward to confirm consent and ensure eligibility criteria were all met. If a woman who had signed consent was still willing to participate in the study, a randomization number was then assigned. After discharge from the hospital and within the first week after delivery, trained nurses carried out daily home visits for both mothers and babies. Mothers were asked to attend JFP again with their babies between days 8 and 13 to be examined by a study clinician. From then, field workers visited the mother/newborn pairs weekly until 8 weeks postpartum.

This active follow-up was complemented with passive follow-up at the study health facility and Medical Research Council clinic. A local safety monitor and a DSMB reviewed all the serious AEs during the course of the trial, and the trial was monitored by an independent clinical trials monitor.

Post hoc Clinical Endpoints

The clinical endpoints were reported in the AE form of the clinical report form, where they were graded as mild, moderate, or severe. These forms were completed in real time, when the study was double-blinded, by the study clinicians based on their clinical judgement.

The endpoints in study women were:

1. Maternal infections, which included any of the following:
   a. Clinical mastitis;
   b. Clinical sepsis;
   c. Related infections (ie, urinary tract infection, pelvic inflammatory disease, endometritis, episiotomy discharge, and septic surgical wound)
   d. Others (ie, acute respiratory infections, sore throat, ear discharge, vaginosis, and skin infections).
2. Fever: axillary temperature ≥38°C either reported by the women or confirmation with a thermometer by the follow-up nurse.
3. Malaria: diagnosed with a rapid diagnostic test.

TABLE 3 Categories of Maternal Clinical Infections by Disease Severity and Study Arm

Maternal	Azithromycin ($N = 414$), n (%)	Placebo ($N = 415$), n (%)	RR (95%CI)	P
Overall infections				
Maternal infections				
Mastitis	6 (1.4)	21 (5.1)	0.29 (0.12–0.70)	.005
Pueperal sepsis	4 (1.0)	5 (1.2)	0.80 (0.22–2.97)	.999
Related infections	3 (0.7)	9 (2.2)	0.33 (0.09–1.23)	.143
Others	2 (0.5)	5 (1.2)	0.40 (0.08–2.06)	.451
Any infection (any of the above)	15 (3.6)	38 (9.2)	0.40 (0.22–0.71)	.002
Fever	8 (1.9)	24 (5.8)	0.33 (0.15–0.74)	.006
Malaria	8 (1.9)	5 (1.2)	1.60 (0.53–4.86)	.42
Mild infections				
Maternal infections				
Mastitis	5 (1.2)	9 (2.2)	0.56 (0.19–1.65)	.42
Pueperal sepsis	1 (0.2)	1 (0.2)	1.00 (0.06–15.97)	.999
Related infections	0 (0)	3 (0.7)	0 (NA–NA)	.249
Others	1 (0.2)	4 (1.0)	0.25 (0.03–2.23)	.373
Any infection (any of the above)	7 (1.7)	17 (4.1)	0.41 (0.17–0.98)	.046
Fever	7 (1.7)	19 (4.6)	0.37 (0.16–0.87)	.027
Malaria	2 (0.5)	3 (0.7)	0.67 (0.11–3.98)	.999
Moderate infections				
Maternal infections				
Mastitis	1 (0.2)	11 (2.7)	0.09 (0.001–0.70)	.006
Pueperal sepsis	0 (0.0)	2 (0.5)	NA	.499
Related infections	3 (0.7)	6 (1.4)	0.50 (0.13–1.99)	.505
Others	1 (0.2)	1 (0.2)	1.00 (0.06–15.97)	.999
Any infection (any of the above)	5 (1.2)	19 (4.6)	0.26 (0.10–0.70)	.006
Fever	1 (0.2)	5 (1.2)	0.20 (0.02–1.71)	.217
Malaria	6 (1.4)	2 (0.5)	3.01 (0.61–14.81)	.177
Infections as cause of hospitalization				
Maternal infections				
Mastitis	0 (0.0)	1 (0.2)	NA	.999
Pueperal sepsis	3 (0.7)	2 (0.5)	1.50 (0.25–8.95)	.686
Related infections	0 (0.0)	0 (0.0)	NA	NA
Others	0 (0.0)	0 (0.0)	NA	NA
Any infection (any of the above)	3 (0.7)	2 (0.5)	1.50 (0.25–8.95)	.686
Fever	0 (0.0)	0 (0.0)	NA	NA
Malaria	0 (0.0)	0 (0.0)	NA	NA

NA, not applicable.

The endpoints in study newborns were:

1. Clinical neonatal infection, which included any of the following:
   a. Skin infections;
   b. Umbilical infections;
   c. Conjunctivitis;
   d. Otitis;
   e. Oral infection;
   f. Clinical sepsis; meningitis and pneumonia.
2. Fever: axillary temperature ≥38°C reported by the mother or confirmed with a thermometer by the follow-up nurse.
3. Malaria: diagnosed with a rapid diagnostic test.

Statistical Analysis

Case-report-forms were reviewed before being double entered into OpenClinica (www.openclinica.com). The analysis was done using Stata (version 13.1; Stata Corp, College Station, TX). For each clinical outcome recorded in the case report forms on mothers, we compared the proportion with the outcome between the placebo group and the azithromycin group. We calculated the risk ratios (RR) with 95% confidence intervals (CI) and Fisher's exact test was used to calculate the P values. The proportion of mothers infected at different times during follow-up was estimated using the Kaplan–Meier method. A similar analysis was done for each of the outcomes recorded on newborns. To compare infections in newborns in the wet (June to October) and dry (November to May) season, we used a Poisson regression model for the number of infections per month. The model included the number of child-years as an offset, and robust variance estimates were used to account for overdispersion. We included twins, but did not adjust confidence intervals and significance tests for the effect of clustering

TABLE 4 Clinical and Laboratory Characteristics of Maternal Admissions Due to Infections

Treatment Given	Admission Diagnosis	Clinical/Laboratory Features
Azithromycin	Puerperal sepsis	Clinical Low abdominal pain, dysuria, bacteriuria Laboratory Negative blood and vaginal swab cultures
	Endometritis	Clinical No fever, low abdominal pain, constipation
	Septic surgical wound	Clinical Cesarean scar (wound) discharge
Placebo	Puerperal sepsis	Clinical Low abdominal pain Laboratory Total WBCC, 23.7; neutrophils, 92.7%; negative blood culture; positive vaginal swab culture[a], urine WBCC, 10/h.p.f
	Puerperal sepsis; mastitis; severe anemia	Clinical Low abdominal pain, offensive vaginal discharge Laboratory Total WBCC, 31.9 × 10^9/L; neutrophils, 93.1% Negative blood and vaginal swab cultures, breast congestion Ultrasound: bulky uterus (USS)

h.p.f, high-power field; USS, ultrasound scan; WBCC, white blood cell count.
[a] *S aureus.*

because the design effect was negligible.

RESULTS

Baseline Information

A total of 1061 women in labor were assessed for eligibility and 829 (78.1%) were recruited, randomized, and treated (414 azithromycin and 415 placebo) (Fig 1). These 829 recruited women delivered 830 live births and 13 stillbirths. The median age of women at enrolment was 26.0 years in the azithromycin group and 25.0 years in the placebo group. Overall, 15 mothers were transferred to the Banjul Teaching Hospital for caesarean delivery (10 in the azithromycin group and 5 in the placebo group), and all of them were given intrapartum intramuscular/intravenous antibiotics. Details of the baseline characteristics of the study women and the newborns are shown in Table 1 and 2.

Maternal Infections

Fever and infections were less common in the azithromycin group than the placebo group during the follow-up period (Fig 2, Table 3). The occurrence of fever was 1.9% for women in the azithromycin group compared with 5.8% in the placebo group (RR, 0.33; 95% CI, 0.15–0.74; $P = .006$), and the overall occurrence of maternal infections was 3.6% vs 9.2% (RR, 0.40; 95% CI, 0.22–0.71; $P = .002$). Mastitis was the most common infection and occurred less frequently in the azithromycin group than the placebo group (1.4% vs 5.1%; RR, 0.29; 95% CI, 0.12–0.70; $P = .005$). Differences between the arms in the occurrence of fever, maternal infections, and mastitis remained significant in the mild and moderate categories. Only 5 women were hospitalized due to an infection (3 in the azithromycin group and 2 in the placebo group). The criteria used to diagnose these women are given in Table 4. The incidence of malaria was similar in both groups (1.9% vs 1.2%; RR, 1.60; 95% CI, 0.53–4.86; $P = .420$).

Neonatal Infections

Fever and infections were common among the newborns during the follow-up period, and the incidence of infection peaked during the rainy season (0.86 vs 2.46 per person-year; RR, 2.86; 95% CI, 1.95–4.23; $P < .001$). Although we did not observe a difference between study arms in the occurrence of fever ($P = .235$), the overall prevalence of infections was lower in the azithromycin group (18.1% vs 23.8%; RR, 0.76; 95% CI, 0.58–0.99; $P = .052$) (Fig 2, Table 5). Differences between study arms remained significant in the mild and moderate categories for overall infections (13.4% vs 19.6%; RR, 0.68; 95% CI, 0.50–0.93; $P = .016$) and skin infections (3.1% vs 6.1%; RR, 0.51; 95% CI, 0.26–0.97; $P = .048$). Overall, 38 newborns were admitted for infections, most of them during the first week of life (63.6%). There were no cases of malaria in the placebo group and only 1 case in the azithromycin group.

Neonatal Deaths

Seven out of the 16 deaths that occurred during the follow-up period had a diagnosis of infection, although none had microbiological confirmation. Three out of these 7 deaths occurred in the azithromycin group and 4 in the placebo group. None of the 4 deaths in the placebo group had any underlying

TABLE 5 Categories of Neonatal Clinical Infections by Disease Severity and Study Arm

Neonates	Azithromycin ($N = 419$), n (%)	Placebo ($N = 424$), n (%)	RR (95% CI)	P
Overall infections				
Neonatal infections				
Skin infection	13 (3.1)	27 (6.4)	0.49 (0.25–0.93)	.034
Umbilical infection	1 (0.2)	4 (0.9)	0.25 (0.03–2.25)	.374
Conjunctivitis	37 (8.8)	45 (10.6)	0.83 (0.55–1.26)	.417
Otitis	3 (0.7)	5 (1.2)	0.61 (0.15–2.52)	.725
Oral infection	12 (2.9)	13 (3.1)	0.93 (0.43–2.02)	.999
Sepsis	18 (4.3)	15 (3.5)	1.21 (0.62–2.38)	.598
Meningitis	0 (0.0)	1 (0.2)	NA	.999
Pneumonia	3 (0.7)	4 (0.9)	0.76 (0.17–3.37)	.999
Any infection (any of the above)	76 (18.1)	101 (23.8)	0.76 (0.58–0.99)	.052
Fever	54 (12.9)	43 (10.1)	1.27 (0.87–1.85)	.235
Malaria	1 (0.2)	0 (0.0)	NA	.497
Mild/moderate infections				
Neonatal infections				
Skin infection	13 (3.1)	26 (6.1)	0.51 (0.26–0.97)	.048
Umbilical infection	1 (0.2)	4 (0.9)	0.25 (0.03–2.25)	.374
Conjunctivitis	37 (8.8)	45 (10.6)	0.83 (0.55–1.26)	.417
Otitis	2 (0.5)	5 (1.2)	0.40 (0.08–2.07)	.451
Oral infection	12 (2.9)	13 (3.1)	0.93 (0.43–2.02)	.999
Sepsis	0 (0.0)	1 (0.2)	NA	.999
Meningitis	0 (0.0)	0 (0.0)	NA	NA
Pneumonia	0 (0.0)	2 (0.5)	NA	.499
Any infection (any of the above)	56 (13.4)	83 (19.6)	0.68 (0.50–0.93)	.016
Fever	53 (12.6)	41 (9.7)	1.31 (0.89–1.92)	.189
Malaria	1 (0.2)	0 (0.0)	NA	.497
Infections as cause of hospitalization				
Neonatal infections				
Skin infection	0 (0.0)	1 (0.2)	NA	.999
Umbilical infection	0 (0.0)	0 (0.0)	NA	NA
Conjunctivitis	0 (0.0)	0 (0.0)	NA	NA
Otitis	1 (0.2)	0 (0.0)	NA	.497
Oral infection	0 (0.0)	0 (0.0)	NA	NA
Sepsis	17 (4.1)	15 (3.5)	1.15 (0.58–2.27)	.722
Meningitis	0 (0.0)	1 (0.2)	NA	.999
Pneumonia	3 (0.7)	2 (0.5)	1.52 (0.25–9.04)	.685
Any infection (any of the above)	19 (4.5)	19 (4.5)	1.01 (0.54–1.88)	.999
Fever	2 (0.5)	2 (0.5)	1.01 (0.14–7.15)	.999
Malaria	0 (0.0)	0 (0.0)	NA	NA

NA, not applicable.

condition, whereas the 3 deaths in the azithromycin group were all potentially attributable to an underlying condition: 1 newborn had a congenital heart defect, 1 had aspiration at birth, and the third had a clinical diagnosis of hemorrhagic disease, possibly due to vitamin K deficiency (Table 6). One of these 7 deaths occurred after the first week of life.

DISCUSSION

Although the WHO does not recommend the use of prophylactic antibiotics for all deliveries, it allows such prophylaxis when the risk of sepsis is high.[12] This is the case in SSA, where most of the population is poorly nourished, women often deliver in unhygienic conditions, female genital mutilation is common practice,[18–20] tears and episiotomies are frequent, the rate of bacterial colonization is high (in the vaginal tract and in breast milk),[16] and, importantly, most personnel attending deliveries are poorly trained to identify pregnancies at high risk of neonatal or puerperal sepsis. Our study shows that in this setting, the prophylactic use of 1 oral dose of azithromycin, an antibiotic that is not used for clinical care in The Gambia, has the potential to reduce the risk of infections among women in the puerperal period and among their offspring during the neonatal period.

Maternal infections were frequent among our participants, as was the occurrence of mastitis, clinical sepsis, and related infections. Thanks to the high standard of care offered during the trial, most infections were cured and none of the mothers died. The rate of maternal mortality was therefore

TABLE 6 Clinical and Laboratory Characteristics of 7 Neonatal Deaths Due to Infections

Treatment Given	Admission Diagnosis and Associated Cause of Death	Clinical/Laboratory Features
Azithromycin	Neonatal sepsis and jaundice; aspiration	Clinical Cough, vomiting, difficult breathing, refusal to feeds, jaundice, unconscious, tarchypnoea (70 breaths per minute), apnoea Laboratory FBC: WBC, 19.4 × 10^9/L (high); NEU, 58.8%; LYM, 33.4%; HGB, 12.1 g/dL; PLT, 448 × 10^9/L; Blood group: B, Rh positive Total BIL, 773 µmol/L Conj BIL, 0 µmol/L UNCON BIL 669 µmol/L
	Neonatal sepsis; congenital heart disease	Clinical Refusal to breastfeed, grunting, heart murmur, poor neonatal reflexes, bilateral talipes deformity Laboratory RBG, 1.8 mmol/L (low)
	Neonatal sepsis; haemorrhagic disease of the newborn	Clinical Excessive cry, refusal to breastfeed, severe pallor, irritability, ptosis and right opthalmoplegia, hematochesia, malaena, coffee-colored vomitus, prolonged bleeding from puncture sites Laboratory FBC: WBC, 19 × 10^9/L (high); NEU, 48%; LYM, 47%; PLT, 287 × 10^9/L Biochemistry: Na, 156; K, 6.3; U, 23.8; Crea, 86 µmmol/L; Total BIL, 99 µmmol/L Blood culture: negative CSF analysis: xanthochromic, clear; WBC, 4 × 10^6/L; RBC, 40 × 10^6/L; gram stain, no organism seen; latex agglutination, negative
Placebo	Early onset sepsis	Clinical Excessive cry, refusal to breastfeed, fever (39°C), cyanosed, tachypnoeic (40 breaths per minute) Laboratory FBC: WBC, 49.4 × 10^9/L (high); NEU, 12.6%; LYM, 61%; HGB, 10.9 g/dL; PLT, 173 × 10^9/L Blood culture, no growth after 72 h
	Neonatal sepsis	Clinical Twin with low birth weight (1.5 kg); lethargic, grunting, acrocyanosis, hypothermia (33.3°C), bradycardia (90 beats per minute) Laboratory RBG, 1.5 mmol/L (low)
	Pneumonia	Clinical Fever (39.9°C), tachypnoeic (72 breaths per minute); SPO_2, 93% on air; lethargic, absent neonatal reflexes Laboratory RBG: 0.7 mmol/L (low) FBC: WBC 24.8 × 10^9/L (high); NEU, 70%; LYM, 22.3%, HGB, 16.1g/dL, PLT, 445 × 10^9/L CSF analysis: clear, xanthochromic, protein, 1.2 g/dL; glucose, 0.6 mmol/L; WBC, 0 × 10^6/L, RBC, 20 × 10^6/L Gram stain: no organism seen; no growth on culture Blood culture: no growth after 72 h Chest radiograph, normal lung parenchyma; thymic shadow.
	Meningitis	Clinical Sudden projectile vomiting, excessive cry, convulsion, full and tense anterior fontanelle Laboratory FBC: WBC 10.9 × 10^9/L; LYM ,6.2 × 10^9/L; GRAN, 11.4 × 10^9/L; LYM%, 32.6%; GRA%, 59.9%; HGB, 10.1 g/dL; PLT, 431 × 10^9/L CSF analysis: no organism seen, 70% polymorphs, 30% lymphocytes.

Conj BIL, conjugated bilirubin; Creat, creatinine; FBC, full blood count; GRA%, granulocyte percentage; GRAN, granulocyte; HGB, hemoglobin; K, potassium; LYM, lymphocyte; LYM%, lymphocyte percentage; Na, Sodium; NEU, neutrophil; PLT, platelet; RBC, red blood cell; RBG, random blood glucose; Rh, rhesus; SPO_2, partial pressure of oxygen; Total BIL, total bilirubin; U, urea; unconj BILI, unconjugated bilirubin; WBC, white cell count.

much lower than expected (in this setting, a maternal mortality ratio of 461 per 100 000 live births has been reported[13] and, therefore, ~4 deaths would have been expected). As well as reducing infections by 60% to 90%, the intervention also reduced the occurrence of fever by more than two-thirds. Although azithromycin has been reported to be effective for malaria prophylaxis and treatment, either as monotherapy or in combination with other drugs,[17,18] no effect on malaria was observed. This may be due to the low risk of malaria in this area.

Clinical infections were also common among newborns during the neonatal period, but the close follow-up provided by the trial team may have limited their consequences.[21] Early detection of outpatient infections prevents hospitalization and death,[22] especially some potentially threatening infections, such as skin infection (common) or umbilical infections (less common).[23,24] The incidence of outpatient infections was 30% lower in the azithromycin group and skin infections decreased by >50%. The number of umbilical infections was surprisingly low (1 case in the azithromycin group and 4 cases in the placebo group). This may be due to the local practice of applying shea butter to the umbilical stump, which has been shown to be protective.[25] In the azithromycin group, the lower incidence of these infections, as well as of otitis and conjunctivitis, probably reflects the effect of the intervention on colonization by *S aureus* and *Streptococcus* species in the newborns,[16] because these bacteria are major causes of both conditions.[26–28] The absence of an effect of the intervention on oral infections may reflect the antiinflamatory effects of breast milk that are protective of such lesions in this early neonatal period.[29] We did not observe a difference in fever between the study arms, but it is known that fever is not always part of the response to infection among neonates.[30]

Azithromycin, which is rarely used in clinical care in The Gambia,[31] has been used in mass drug administration programs that aim to eliminate trachoma.[32] Several studies have also used azithromycin during pregnancy to protect against malaria and increase birth weight. A meta-analysis of these trials has failed to show an improvement on neonatal outcomes.[33] Our study differed from these previous studies because it was the first to administer azithromycin to women in labor. The primary outcome of the trial was bacterial carriage[16] and the analysis of clinical outcomes, which we report in this article, was conducted post hoc. A limitation of our analysis is that clinical conditions were not predefined and were based on clinical assessment, without laboratory confirmation. For example, although several participants were hospitalized with a clinical diagnosis of sepsis, meningitis, or pneumonia, none of them had a positive microbiological culture of blood and/or cerebrospinal fluid (CSF). However, the major strength of the analysis is that because the study clinicians were blind to the treatment allocation, any possible bias in recording these outcomes would have been avoided.

Our results show that azithromycin administered to women in labor reduces maternal and neonatal infections and maternal episodes of fever. This intervention, with an antibiotic rarely used in clinical care in SSA, has the potential to reduce neonatal and puerperal sepsis in periurban and rural SSA. Larger trials designed to assess the effect of the intervention on severe morbidity and mortality are urgently needed. The advantages of our approach are its simplicity, low cost, the possibility of simultaneously targeting several pathogens, and the integrated approach of protecting mothers and babies with the same intervention.

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ABBREVIATIONS

AE: adverse event
CI: confidence interval
CSF: cerebrospinal fluid
DSMB: data safety monitoring board
GBS: group B streptococcus
IMP: investigational medicinal product
JFP: Jammeh Foundation for Peace
RR: risk ratio
SSA: sub-Saharan Africa
WHO: World Health Organization

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