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Prevention of young infant infections using oral azithromycin in labour in Fiji (Bulabula MaPei): study protocol of a randomised control trial

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ABSTRACT

Introduction Infections are a leading cause of neonatal mortality globally and can be transmitted from mother-to-child vertically or horizontally. Fiji has higher rates of serious neonatal infections and infant skin and soft tissue infections (SSTIs) than high-income countries. Research from the Gambia found that a single dose of oral azithromycin in labour decreased bacterial carriage and infections in mothers and infants, particularly infant skin infections. The Bulabula MaPei clinical trial evaluates the safety and efficacy of a single dose of azithromycin in labour in reducing the incidence of maternal and infant SSTIs and other infections and the impact on bacterial carriage. It will also describe the effect of azithromycin on antimicrobial (AMR) resistance, the maternal and infant microbiome, and infant dysbiosis.

Methods and analysis We are conducting a blinded, placebo-controlled randomised clinical trial administering 2 g of oral azithromycin, or placebo, given to healthy, pregnant women (≥18 years) in labour in Suva, Fiji. The primary outcome is the cumulative incidence of SSTIs in infants by 3 months of age. Secondary outcomes include the incidence of other infant and maternal infections, and safety and tolerability of azithromycin in mother and infant. Following informed consent, 2110 pregnant women will be randomised in a 1:1 ratio, with all study staff and participants masked to group allocation. Mother/infant pairs will be followed up for 12 months over six visits collecting clinical data on infections, antimicrobial use, safety and anthropometrics, in addition to nasopharyngeal, oropharyngeal, rectovaginal and vaginal swabs, maternal breastmilk and infant stool samples, in order to compare bacterial carriage, AMR rates and microbiome. Recruitment for Bulabula MaPei started in June 2019.

Ethics and dissemination This trial was approved and is being conducted according to the protocol approved by The Royal Children's Hospital Human Research Ethics Committee, Australia, and the Fiji National Health Research and Ethics Review Committee. The findings of this study will be disseminated in peer-reviewed journals and presented at conferences.

Trial registration number NCT03925480.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This blinded, randomised controlled trial is powered to determine a reduction in skin and soft tissue infections (SSTIs) in infants by 3 months of age, born to Fijian women administered a single dose of oral azithromycin during labour.
⇒ The benefits and potential harms of azithromycin on common bacterial pathogens will be determined by comparing carriage, antimicrobial resistance, and infant and maternal microbiome, including potential sequelae associated with microbiome dysbiosis, between the azithromycin and placebo groups.
⇒ The primary outcome (SSTIs) is determined on clinical criteria by trained study nurses, which may vary between observers in diagnostic sensitivity and interobserver agreement.

INTRODUCTION

Globally, infections cause approximately 21% of 2.4 million neonatal deaths each year and 52% of all under-five deaths,[1–3] with a disproportionate amount of these deaths occurring in low/middle-income countries (LMICs). Meningitis and sepsis are serious and common causes of neonatal morbidity and mortality.[1] The bacterial pathogens responsible for these conditions are age-dependent. They vary between LMICs and high-income countries (HICs), with Group B Streptococcus (GBS), *Staphylococcus aureus* (SA), *Streptococcus pneumoniae* (SPN), Group A Streptococcus (GAS) and *Escherichia coli* being common causes in infants in LMICs.[4 5]

Neonatal infections can be transmitted vertically, from mother to newborn through the placenta or birth canal, or horizontally via close contact during breastfeeding or household members. Vertical transmission of microorganisms including GBS and *E.*

coli are common causes of early-onset neonatal sepsis (NNS) which is associated with a high mortality rate of 10%–15%.[6] Intrapartum antibiotic prophylaxis prevents GBS NNS in HICs.[7] However, lack of resources means that universal GBS screening with intrapartum prophylaxis in pregnancy is not feasible in many LMICs.[7] Additionally, sexually transmitted infections (STIs) such as *Chlamydia trachomatis* can be transmitted vertically, causing neonatal conjunctivitis and pneumonia,[8] and indirectly increase the risk of NNS by increasing the likelihood of prematurity and low birth weight (LBW),[9 10] common contributors to neonatal mortality.

Maternal infections are also common, with approximately 5 million cases of pregnancy-related infection occurring each year, resulting in 75 000 maternal deaths.[11 12] Sepsis causes a greater proportion of maternal deaths in LMICs than HICs.[13 14] Skin infections are a common source of sepsis in both mothers and young infants.[13] For mothers, this occurs through postoperative wound infections after caesarean section and following tears and episiotomies during delivery.[15 16] For infants, omphalitis may be the initial site of invasive disease.[17]

There is emerging evidence that azithromycin may prevent vertical transmission of these pathogens during labour in low-resource settings, and a recent systematic review showed that administration during pregnancy reduced the risk of LBW and prematurity.[18] Azithromycin has Gram-positive (GBS, SA, SPN, GAS) and some Gram-negative bacterial activity and can also treat organisms associated with STIs. A randomised control trial (RCT) of single-dose oral azithromycin during labour in Gambian women reduced GBS, SA and SPN carriage and reduced maternal and infant infections, including infant skin infections by 50% (3.1% vs 6.4%, p=0.034) and maternal mastitis by 70% (1.4% vs 5.1%, p=0.005) up to 2 months postdelivery.[19 20] An RCT of 2013 women in the USA undergoing nonelective caesarean section receiving standard antibiotic prophylaxis with adjunctive azithromycin or standard antibiotic prophylaxis alone decreased the risk of maternal endometritis (3.8% vs 6.1%, p=0.02) and wound infection (2.4% vs 6.6%, p<0.001).[21]

In Fiji, skin and soft tissue infections (SSTIs), including impetigo, are common and occur in up to 12% of infants.[22 23] Moreover, some bacteria commonly associated with impetigo and invasive disease, including SPN, have high carriage rates in Fijian infants. In 2015, SPN carriage was 35% in 5 to 8-week-old infants; 44% in 12–23 months old and 8% in adults caregivers.[24] Rates of young infant meningitis of 2.6 per 1000 live births and 2.4 per 1000 live births for 3–11 months old are higher than rates seen in other middle-income countries,[25 26] and higher than rates in HICs (0.21 per 1000 live births and 0.09–0.14 per 1000 live births, respectively).[27 28] Additionally, the prevalence of 26.8% of *C. trachomatis* and 2.2% *Neisseria gonorrhoeae* in pregnant Fijian women is very high.[29] This high burden of SSTIs and other serious infections, in conjunction with high carriage rates of potentially pathogenic bacteria demonstrate the need for suitable interventions to prevent infections in mothers and infants in Fiji. Evidence of decreased carriage after administration, and known activity against bacteria commonly causing sepsis and specifically SSTIs suggest that azithromycin may be a suitable intervention. We hypothesise that azithromycin administered during labour will reduce the cumulative incidence of SSTIs in infants from birth to 3 months of age, and reduce other maternal and infant infections, antibiotic prescriptions and the bacterial carriage of common pathogens.

METHODS

Aims and objectives

The primary objective of this blinded placebo-controlled randomised trial is to determine the cumulative incidence of SSTI cases in infants from birth to 3 months of age following a single-dose of oral azithromycin administered during labour compared with placebo.

Secondary objectives:

To compare intervention and placebo groups with regard to:

1. Cumulative incidence of infant infection (meningitis, sepsis, pneumonia, SSTI, fever, diarrhoea, urinary tract infection) up to 12 months of age.
2. Cumulative incidence of maternal infection (mastitis, sepsis, postoperative wound infections, SSTI, fever, meningitis, pneumonia, abdominal or pelvic abscess, endometritis, urinary tract infection, pyelonephritis, chorioamnionitis) by 6 weeks postdelivery, and similarly up to 12 months post-delivery.
3. Cumulative incidence of antibiotics prescribed to infants and mothers up to 12 months of age/post-delivery.
4. Prevalence of maternal and infant cases of impetigo with detection of SA and/or GAS.
5. Prevalence of azithromycin non-susceptibility in SA and/or GAS isolates from maternal and infant impetigo cases (up to 3 months and up to 12 months postdelivery).
6. Incidence of maternal cases with chorioamnionitis from placental biopsy histopathology.
7. Prevalence of infants with diagnoses that have been associated with microbiome dysbiosis (eczema, wheeze or adiposity) at 12 months of age.
8. Prevalence of solicited non-serious infant and maternal adverse events (AE).
9. Cumulative incidence of infant and maternal serious adverse events (SAE) throughout the study.
10. Prevalence of maternal and infant bacterial carriage (including GBS, SA, SPN, GAS and *E. coli*) at key time points, principally 7 days post-delivery.
11. Incidence of common organisms relevant to STIs in maternal vaginal samples.
12. Rate of antimicrobial non-susceptibility among maternal and infant bacterial carriage isolates (including GBS, SA, SPN, GAS and *E. coli*) at selected time points.

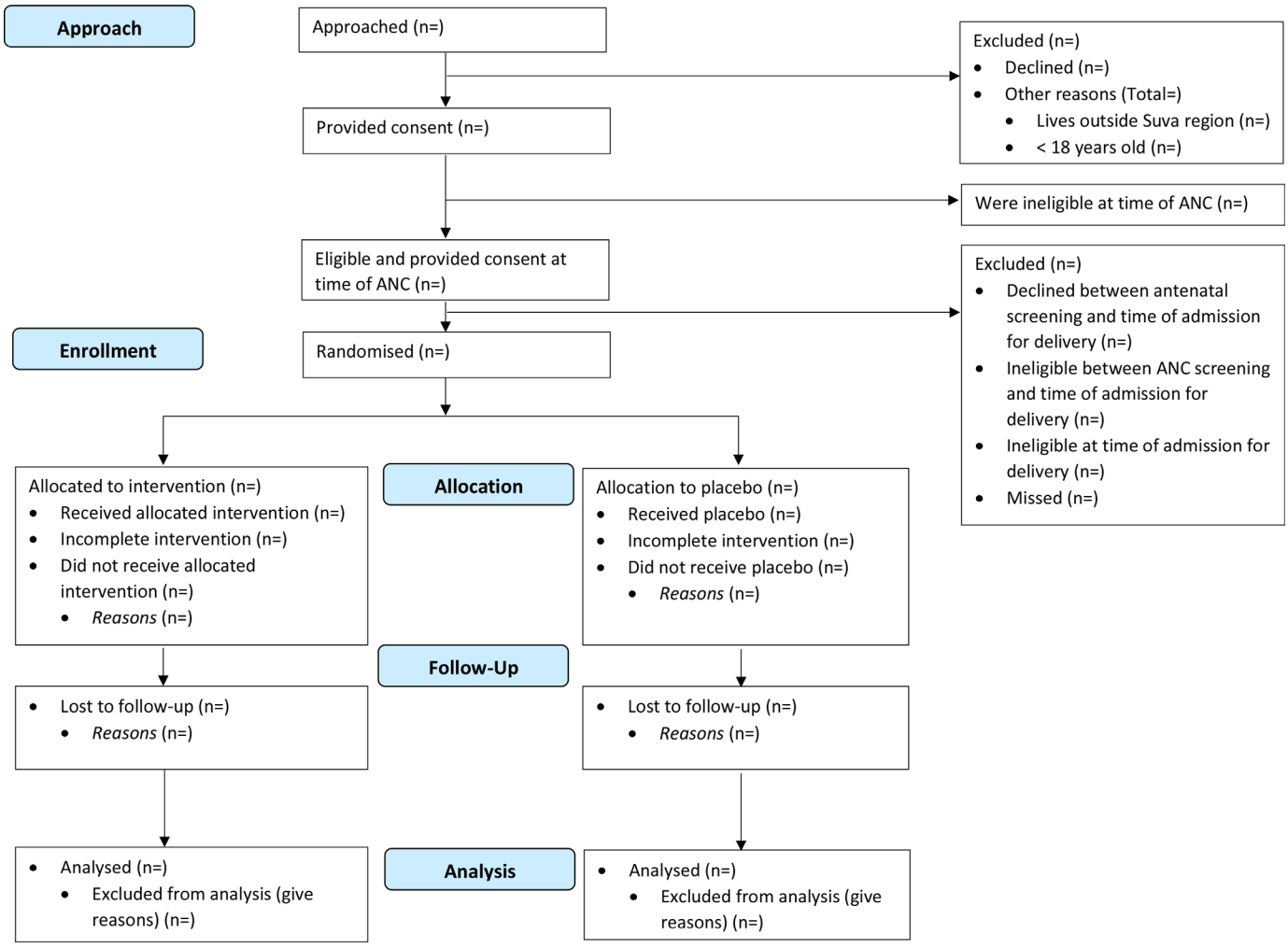

Figure 1 Flow diagram for study procedures. ANC, Antenatal Care.

13. Maternal and infant microbiome composition at key time points.
14. Carriage and transmissibility of antibiotic resistance genes (in microbiome analysis) in mother and infant.

Design

This is a blinded, randomised, placebo trial of a single 2 g dose of azithromycin or placebo, administered to women in labour or immediately prior to delivery in the case of caesarean section. There are 2110 mother/infant pairs being recruited and randomised in a 1:1 ratio to each study arm, with six visits over 12 months of follow-up for the mother/infant pair (figure 1).

Study setting and population

This study is set in Fiji, where the two principal ethnic groups are indigenous Fijians (iTaukei), who comprise 57% of the population, and Fijians of Indian descent, 38% of the population.[30] Recruitment, randomisation and the initial visit occur at Colonial War Memorial Hospital (CWMH), the main tertiary hospital in the capital city Suva where approximately 44% of births occur.[31 32] Follow-up visits will occur at various Maternal Child Health (MCH) clinics in the Greater Suva region.

Patient and public involvement

There was collaboration with CWMH and MCH clinic staff who were not involved in the study, to ensure study processes were appropriately integrated into these settings. Patients were not involved in the design of the study.

Recruitment and informed consent

Study midwives and nurses approach pregnant women at an antenatal clinic. A formal, informed, written and witnessed consent process is conducted if the approached woman is interested in the study. The patient information and consent form is explained to the woman in full and discussed with the family and husband if possible. Recruitment commenced in June 2019 and was completed in February 2022 but was delayed for 42 weeks due to disruptions from the COVID-19 pandemic.

Eligibility

Pregnant women are eligible for inclusion if they are at least 18 years old and intend to deliver at CWMH, who have a principal residence in the Greater Suva area and expect to be available with their infant for the duration of the study. Women admitted for delivery at the time

of final eligibility assessment, prior to randomisation and who gave written informed consent are eligible. Women with cardiac, renal, or hepatic abnormalities, or taking specific drugs that may interact with azithromycin are excluded from the study. For a full list of eligibility criteria, see online supplemental file 1.

Enrolment

After informed consent and the eligibility criteria are met, the pregnant woman is consigned a unique recruitment number. At delivery, eligibility is reconfirmed (including that they were still willing to participate), and the woman is enrolled and randomised (including assigning a randomisation number). Nine hundred and forty mothers will be enrolled in a swab study to assess microbiological outcomes. The first 400 will also be included in the microbiome subset. However, due to COVID-19 disruptions impacting face to face follow-up and the collection of samples, additional participants were enrolled in the microbiome subset to ensure a full set of 400 samples from each participant, as recruitment into this microbiome subset was more substantially impacted by COVID-19.

Interventions

Participants are randomised to receive either 2 g of oral azithromycin (four 500 mg tablets) or a placebo. Those in the placebo group are given four tablets containing regelatinised starch, calcium dibasic phosphate, magnesium stearate and Opadry II White, which look identical to, and are packaged in the same manner as the azithromycin tablets. The azithromycin tablets were manufactured by Laboratorios Cinfa (Spain) and then were repackaged into blister packs by Idifarma (Spain). These tablets are administered during labour (or immediately prior to delivery in the case of caesarean section), witnessed by the study nurse/midwife, who records whether participants vomit the following administration. All participants receive routine clinical care deemed necessary as per CWMH treating medical staff, including administration of routine prophylactic antibiotics (ampicillin and gentamicin) as clinically required by caesarean section or suspected chorioamnionitis.

Randomisation and allocation concealment

Participants are randomised 1:1 to the intervention and control arms with stratification by ethnicity (Indigenous Fijian vs other), given established differences in bacterial carriage and infection rates.[33] Blocked randomisation was performed with permuted blocks of variable length. An independent statistician created a computer-generated randomisation list, and then Idifarma labelled the Investigational Product (IP) according to this list. Randomisation numbers are written on blister packs containing the IP, stored separately by stratum and assigned to participants by study staff based on the participant's self-reported ethnicity consecutively in ascending order (online supplemental file 2). The infant is automatically enrolled and issued a unique identifier linked to the mother's randomisation number. A list of all randomised women and their corresponding recruitment numbers is kept in a secure room.

Blinding and unblinding

The investigators, participating women, parent(s)/guardian(s) of infant participants, sponsor, study staff and laboratory personnel are blinded. Sealed envelopes containing the treatment allocation corresponding to each randomisation number are available at the study site at CWMH for medical emergencies. A list is kept by the independent statistician that can be used to provide treatment allocation information if requested by the Data Safety Monitoring Board (DSMB) if concerns are raised through a review of study safety data. Overall study unblinding will occur after all data collection has ceased, the statistical analysis plan is finalised and the database has been locked.

Study procedures

Study procedures are performed according to Standard Operating Procedures and Good Clinical Practice. Baseline demographic and health information is collected from participants prior to delivery. After delivery of the infant, the placenta is collected to perform placental biopsies for histopathological diagnosis of chorioamnionitis (online supplemental file 3). The unique hospital identifier of the mother and infant are recorded to allow the study doctor to search for any subsequent hospitalisations for each participant, and relevant delivery outcomes for mother and infant are extracted by study staff from medical records.

At each study visit, the mother and infant have their axillary temperatures recorded and are examined for SSTI, and if found, the location is recorded to classify SSTI as new or pre-existing since the last visit. Antibiotic use since the last visit, history of AEs (for a full list of AE to be recorded, see online supplemental file 4), recent illnesses/hospitalisations and outpatient treatment are also recorded. Additional procedures for the infant include measuring the length and respiratory rate and assessing for any signs of severe disease.[34] The caregiver is also asked about the infant's feeding, as exclusive breast feeding is associated with a reduced risk of some infections,[35] and screening questions at specified visits for signs of infantile hypertrophic pyloric stenosis (up to 6 weeks old) and hearing impairment as they are SAEs that can be associated with azithromycin.[36 37] Visits 2 through 6 are conducted at MCH clinics at various times up to 12 months of age of the infant (see table 1). If impetigo is detected by study staff at visit 4 (3 months) and/or visit 6 (12 months), a single swab per participant is taken of one impetigo lesion (online supplemental file 5). These swabs will be tested for SA and/or GAS, and if positive, antimicrobial resistance (AMR) testing will also be undertaken. All enrolled participants are expected to complete all their study visits by February 2023, which is the expected end date of the study.

Table 1 Timing and details of study visits

	Screening	Enrolment/allocation	Postallocation				Close-out
Visit	**Antenatal contact**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**
Timing	**Antenatal prior to enrolment**	**CWMH admission to discharge**	**7 days postnatal ±3 days**	**6 weeks postnatal ±4 days**	**3 months postnatal±7 days**	**6 months postnatal±7 days**	**12 months postnatal±14 days**
Enrolment							
Informed consent	×						
Confirm desire to proceed		×					
Confirm eligibility		×					
Randomisation		×					
Intervention							
2 g oral azithromycin administered		×					
Oral placebo administered		×					
Assessment							
Demographic/baseline data*	×	×	×				
Placental sample taken		×					
Examination of the infant		×	×	×	×	×	×
Adiposity measures of the infant							×
Examination of the mother		×	×	×	×	×	×
Feeding review		×	×	×	×	×	×
Adverse event review		×	×	×	×	×	×
History of illness between visits		×	×	×	×	×	×
Antibiotic use review		×	×	×	×	×	×

*Includes demographic and health data (baseline symptoms of sexually transmitted infections and hearing impairment, rural/urban status, marital status, number in household, family income, tobacco exposure, substance use, maternal education, asset index) and delivery outcomes (time and date of membrane rupture, induction of labour, number of vaginal examinations during delivery, mode of delivery, signs of chorioamnionitis, meconium exposure and Apgar scores).
CWMH, Colonial War Memorial Hospital.

Microbiological outcomes

Samples for microbiological analyses are being collected at different time points (table 2) and transported to the Fiji Centre for Disease Control laboratory within 6 hours of collection for storage.

Bacterial carriage

Dual flocked swabs (Puritan) are used to collect oropharyngeal, vaginal and rectovaginal samples, with one swab head used for bacterial carriage and the other for microbiome analysis where applicable. Oropharyngeal swabs are collected by study staff from the tonsillar area of the throat; vaginal swabs are collected by inserting a swab 1–2 cm into the vagina, with this process repeated for rectovaginal swabs before inserting the same swab 1 cm into the anus. Nasopharyngeal swabs are collected by study staff from the posterior nasopharynx as per WHO carriage guidelines.[38] Swabs are placed into 1 mL skim milk-tryptone-glucose-glycerol, except vaginal swabs, which are placed into universal transport media (Copan). For infants, three small scoops of stool are taken from a soiled nappy and put into a specimen container. Breast milk samples are collected from mothers asked to express their milk manually. All bacterial carriage samples are placed in a cool box immediately after collection.

Microbiome

One head of the dual-headed swabs from the oropharyngeal, vaginal and rectovaginal swabs are placed into DNA/RNA shield collection tubes (Zymo Research). Furthermore, at certain visits, a second infant stool sample is taken and put into a DNA/RNA shield faecal collection tube (Zymo Research). All microbiome samples are kept at room temperature after collection and during transportation to the laboratory.

See online supplemental file 6 for further sample collection details.

Primary outcome definitions and assessment

The primary outcome of SSTIs is defined as the occurrence of impetigo, furuncle, omphalitis, abscess, cellulitis and/or staphylococcal scalded skin syndrome in infants up to 3 months of age. SSTIs are assessed at each study visit by study staff, with training and assessment informed by established guidelines and methodology used by other similar published studies (online supplemental file 7).[39–41] Further, if SSTIs are identified during visits, staff discuss and send photos of these to the study doctor for confirmation, with the study doctor making the final assessment based on these photos and history provided by staff.

The cumulative incidence of SSTIs will be calculated from SSTI data collected at each study visit and any hospitalisations which document SSTIs as recorded by the treating doctor.

Impetigo is defined as an active bacterial skin infection characterised by sores that start as round or oval pus-filled bumps which progress into blisters, or the sores produce a clear honey-coloured fluid that forms a crust on the skin. When the crusts are removed, the area underneath appears red and eroded.[22]

Furuncle is defined as pus-filled lesions that are painful and usually firm, occurring when infection around the hair follicles spreads deeper.

Omphalitis is defined as a newborn infection of the umbilical stump, which presents as superficial cellulitis that may involve the entire abdominal wall.

Skin abscess is defined as a collection of pus built up within the body's tissue with redness, pain, warmth, and swelling of the affected area.[41]

Cellulitis is defined as a skin infection that is red, painful, swollen, tender and warm to the touch.[41]

Staphylococcal scalded skin syndrome is defined as an illness characterised by red, blistering skin that looks like a burn or scald.

Secondary clinical outcome definitions

1. Infant infections, a binary composite variable, defined as the occurrence of one or more of: meningitis; sepsis; pneumonia; SSTI; diarrhoea; urinary tract infection; ophthalmia neonatorum or fever up to 12 months of age.
2. Maternal infections, a binary composite variable, defined as the occurrence of one or more of: mastitis; sepsis; postoperative wound infections; SSTI; fever; meningitis; pneumonia; abdominal or pelvic abscess; endometritis; urinary tract infection; pyelonephritis; or chorioamnionitis by 6 weeks postdelivery, and 12 months postdelivery. SSTI in participating mothers is the occurrence per the previous definition, plus mastitis and postoperative wound infection.

See online supplemental file 8 for further definitions.

Trial safety and conduct

Safety outcomes collected in the study include solicited non-serious AE in mother and infant collected at all study visits that are known common adverse drug reactions associated with azithromycin such as nausea in maternal participants, and are solicited through relevant questions in the Case Report Form (CRF). Any concerns regarding these events are discussed with the study doctor and referred as appropriate. SAEs (online supplemental file 4) are identified and reported by the study doctor throughout the study, detected through searching electronic hospitalisation records, solicited at each study visit and as indicated by participants and study staff. Voluntary withdrawals from the study will also be asked for permission to continue to check these hospital records for the normal study follow-up period in order to collect safety and outcome data. Before recruitment, an independent DSMB was established that regularly reviews data related to AE and SAEs.

External study monitoring by a clinical trials monitor is conducted.

Required changes to study procedures during COVID-19

Recruitment started in July 2019 but stopped between 19 March 2020 and 30 June 2020 and from 21 April 2021 and

Table 2 Timing and description of sample collection for microbiological outcomes in a subset of participants

		Visit timing						
		Enrolment/allocation		Postallocation				Close-out
		Visit 1		Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
		CWMH admission to discharge		7 days postnatal±3 days	6 weeks postnatal±4 days	3 months postnatal±7 days	6 months postnatal±7 days	12 months postnatal±14 days
Participant	Microbiological study subset	Preintervention	Postintervention					
	Swab study							
Infant	Nasopharyngeal swab		×	×	×		×	×
	Oropharyngeal swab		×	×	×		×	×
	Stool		×	×	×		×	×
	Microbiome							
	Oropharyngeal swab			×	×		×	×
	Stool			×	×		×	×
	Swab study							
Maternal	Nasopharyngeal swab	×		×	×		×	×
	Oropharyngeal swab	×		×	×		×	×
	Rectovaginal swab	×		×	×			×
	Vaginal swab	×			×			×
	Breastmilk			×				
	Microbiome							
	Oropharyngeal swab	×		×	×		×	×
	Rectovaginal swab	×		×	×			×
	Vaginal swab	×			×			×

CWMH, Colonial War Memorial Hospital.

6 November 2021 because of COVID-19. During these periods, follow-up visits were performed via phone, but no physical examination or collection of microbiological samples could occur. As physical examinations were not possible, participants were asked about new skin lesions since the last visit and then asked to send photos for verification by the study doctor. For participants recruited from 6 November 2021, there will be no collection of microbiological samples at 6 weeks and 12 months (at visits 3 and 6) due to difficulties with importing specific consumables required in the context of COVID-19.

Data management

The data from CRFs are entered into a REDCap (Research Electronic Data Capture) database hosted at the Murdoch Children's Research Institute,[42 43] with 100% data verification for all CRF data related to primary outcomes and SAEs to ensure this matches database entries. There is a separate REDCap database for laboratory data. Data are cleaned in an ongoing manner.

Study records are stored so that participants' confidential information is only accessed within the study team as necessary and protected from unauthorised access.

Sample size

To detect a 50% decrease in SSTIs, from 6% in the controls to 3% in the intervention arm, with 90% power and a two-sided alpha of 0.05, a sample size of 1002 participants per arm is required. These assumptions were based on rates of impetigo in infants in Fiji and declines in skin infection in the Gambia following 2 g of oral azithromycin.[19 22] This sample size was inflated to 1055 participants per arm (total n=2110) to allow for 5% dropout.[39 44]

For the secondary outcome of bacterial infant carriage at 7 days of age, 940 mother/infant pairs (470 per arm) will provide 95% power at a two-sided 0.05 alpha level to detect an 80% reduction in infant GBS carriage with the intervention, assuming 5% placebo group infant GBS carriage and no loss to follow-up. These assumptions were based on maternal carriage rates in Suva,[45] an assumed 50% likelihood of GBS transfer to neonates from colonised mothers[46] and carriage reduction levels found in the Gambian trial.[20] This sample size will also detect reductions in the infant carriage rate for all relevant bacteria.

Statistical analysis

Participant characteristics in each trial arm will be described. Continuous variables will be summarised using means and SDs (or medians and IQRs for non-symmetrical data), and categorical variables reported as frequencies and percentages. The primary analysis will be performed according to the intention-to-treat principle. A secondary analysis conducted with the per-protocol population may exclude those who did not receive complete administration of the IP as allocated or were later found to be ineligible at the time of randomisation. The primary outcome will be expressed as a cumulative incidence: the proportion of infants who develop an SSTI within the first 3 months of life. The comparison between trial arms will be presented as a risk ratio with 95% CIs and p values, estimated using log-binomial regression with the stratification variable (ethnicity) as a covariate. A risk difference with 95% CIs and p values will be presented as a secondary analysis. The same analysis methods will be used for other clinical secondary outcomes. Carriage rates and antibiotic nonsusceptibility will be compared between groups using risk ratios and 95% CI. For the primary outcome, multiple imputation will be used to handle missing data, and sensitivity analyses adjusting for time period will be performed to assess the impact of changes to outcome assessment due to COVID-19-related restrictions across the study duration. SSTIs will be tabulated by visit and mode of assessment to see if there is variation in diagnosis of SSTIs by mode of assessment across these study visits. All statistical analyses will be performed using Stata 16.

DISCUSSION

Reducing neonatal mortality is essential for improving child health globally. In 2019, 47% of all under-five deaths occurred in the newborn period,[2 47] with approximately a third of all neonatal deaths happening on the first day of life, and three-quarters within the first week.[48] As infections are a common cause of neonatal and maternal mortality, developing targeted interventions in these periods is critical for achieving the 2030 Sustainable Development Goal targets. Administering azithromycin during labour should be considered an emerging intervention in this area, having beneficial effects through decreasing carriage of potential pathogens in mothers and infants, thereby reducing the likelihood of transmission and development of serious infections including invasive pneumococcal disease, GBS NNS and neonatal infections caused by STIs such as chlamydia and gonorrhoea.

Despite the broader potential impact on other serious infections, this study will primarily look at the effect on the incidence of SSTIs in infants up to 3 months of age whose mothers received azithromycin during labour. Our study is powered accordingly to investigate this, making it different from the previous Gambian study that was powered to look at their primary outcome of the effect on bacterial carriage.[20] Building on the Gambian study, we will look at potential sequelae of this intervention on microbiome dysbiosis, by assessing conditions of wheeze, eczema and adiposity previously associated with microbiome dysbiosis.[49 50]

Despite receiving the same training and assessment requirements for the study, staff may have different skill levels, creating some differences in primary outcome reporting from study visit examinations. However, this is mitigated as participants are asked if any hospitalisations have occurred since the last study visit. Further, the electronic medical record system is searched for hospitalisations for infections and other SAEs covering the duration

of the follow-up period, and these hospital admissions for SSTIs are included in the primary outcome.

Samples are being collected to determine the effects of azithromycin and on AMR up to 12 months of age. The Gambian study reported significantly higher levels of azithromycin resistance associated with the intervention in the neonatal period (at 4 weeks), but this returned to baseline 12 months after administration, with no differences between groups.[51] A systematic review synthesising evidence on the emergence of AMR after mass azithromycin distribution found an increase in macrolide resistance immediately after treatment, which seemed to dissipate with time.[52] Dysbiosis, when antibiotic exposure alters the structure and function of the human microbiome,[53] has been associated with a variety of chronic health conditions in children,[54] including asthma and obesity.[49 50] Two studies examining the short-term effects of azithromycin administered to infants and young children found reductions in microbial diversity and changes in bacterial composition compared with placebo groups.[55 56] However, very few studies examine the immediate effect of intrapartum antibiotic prophylaxis on the infant microbiome or the longer-term effects of antibiotic use on the infant microbiome. Our study will provide useful information related to these areas.

Administration of azithromycin during labour may be a cheap and simple intervention that could improve neonatal morbidity and mortality in LMICs, alongside strengthening maternal-child health services. This study, together with other large clinical trials that are currently being undertaken in Africa and Asia documenting the effectiveness of azithromycin administered during pregnancy or in labour, on stillbirths, maternal and neonatal infections, and mortality,[57] will add to the evidence for consideration at both national levels and by multilateral groups such as WHO involved in international guideline setting.

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Competing interests CDN is a coinvestigator on a Merck Investigator Studies Programme grant funded by MSD on pneumococcal serotype epidemiology in children with empyema and an investigator on a Pfizer-funded clinical research collaboration of PCV vaccination in Mongolia.

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