BMC Medicine

RESEARCH

Open Access

The safety and efficacy of a single dose of oral azithromycin given in labour to prevent skin and soft tissue infections in young infants in Fiji: a randomised controlled trial

Maeve Hume-Nixon[1,2*], Stephanie Clark[2,3], Tupou Ratu[2], Cattram D. Nguyen[1,2], Eleanor F. G. Neal[1,2,4], Kathryn Bright[2,4], Aneley Getahun Strobel[5], Emma Watts[4], John Hart[1,6], James Fong[3], Eric Rafai[3], Kelera Sakumeni[3], Andrew Steer[1,6,7], Ilisapeci Tuibeqa[3] and Fiona M. Russell[1,2]

Abstract

Background Prophylactic azithromycin in pregnancy has been shown to lower infections in birthing parents and newborns, particularly skin and soft tissue infections (SSTIs) which are common in Fiji. We aimed to determine the safety and efficacy of 2 g of oral azithromycin administered during labour on infant SSTIs.

Methods This blinded, randomised placebo-control trial included healthy, pregnant adults and their infants presenting for delivery at a tertiary hospital in Suva, Fiji. Participants in labour were randomly assigned a single dose of 2 g of oral azithromycin or placebo in a 1:1 ratio, stratified by ethnicity. Active and placebo drugs were identical to mask treatment allocation. The primary outcome was cumulative incidence of infant SSTIs by 3 months of age. Intention-to-treat analysis was used and included participants with SSTI data collected at all visits. Safety outcomes were described as percentages by arm at specified time points.

Results From June 2019 to January 2022, 2110 pregnant persons were enrolled and randomised, with 1059 and 1063 births in the azithromycin and placebo groups, respectively. 1671 infants were included in the primary analysis (816 in azithromycin and 855 in placebo group). We found a 27% decrease in infant SSTIs in the azithromycin group (5.8%; 95% CI 4.4–7.6) compared to placebo (7.8%; 95% CI 6.2–9.8), but the 95% confidence interval crossed the null value (RR 0.73; 95% CI 0.51–1.06). We observed similar numbers of serious adverse events in both arms, and no cases of infant hypertrophic pyloric stenosis.

Conclusions There was a modest relative reduction in infant SSTIs but this was small in absolute terms with no statistically discernible difference. Our findings do not support routine intrapartum azithromycin prophylaxis for this outcome alone. However, the rates of SSTIs highlight the importance of prevention and timely treatment in Fiji.

Trial registration 2019–04-18, ClinicalTrials.gov identifier: NCT03925480

Keywords Global Child Health, Azithromycin, Intrapartum azithromycin, Paediatric infectious disease, Skin infections, Global health

*Correspondence:
Maeve Hume-Nixon
Maeve.humenixon@gmail.com
Full list of author information is available at the end of the article

Background

Infection is an important contributor to morbidity and mortality during the perinatal period, causing 11% of maternal deaths and 21% of 2.4 million neonatal deaths each year, with the burden disproportionately affecting low-income and middle-income countries [1–3]. Intrapartum antibiotic prophylaxis, commonly benzylpenicillin, has been very successful in reducing Group B Streptococcal neonatal sepsis in high income countries [4]. Recently, many clinical trials have been done in low-income and middle-income countries to determine whether intrapartum azithromycin is effective in preventing maternal and infant mortality, stillbirths and infection [5–8]. Azithromycin is a broad-spectrum antibiotic with antibacterial activity against gram-positive and gram-negative organisms, as well as pathogens causing sexually transmitted infections; all of which can cause vertical infections in newborns including neonatal sepsis.

One of the most common causes of neonatal sepsis in low-income and middle-income countries, *Staphylococcus aureus* [9], also causes skin and soft tissue infections (SSTIs). Infectious skin conditions are not only common, with impetigo affecting one in five children aged 0 to 4 years globally, but are the largest contributors to disability for communicable disease in children [10]. SSTIs are also caused by *Streptococcus pyogenes* (Group A Streptococcus; GAS), and are common clinical foci for invasive *S. aureus* and *S. pyogenes* disease. Fiji has a high incidence of SSTIs, with survey from 2006/2007 finding rates of impetigo in infants to be 13.3% overall; 6% in those aged 0 to 6 months, and 23.7 in those aged 7 to 12 months [11]. There has also been a higher incidence of serious sequalae of SSTIs reported in Fiji including hospitalisation and invasive *S. aureus* and *S. pyogenes* disease, as well as a higher case fatality rate compared to those documented from other countries [12–15].

Previous clinical trials from Africa found that intrapartum azithromycin reduced infant skin infections. In 2015, the Gambian PregnAnZI trial found a 51% reduction (Relative risk (RR) 0.49; 95% Confidence interval (CI) 0.25–0.93) in skin infections (6.4% in the placebo group versus 3.1% in the azithromycin group) [16]. This study also found a 24% reduction in infant infections and a 60% reduction in maternal infections overall, and a reduction in carriage of potentially pathogenic bacteria including Group B Streptococcus, *S. aureus* and *Streptococcus pneumoniae* [6, 16]. Another trial by the same group (The PregnAnZI-2 study) found a similar reduction in the odds of newborn skin infection (odds ratio (OR) 0.58; 95% CI 0.34–0.67) but a smaller absolute reduction from 1.7% in the placebo group to 0.8% in the azithromycin group [7]. A 2024 systematic review and meta-analyses synthesising the results of both these studies found that intrapartum azithromycin reduced omphalitis and infant skin infections by 42% and 52%, respectively (omphalitis; RR: 0.58, 95% CI.0.34–0.98, skin infections; RR: 0.48, 95% CI 0.36–0.65) [17].

In the context of Fiji's high burden of SSTIs and invasive infections caused by *S. aureus* and *S. pyogenes*, we conducted the Bulabula MaPei study in Fiji to examine whether intrapartum azithromycin was a suitable intervention to reduce these infections. To our knowledge this is the first intrapartum azithromycin clinical trial to investigate SSTIs as a primary outcome. Furthermore, it was the first study of this type to be conducted in the Western Pacific Region; one of the regions with the highest burden of SSTIs in the world. Our study aimed to determine whether oral azithromycin administered during labour reduced the cumulative incidence of SSTIs in infants up to 3 months of age. Secondary outcomes include the safety and tolerability for birthing parents and infant participants, as well as other infant infections, infections in birthing parents including chorioamnionitis, and antibiotic prescription. Here we report on the primary outcome of the trial and the adverse events following azithromycin administration.

Methods

Study design and setting

This phase III blinded, randomised, placebo-controlled trial was designed to assess cumulative incidence of SSTIs in infants at 3 months of age, born to those receiving a single-dose of oral azithromycin during labour compared to infants born to those receiving placebo. This study was conducted in Suva, the capital of Fiji. Fiji has a publicly funded healthcare system including pregnancy care. The population of Fiji comprises 57% indigenous Fijians (iTaukei) and 38% Fijians of Indian descent [18]. Recruitment, randomisation and the initial visit occurred at the Colonial War Memorial Hospital. The Colonial War Memorial Hospital is the largest tertiary hospital in Fiji where there are approximately 8200 births per year[1], comprising 46% of Fiji's annual birth cohort [19]. Postpartum participants and their infants were followed-up in six visits over 12 months, which occurred at maternal child health clinics in the wider Suva area.

2110 pregnant people were recruited and randomised in a 1:1 ratio to receive either a single 2 g oral dose of azithromycin or placebo in labour, or immediately prior to delivery in the case of caesarean section. Further details can be found in the published protocol [20]. There was an independent Data Safety Monitoring Board that

[1] Labour ward monthly report annual 2019. Hume-Nixon M. 2019.

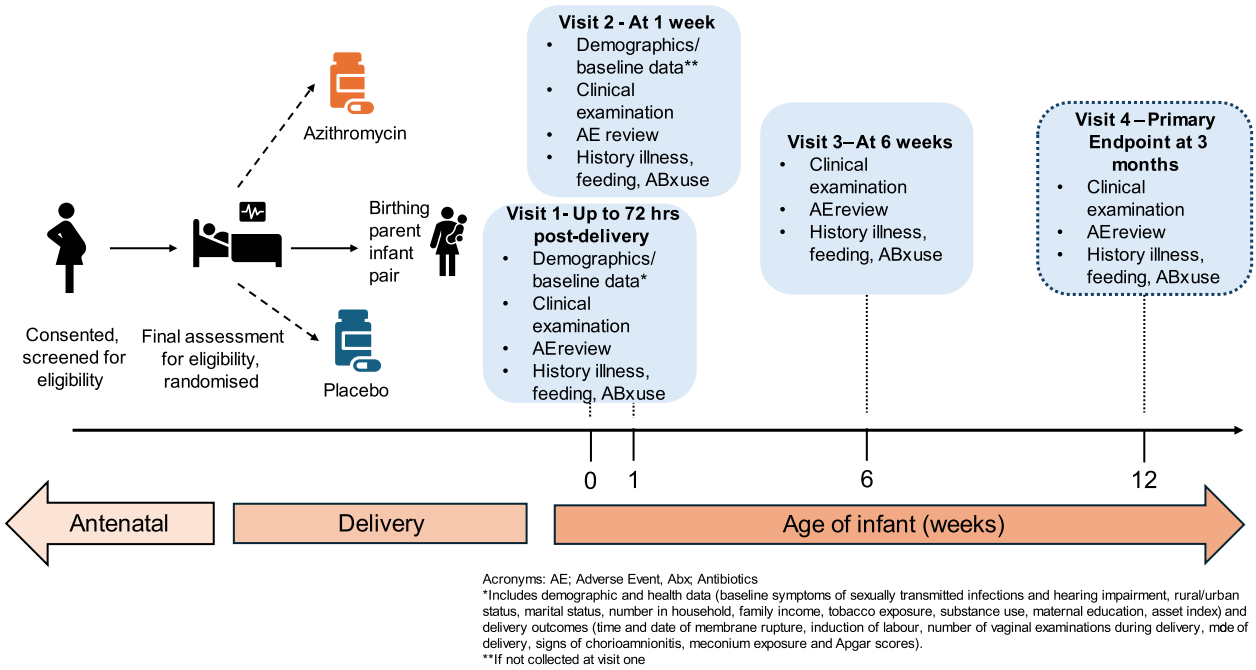

Fig. 1 Study procedures up to and including primary endpoint at 3 months of age (visit four)

regularly reviewed safety data, and the study was registered prior to study start (April 18th 2019, ClinicalTrials.gov identifier: NCT03925480).

Enrolment and participants

Study midwives and nurses initially approached pregnant persons at an antenatal clinic, and for those interested in the study, a witnessed, written informed consent process was done. Pregnant persons were eligible for inclusion if they were at least 18 years old, intended to deliver at the Colonial War Memorial Hospital, lived in Greater Suva and expected to be available for the 12-month study duration. Individuals with cardiac, renal, or hepatic abnormalities, or taking specific drugs that may interact with azithromycin were excluded; for example antiarrhythmics, antipsychotics and antidepressants (see Additional File 1: Supplementary Textbox 1, full eligibility criteria).

Final eligibility was reconfirmed when individuals were admitted for delivery, and if still eligible, consent was reaffirmed prior to randomisation. Initially study staff were stationed Monday to Friday during standard office hours. After 8 months, study nurses operated on a 24/7 schedule.

Intervention, randomisation, and masking

An independent statistician produced a computer-generated randomisation list, using stratified randomisation (by ethnicity; iTaukei/Indigenous Fijian versus other) with permuted blocks of variable length. Randomisation numbers were written on blister packs containing the investigational product (IP) and were stored separately by ethnicity stratum.

After confirmation of eligibility, enrolment and randomisation were performed by study staff by assigning the next available randomisation number from the randomisation list consecutively in ascending order, based on the participant's self-reported ethnicity. The corresponding blister pack was administered to the participant. The placebo was prepared to appear identical to the azithromycin tablets, so although study staff involved in treatment allocation may also have been involved in assessing primary outcome, all study staff and participants were blinded to treatment allocation. The Statistical Analysis Plan and primary analysis code were written before the database base was locked and study unblinded.

Procedures

Participants in labour were randomised to receive the investigational product, either 2 g of oral azithromycin (four 500 mg tablets) or placebo. Azithromycin was manufactured by Laboratorios Cinfa (Spain) and then repackaged into blister packs by Idifarma (Spain). Placebo tablets were manufactured and then repackaged into blister packs by Idifarma (Spain).

Following randomisation, the primary outcome was assessed at 3 months (visit intervals shown in Fig. 1). When face-to-face study visits were restricted during the

Table 1 Skin and soft tissue infection definitions

• Impetigo was 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 [11]
• Furuncle was defined as pus-filled lesions that are painful and usually firm, occurring when infection around the hair follicles spreads deeper
• Omphalitis was defined as a newborn infection of the umbilical stump, which presents as superficial cellulitis that may involve the entire abdominal wall
• Skin abscess was defined as a collection of pus built up within the body's tissue with redness, pain, warmth, and swelling of the affected area [23]
• Cellulitis was defined as a skin infection that is red, painful, swollen, tender, and warm to the touch [23]
• Staphylococcal scalded skin syndrome is defined as an illness characterised by red, blistering skin that looks like a burn or scald

COVID-19 pandemic from 19/03/2020 to 30/06/2020, and from 21/04/2021 to 6/10/2021, follow-up study visits were performed via phone, asking questions from the Data Collection Form around adverse events, history of illness, feeding and antibiotic use, but no in-person physical examination occurred. Instead of physical examination, birthing parents were asked to self-report the occurrence of new skin infections in their infant or themselves since the last study visit, as well as sending photos of specified areas of skin and/or any skin lesion to the study team. The study doctor then reviewed these photos to confirm final diagnosis of SSTI.

The first study visit occurred in hospital after delivery, and the remaining follow-up visits occurred at maternal child health clinics. At the initial visits demographics and pregnancy information was collected. At each face-to face study visit, the birthing parent and infant had their axillary temperatures recorded and were examined for SSTIs which were classified as new or pre-existing since the last study visit. Participants were also asked about diagnoses of SSTIs since the last visit, antibiotic use, adverse events (AEs), recent illnesses/hospitalisations, and outpatient treatment. Additional clinical information for the infant was collected including weight, length, and assessment for clinical warning signs, as well as questions that screened for infantile hypertrophic pyloric stenosis (up to 6 weeks of age) and hearing impairment; AEs specifically associated with azithromycin [21, 22]. Hearing impairment was also monitored through recording routine newborn hearing screening. Routine newborn hearing screening was performed prior to discharge following delivery. Additionally, screening questions for hearing impairment were asked that were developmentally appropriate at each follow-up visit (see Additional File 1: Supplementary Textbox 2).

Outcomes

The primary outcome of SSTIs was defined as the occurrence of impetigo, furuncle, omphalitis, abscess, cellulitis, and/or staphylococcal scalded skin syndrome in infants up to 3 months of age as determined by trained study staff. When face-to-face study visits were paused during the pandemic, additional modes of assessment for SSTIs were added. Birthing parents were asked about the occurrence of new skin infections in their infant or themselves since the last study visit and asked to send photos for verification of SSTI by the study doctor (Table 1). These processes, including relevant staff training, are described elsewhere [20].

Secondary safety and tolerability outcomes for participants were also documented at each study visit (Fig. 1) and by searching electronic hospital records of participants. An AE was any untoward, undesired or unexpected clinical event that occurred in a participant exposed to the IP, irrespective of whether it was related. AEs that resulted in death; were life-threatening; required inpatient hospitalisation (including admission to baby unit) or prolonged existing hospitalisation; and/or resulted in persistent or significant disability or incapacity, were classified as serious adverse events (SAEs). Drug reactions associated with azithromycin and symptoms associated with microbiome dysbiosis were asked about at each study visit. SAEs were identified and reported by the study doctor throughout the study, via participant report with confirmation in medical records. There were also regular searches in electronic hospitalisation records conducted, including a final search at the end of participant follow-up. For a complete list of all other secondary outcomes see Additional File 1: Supplementary Textbox 3.

Statistical analysis

A sample size of 1055 participants per arm (total $n=2110$) would have 90% power to detect a 50% decrease in SSTIs, from 6% in the placebo arm to 3% in the intervention arm, with a two-sided alpha of 0.05 and allowing for 5% loss to follow-up as seen in previous studies in Fiji [24, 25]. These assumptions were based on rates of impetigo in infants in Fiji (6%) [11] and the expected effect size (50%) of 2 g of oral azithromycin on skin infection based on the findings from the Gambian clinical trial [16]. Detailed sample size calculations were published previously in the protocol paper [20].

Data were entered into REDCap (Research Electronic Data Capture) [26, 27] and all statistical analyses were performed using Stata 18.0 following cleaning [28].

Participant characteristics were summarised by treatment allocation. Continuous variables were summarised using means and standard deviations (or medians and interquartile ranges for non-symmetrical data), and categorical variables reported as frequencies and percentages. The primary analysis was performed according to the intention-to-treat principle, and the secondary analysis was a per-protocol analysis. Safety and tolerability outcomes were binary; defined as an occurrence for each event and described as proportions in each arm at specified time points. The denominator used was everyone who received the allocated dose including those that withdrew following administration of the IP, reflecting total number of births (including stillbirths) for infant participants. For comparison between azithromycin and placebo groups, risk ratios and risk differences with 95% CI and *p*-values were calculated, estimated using binomial regression (using log and identity links, respectively) with stratification variable (ethnicity) as a covariate.

There were missing data due to the pandemic effects on enrolment and data collection. For the primary outcome, the primary analysis was a complete case analysis (including participants with observed SSTI data at all visits), and multiple imputation was performed as a secondary analysis. Multivariate imputation by chained equations was used, with the univariate imputation methods of logistic regression performed for binary variables, and linear regression for continuous variables. Auxiliary variables included in the imputation model were identified based on association with outcome of SSTIs and association with missing data, initially suggested by literature review and confirmed through statistical exploration of association by logistic regression. Variables included breastfeeding, infant antibiotic use, ethnicity, educational attainment, total number of household members, smoke exposure, household income, mode of delivery, residential location (e.g. rural/urban/peri-urban) and infant sex. Multiple imputation was performed separately by allocation group, and 50 imputed datasets were created and multiple results combined using Rubin's rules. Additional analyses were conducted to explore how the mode of assessment of SSTIs was distributed across the two arms, as this changed over the course of the study due to COVID-19-related restrictions. Sensitivity analyses were also performed to explore incomplete case analysis, mode of delivery, and time from administration of the investigational product to delivery (see Additional File 1: Supplementary Textbox 4).

Results

Between 1 July 2019 and 31 January 2022, 2110 pregnant persons were enrolled and randomised (1055 in each arm), with 1059 and 1063 births in the azithromycin and placebo groups which included six and eight twin deliveries in each group, respectively. Recruitment was paused between Mar 19, 2020 and Jun 30, 2020 and from Apr 21, 2021 and Nov 6, 2021 due to COVID-19 pandemic restrictions. The trial ended when the final participant completed their last follow-up visit on Feb 28, 2023.

Figure 2 shows the flowchart for study recruitment. A total of 10,827 pregnant persons were screened for eligibility. 6641 did not meet the eligibility criteria or declined to participate, with the most common reason that they lived outside Suva ($n=4521$). Of those 4186 who remained eligible following initial screening, 2076 people were unable to be randomised at delivery; mostly as they were missed at delivery ($n=1992$) either due to lack of 24/7 staff coverage in the initial period of the study, insufficient time to randomise, and/or they delivered during a period with pandemic restrictions. In total, 45 (2.1%) birthing parents were withdrawn. Of infant participants, 92.5% completed a follow-up visit at 3 months of age (see Additional File 1: Supplementary Table 1). However, only 1671 (78.8%) infant participants had skin assessments at each study visit consecutively up to and including 3 months of age and were therefore included in the complete case analysis (see Additional File 1: Supplementary Table 1).

Table 2 shows key demographic and clinical features of the two groups. There was no apparent imbalance between the two groups across multiple factors (Additional File 1: Supplementary Table 2 and 3). Most were of iTaukei ethnicity (82.6%), 23.3% delivered via caesarean section, and the median number of hours between administration of the IP and delivery was 10.8 h (IQR 3.9–33.8). The percentage treated with other antibiotics during admission (excluding the IP) was 35.7% overall, slightly lower in the azithromycin group (33.8%) compared to the placebo group (37.6%).

Table 3 shows that in the intention-to-treat population, 1671 infants that completed all study visits were included in the primary endpoint analysis at 3 months of age. The cumulative incidence of infant SSTIs was lower in the azithromycin group (5.8%; 95% CI 4.4–7.6) compared to the placebo group (7.8%; 95% CI 6.2–9.8), showing a 27% decreased risk of SSTIs at 3 months (RR 0.73; 95% CI 0.51–1.06), however the 95% CI included the possibility of no effect. When ITT analysis was performed on multiply imputed datasets there was a slightly reduced effect of azithromycin compared to complete case analysis (RR 0.79; 95% CI 0.54–1.13) with no evidence of a true difference between groups. Similarly, the incidence of infant SSTIs was lower in the azithromycin group (5.1%; 95% CI 3.3–7.6%) compared to placebo group in the per-protocol analysis (7.6%; 95% CI 5.5–10.4%), corresponding to a 34% decreased risk of SSTIs at 3 months (RR 0.66;

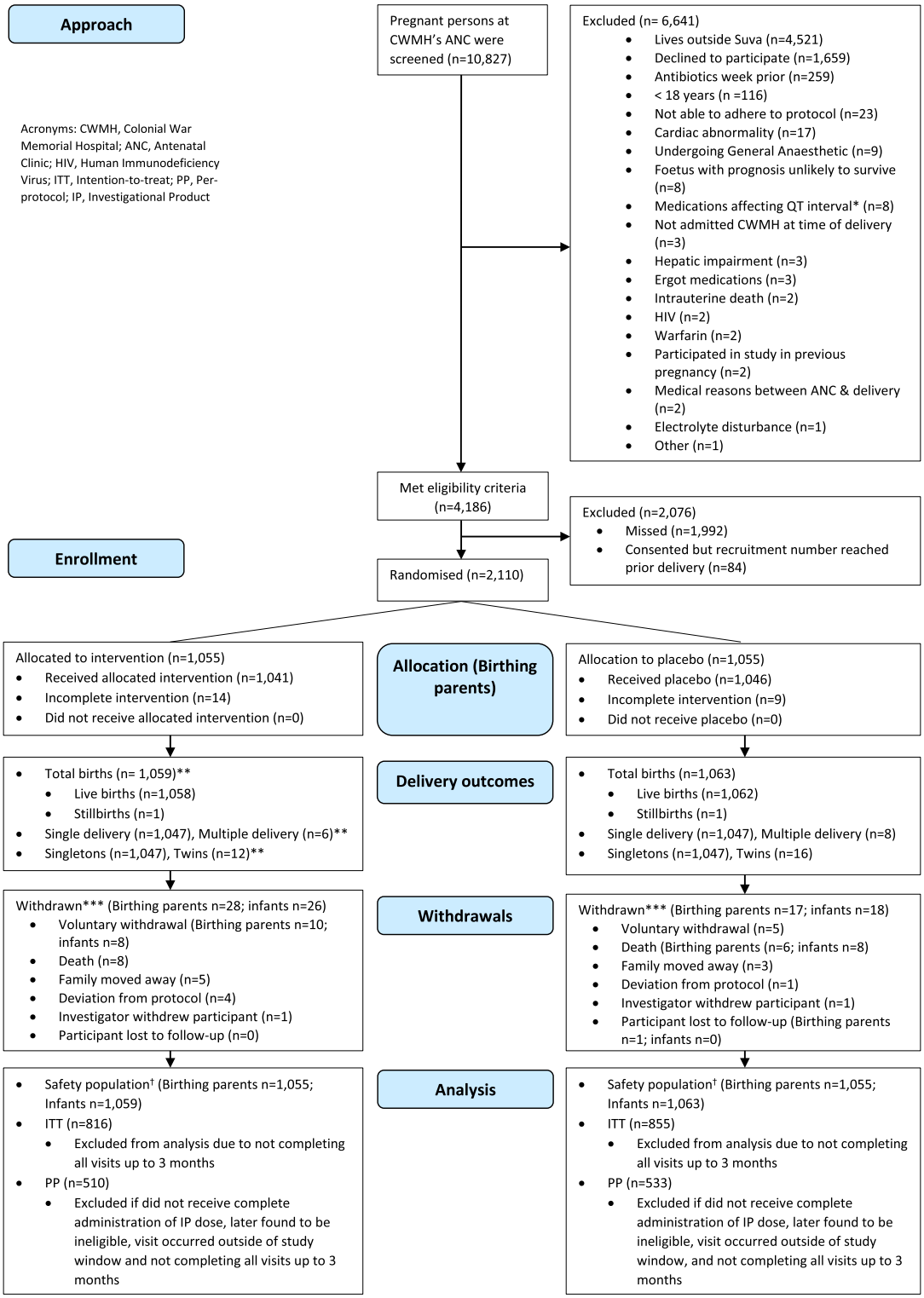

Fig. 2 Enrolment and participant status

Table 2 Characteristics of birthing parents and infant, by treatment allocation

	Azithromycin, n (%)	Placebo, *n* (%)
All birthing parents	*N* = 1055*	*N* = 1055*
Age in years, median (IQR)	27.4 (23.1–31.9)	27.4 (23.2–32.3)
Ethnicity		
Other	183 (17.3%)	184 (17.4%)
iTaukei/Indigenous Fijian	872 (82.7%)	871 (82.6%)
Residential location		
Rural	67 (6.4%)	67 (6.4%)
Urban	452 (42.8%)	436 (41.3%)
Peri-urban	536 (50.8%)	552 (52.3%)
Total number of household members, median (IQR) (*N* = 2110)	6.0 (4.0–8.0)	6.0 (4.0–8.0)
Estimated weekly family income, $FJ median (IQR) (*N* = 2107)	300.0 (200.0–400.0)	300.0 (200.0–400.0)
Cigarette use	103 (9.8%)	121 (11.5%)
Mode of delivery (*N* = 2107)		
Vaginal—non-instrumental	807/1052 (76.7%)	791 (75.0%)
Vaginal—instrumental	9/1052 (0.9%)	10 (0.9%)
Caesarean	236/1052 (22.4%)	254 (24.1%)
Treated with other antibiotics during admission	355/1049 (33.8%)	396/1054 (37.6%)
Hours between rupture of membrane and delivery, median (IQR)	1.5 (0.2–6.3)	1.4 (0.2–6.9)
Hours between study drug and delivery, median (IQR) (*N* = 2107)	10.2 (3.8–32.6)	11.2 (3.9–34.3)
72 h or greater between administration of study drug and delivery	125/1052 (11.9%)	131 (12.4%)
Multiple delivery (*N* = 2107)**	6/1053 (0.6%)	8 (0.8%)
All newborns	*N* = 1059*†	*N* = 1063*
Sex (*N* = 2121)		
Female	531/1058 (50.2%)	504/1063 (47.4%)
Apgar score at birth (*N* = 2117)		
1–6	49/1056 (4.6%)	35/1061 (3.3%)
7–10	1007/1056 (95.4%)	1026/1061 (96.7%)
Birthweight (*N* = 2106)		
Mean (SD)	3441.0 (493.9)	3422.6 (496.8)
Low birth weight < 2500 g	26/1050 (2.5%)	23/1056 (2.2%)
Gestational age (*N* = 2109)		
Mean (SD)	39.7 (1.4)	39.5 (1.6)
Preterm birth (< 37w)	29/1051 (2.8%)	35/1058 (3.3%)
Exclusive breastfeeding at 3 months	535/952 (56.2%)	540/972 (55.6%)
Wasting‡ at 3 months	28/378 (7.4%)	22/428 (5.1%)

*Unless otherwise specified

**Two birthing parents had missing delivery data as they were withdrawn prior to this being collected

† One infant in azithromycin group withdrew before baseline data collected, so for most variables 1058 was the denominator

‡ Using WHO child growth standards (based on age) *Wasted*: Weight-for-length *z*-scores < − 2

95% CI 0.40–1.11), though the evidence was insufficient to conclude a true effect of the intervention. These findings were consistent with the results of the per-protocol analysis on multiply imputed datasets (RR 0.72; 95% CI 0.43–1.19), suggesting that the results were robust to the different approaches for handling missing data. Figure 3 shows a lower cumulative incidence of SSTIs at each time point in the azithromycin group compared to the placebo group.

There were eleven infant deaths overall, with four in the azithromycin group and seven in the placebo group (Additional File 1: Supplementary Table 4). There were no cases of hypertrophic pyloric stenosis and no cases of hearing impairment. In total there were 521 SAEs, with 326 of these being neonatal conditions; most commonly prolonged rupture of membranes, positive maternal syphilis serology and respiratory distress syndrome (see Additional File 1: Supplementary Table 5). These

Table 3 Cumulative incidence of infant skin and soft tissue infections at 3 months by study arm

	Azithromycin *n**/*N* (%; 95 CI)	Placebo *N**/*N* (%; 95 CI)	Risk ratio (95% CI)	*p*-value	Risk difference (%) (95% CI)	*p*-value
ITT analyses						
ITT population (complete case analysis), *n* = 1671	47/816 (5.8; 4.4–7.6)	67/855 (7.8; 6.2–9.8)	0.73 (0.51–1.06)	0.098	−2.1 (−4.5–0.4)	0.094
ITT population (multiple imputation), *n* = 2122	(6.4; 4.6–8.2), *N* = 1059	8.1 (6.3–10.0), *N* = 1063	0.79 (0.54–1.13)	0.20	−1.7 (−4.3–0.9)	0.19
PP analyses						
PP population (complete case analysis), *n* = 908	22/435 (5.1; 3.3–7.6)	36/473 (7.6; 5.5–10.4)	0.66 (0.40–1.11)	0.12	−2.1 (−4.5–0.4)	0.094
PP population (multiple imputation), *n* = 1043	(5.6; 3.3–7.8), *N* = 510	(7.7; 5.3–10.1), *N* = 533	0.72 (0.43–1.19)	0.20	−2.2 (−5.4–1.1)	0.19

Acronyms: *ITT* Intention-to-treat, *PP* Per-protocol, *CI* Confidence interval

*numerator not provided for multiple imputation

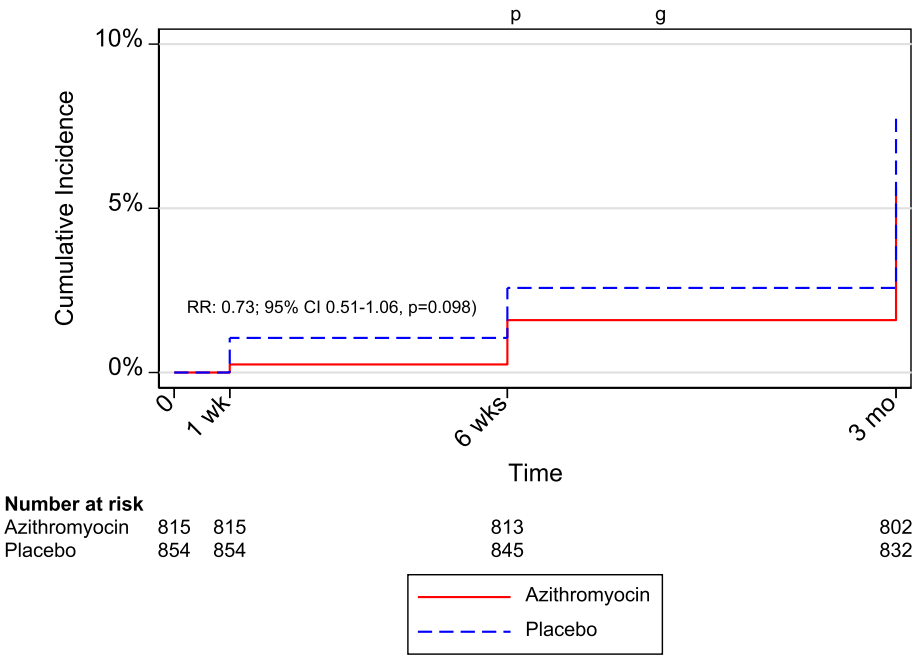

Fig. 3 Cumulative incidence of skin and soft tissue infections up to and including 3 months old

were mostly unrelated (*n* = 503 (96.5%)), or unlikely to be related to the IP (*n* = 18 (3.5%)). None were considered probably, possibly or definitely related to the IP. There were 12 non-serious infant AEs, including vomiting (*n* = 6), diarrhoea (*n* = 5), and feeding difficulty (*n* = 1). A greater number of infant AEs occurred in the placebo arm (*n* = 9) than in the intervention arm (*n* = 3).

There were 66 SAEs reported in 63 birthing parents (3.0%) (Appendix File 1: Supplementary Table 6). There was one death in birthing parents within 3 months of IP administration. The most common SAEs in birthing parents were specific disorders of pregnancy followed by other infections. SAEs were considered unrelated (*n* = 58 (87.9%)), 7 (10.6%) were considered unlikely, and 1 (1.5%) considered possibly related to the IP. There were 183 non-serious AEs reported and the rates were similar by allocation group; 75 (7.1%) in the azithromycin arm and 62 (5.9%) in the placebo arm. The most common non-serious AEs for birthing parents were headache (azithromycin 2.4% vs placebo 3.0%) and abdominal pain (azithromycin 0.9% vs placebo 1.7%).

Sensitivity analysis was undertaken to adjust for having at least one visit during lockdown due to the potential of ascertainment bias. This did not impact the primary outcome results (RR 0.73; 95% CI 0.51–1.05) (Additional File 1: Supplementary Table 7). In those infants delivered by

caesarean section, there was a 46% reduction in SSTIs in the azithromycin group compared to the placebo group (RR 0.54; 95% 0.21–1.39). However, this analysis included only 385 infants. Little differences in effect of the intervention on SSTIs were shown by subgroup analyses for vaginal births, and for participants who delivered within 72 h of IP administration. The rate of diagnosis of SSTIs at each visit by mode of diagnosis (physical examination, photo diagnosis and parent-report) was much lower in photo diagnosis and parent-report compared to physical examination (Additional File 1: Supplementary Table 8). However, the rate for each mode of diagnosis was similar for each study arm.

Discussion

In our clinical trial of the efficacy of intrapartum azithromycin on SSTIs in infants, we found a moderate relative reduction (27%) in SSTIs at 3 months of age with azithromycin compared to placebo; however, the 95% CI crossed the null value. Furthermore, the absolute risk reduction was only 2% corresponding to a number needed to treat (NTT) of 50 to prevent one case of infant SSTI. Our findings do not provide sufficient support to recommend widespread routine use of intrapartum azithromycin to prevent infant SSTIs in Fiji.

While our study did not reach statistical significance and the magnitude of the effect size was smaller than previous studies, our findings are comparable to several key studies. The Gambian PregnAnZI trial found a 51% (RR: 0.49; 95% CI 0.25–0.93) reduction in skin infections, with an absolute reduction of 3.3% [16]. The PregnAnZI-2 trial found a 52% reduced odds of skin infections; however, this corresponded to a smaller absolute reduction of 0.90% (95% CI 0.49–1.30) [7]. A 2024 systematic review and meta-analysis demonstrated overall that intrapartum azithromycin reduced skin infections by 52% (RR: 0.48; 95% CI 0.36–0.65, NNT 60)—a similar NNT skin infections as observed in our study [17].

Our study showed a similar direction of effect to previous studies, but the reduced effect size observed is likely related to differences in the study populations. Our study population had a higher average gestation compared to babies in the PregnAnZI study (39.6 weeks vs 36.0 weeks) [6], and lower percentage of babies that were low birth weight (2.3% vs 9.4%) [7]. These infant characteristics likely reflect the inclusion of birthing parents with fewer pregnancy risk factors compared with the general population of Fiji, explained by strict eligibility criteria and randomisation processes, and supported by the lower observed prevalence of conditions such as diabetes and chorioamnionitis [29]. As our study mainly recruited from urban and peri-urban areas, a smaller proportion of our study population were from rural areas compared to previous studies (6.4% vs 44%) [7]. These features of our study population also limit the generalisability of our results. In addition to these differences, our study did not exclude participants with planned elective caesarean sections resulting in a higher rate of caesarean sections in our study compared to PregnAnZI-2 and PregnAnZI studies (23.3% vs 1.2% and 2.0%, respectively), and the associated high rate of antibiotic use during delivery may account for the reduced effect of azithromycin seen in our study [6, 7]. There was also variation in the definition of skin infections used across studies, and the PregnAnZI-2 included cutaneous manifestations of syphilis, which could contribute to the increased impact of azithromycin observed by this study since azithromycin is an effective treatment for *Treponema pallidum* [30, 31].

The effects of intrapartum azithromycin on SSTIs may be due to reduced parental carriage and horizontal transmission of potential pathogens on the skin and nasopharynx, supported by previous findings that intrapartum azithromycin decreases *S. aureus* carriage in newborns and mothers [6]. Azithromycin has been shown to be particularly effective against *S. aureus* skin infection (OR 0.33%; 95% CI 0.18–0.62), which may explain the increased effect of azithromycin observed in the PregnAnZI-2 study, as *S. aureus* made up a disproportionately high amount of bacterially confirmed skin infections in the placebo group [7]. Differences in macrolide resistance patterns between settings may also have contributed to the varying results. In Fiji, azithromycin is currently only recommended for STI treatment and for typhoid fever that is severe and/or not responding to ciprofloxacin [32, 33]. Although typhoid fever is endemic in Fiji with a reported increase in typhoid fever notifications over the last decade [34], increased macrolide resistance is not supported by a 2024 study of CWMH samples showing that 90% of *S. aureus* isolates were susceptible to erythromycin [35]. Therefore, antimicrobial resistance patterns are unlikely to explain the different efficacy observed between our study and the Gambian trials, and this variation is more likely explained by differences in bacterial carriage rates, particularly of *S. aureus*, and the aetiology of skin infections across these settings.

Our study found that azithromycin was well tolerated, with serious adverse events, particularly those associated with azithromycin such as cardiovascular events in birthing parents, evenly distributed between arms. There were also no infant cases of pyloric stenosis or hearing impairment. This is consistent with findings from previous studies of intrapartum azithromycin, as well as specific studies looking at the association between macrolide exposure and pyloric stenosis that have not shown an association between azithromycin use during pregnancy

and pyloric stenosis [36, 37]. The A-PLUS study reported 11 cases of pyloric stenosis in 29,414 infants, with more cases of pyloric stenosis observed in the azithromycin group ($n=8$) compared to placebo ($n=3$) [5], signalling that this will need continued monitoring in further intrapartum azithromycin studies. Post hoc analysis of the PregnAnZI-2 RCT has shown that intrapartum azithromycin alters gut microbiota development and increases proinflammatory bacteria in the first month of life; however, subsequently both arms converged to similar microbiota, with no differences shown between arms at year three, suggesting that the intervention does not alter the long-term gut microbiota development [38]. However, further research is required to understand the effects of intrapartum azithromycin on the overall gut resistome, all of the antibiotic resistance genes [38], and long-term public health consequences for antimicrobial resistance.

Conclusions

While azithromycin is not recommended to prevent infant SSTIs based on our study results, consideration of this intervention should be viewed alongside demonstrated benefits for other important outcomes such as maternal sepsis, maternal infections, endometritis, and surgical site infections [17], as well as use of azithromycin combination therapy for intermittent preventive treatment for malaria in pregnancy [39]. Future research from this study will contribute to the evidence base for the use of intrapartum azithromycin by looking at impacts on other infant infections, and SSTIs and other infections in birthing parents. Given current slow progress in improving maternal and child health outcomes further research is warranted. Regardless, the high incidence of SSTIs found even within the context of COVID-19 related restrictions demonstrate their ongoing significance as a public health issue in Fiji, and the need for improved prevention, early diagnosis and treatment to decrease serious sequalae.

Abbreviations

RR	Relative risk
OR	Odds ratio
CI	Confidence interval
SSTI	Skin and soft tissue infection
IP	Investigational product
AE	Adverse event
SAE	Serious adverse event
ITT	Intention-to-treat
PP	Per-protocol
NNT	Number needed to treat

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-04070-6.

Additional File 1. Supplementary Textbox 1. Full eligibility criteria. Supplementary Textbox 2. List of all secondary outcomes. Supplementary Textbox 3: Details on Statistical analysis. Supplementary Textbox 4: Details on hearing screening. Supplementary Table 1. Infant participants study visits and complete cases analysis. Supplementary Table 2: Characteristics of pregnant people. Supplementary Table 3: Infant characteristics. Supplementary Table 4: Adverse events in infants. Supplementary Table 5: Infant SAE category 'Other neonatal conditions'. Supplementary Table 6: Adverse events in birthing parents. Supplementary Table 7. Primary outcome sensitivity analyses. Supplementary Table 8. Point prevalence of SSTIs in infants by mode of assessment. Supplementary Table 9. Births and study visits during COVID-19 lockdown. Supplementary Table 10. Birthing parents study visits and complete cases analysis.

Additional File 2. CONSORT 2010 checklist of information to include when reporting a randomised trial. Assessment of primary results reporting against CONSORT checklist.

Acknowledgements

We sincerely thank the participating families on the Bulabula MaPei study and all the acknowledge the dedicated Fijian study staff for their outstanding achievement on completing study visits, despite considerable uncertainty and major disruptions during the COVID-19 pandemic – vinaka vaka levu. We also wish to thank the Ministry of Health and Medical Services and the Fiji Centre for Disease Control for supporting this study including provision of study office, clinic and laboratory space. We sincerely thank the Data Safety Monitoring Board for their helpful comments, time and experience including Prof Jeremy Oats (Chair), Dr Sabine Braat, Prof Keith Grimwood, Prof Philip Hill, and Dr Pushpa W. Nusair. We acknowledge the input and management of Darren Ong. We thank Professor Anna Roca for her early advice on the trial design.

Authors' contributions

F.R. conceived the study and was responsible for the overall design with input from J.F., E.F., K.S., I.T., and A.S. F.R. and E.W. finalised the protocol. M.H.N., T.R. and S.C. finalised the SOPs, except for placental biopsies which were further developed and coordinated by J.H. T.R. managed the fieldwork and staff in Fiji with input from M.H.N., S.C., and K.B. S.C. was the study doctor responsible for clinical outcomes and SAE reporting, and A.G.S. supported sponsor review of events. J.F., E.F., K.S., and I.T. provided support and guidance related to approval processes in Fiji. EN provided database curation and management for the study. M.H.N. and C.N. developed the Statistical Analysis Plan, and developed do.files for data analysis. M.H.N. ran the final analysis, and this was reviewed by C.N. C.N. provided statistical oversight for the study. M.H.N. drafted and finalised the manuscript under the supervision of C.N. and F.R., with input from all authors.

Funding

This work was supported by the National Health and Medical Research Council (NHMRC) GNN1144111. FMR was funded by an NHMRC Translating Research into Practice (TRIP) fellowship and NHMRC Investigator grant. This study was supported by the Victorian Government's Operational Infrastructure Support Programme (grant number: N/A). MHN was supported by a RACP Research Entry Scholarship from the RACP Foundation.

Data availability

The datasets used and/or analysed during the current study are available from Professor Fiona Russell: fmruss@unimelb.edu.au on reasonable request.

Declarations

Ethics approval and consent to participate

The study is conducted according to the protocol approved by the Royal Children's Hospital Human Research Ethics Committee (RCH HREC) (RCH HREC Reference Number 38057) and the Fiji National Health Research and Ethics Review Committee (FNHRERC) (FNHRERC Number 2018.190.C.D.).

Consent for publication

Not applicable.

Competing interests
Cattram Nguyen (CN) is a co-investigator on a Merck Investigator Studies Program 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.

Author details
[1]Department of Paediatrics, The University of Melbourne, Melbourne, Australia. [2]Asia-Pacific Health, Murdoch Children's Research Institute, Melbourne, Australia. [3]Ministry of Health & Medical Services, Suva, Fiji. [4]New Vaccines, Murdoch Children's Research Institute, Melbourne, Australia. [5]Department of Microbiology and Immunology, The University of Melbourne at Peter Doherty Institute for Infection and Immunity, Melbourne, Australia. [6]Tropical Diseases Research Group, Murdoch Children's Research Institute, Melbourne, Australia. [7]Department of General Medicine, Royal Children's Hospital, Melbourne, Australia.

Received: 11 October 2024 Accepted: 10 April 2025
Published online: 28 April 2025

References

1. Lawn J, Kerber K, Enweronu-Laryea C, Massee Bateman O. Newborn survival in low resource settings—are we delivering?. BJOG. 2009;116:49–59.
2. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, Colombara DV, Ikuta KS, Kissoon N, Finfer S, Fleischmann-Struzek C, Machado FR, Reinhart KK, Rowan K, Seymour CW, Watson RS, West TE, Marinho F, Hay SI, Lozano R, Lopez AD, Angus DC, Murray CJL, Naghavi M. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. Lancet. 2020Jan 18;395(10219):200–11. https://doi.org/10.1016/S0140-6736(19)32989-7. Cited.In:Pubmed;PMID31954465.
3. Say L, Chou D, Gemmill A, Tuncalp O, Moller AB, Daniels J, Gulmezoglu AM, Temmerman M, Alkema L. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health. 2014;2(6):e323–33. Epub 20140505. https://doi.org/10.1016/S2214-109X(14)70227-X. Cited in: Pubmed; PMID 25103301.
4. Di Renzo GC, Melin P, Berardi A, Blennow M, Carbonell-Estrany X, Donzelli GP, Hakansson S, Hod M, Hughes R, Kurtzer M, Poyart C, Shinwell E, Stray-Pedersen B, Wielgos M, El Helali N. Intrapartum GBS screening and antibiotic prophylaxis: a European consensus conference. J Matern Fetal Neonatal Med. 2015;28(7):766–82. Epub 2014/08/28. https://doi.org/10.3109/14767058.2014.934804. Cited in: Pubmed; PMID 25162923.
5. Tita ATN, Carlo WA, McClure EM, Mwenechanya M, Chomba E, Hemingway-Foday JJ, Kavi A, Metgud MC, Goudar SS, Derman R, Lokangaka A, Tshefu A, Bauserman M, Bose C, Shivkumar P, Waikar M, Patel A, Hibberd PL, Nyongesa P, Esamai F, Ekhaguere OA, Bucher S, Jessani S, Tikmani SS, Saleem S, Goldenberg RL, Billah SM, Lennox R, Haque R, Petri W, Figueroa L, Mazariegos M, Krebs NF, Moore JL, Nolen TL, Koso-Thomas M, Group APT, Tita ATN, Carlo WA, McClure EM, Mwenechanya M, Chomba E, Hemingway-Foday JJ, Kavi A, Metgud MC, Goudar SS, Derman R, Lokangaka A, Tshefu A, Bauserman M, Bose C, Shivkumar P, Waikar M, Patel A, Hibberd PL, Nyongesa P, Esamai F, Ekhaguere OA, Bucher S, Jessani S, Tikmani SS, Saleem S, Goldenberg RL, Billah SM, Lennox R, Haque R, Petri W, Figueroa L, Mazariegos M, Krebs NF, Moore JL, Nolen TL, Koso-Thomas M, Group APT. Azithromycin to Prevent Sepsis or Death in Women Planning a Vaginal Birth. N Engl J Med. 2023;388(13):1161–70. Epub 20230209. https://doi.org/10.1056/NEJMoa2212111. Cited in: Pubmed; PMID 36757318.
6. Roca A, Oluwalana C, Bojang A, Camara B, Kampmann B, Bailey R, Demba A, Bottomley C, D'Alessandro U. Oral azithromycin given during labour decreases bacterial carriage in the mothers and their offspring: a double-blind randomized trial [Clinical Trial, Phase III Randomized Controlled Trial]. Clinical Microbiology & Infection. 2016;22(6):565.e1–9 Cited in: Pubmed; PMID 27026482.
7. Roca A, Camara B, Bognini JD, Nakakana UN, Some AM, Beloum N, Rouamba T, Sillah F, Danso M, Jones JC, Graves S, Jagne I, Getanda P, Darboe S, Tahita MC, Ndure E, Franck HS, Edmond SY, Dondeh BL, Nassa WGJ, Garba Z, Bojang A, Njie Y, Bottomley C, Tinto H, D'Alessandro U, PregnAn ZIWG. Effect of Intrapartum Azithromycin vs Placebo on Neonatal Sepsis and Death: A Randomized Clinical Trial. JAMA. 2023;329(9):716–24. https://doi.org/10.1001/jama.2022.24388. Cited in: Pubmed; PMID 36881034. Conflict of Interest Disclosures: Dr Nakakana reported being an employee of GlaxoSmithKline and owning shares of the company. Dr Tinto reported receiving grants from Medical Research Council that supported the achievement of the study activities in Burkina Faso during the conduct of the study. Drs Roca and D'Alessandro reported receiving grants from Joint Global Health Trial (JGHT) Scheme (Wellcome), UK Department for International Development, and the Bill & Melinda Gates Foundation during the conduct of the study. No other disclosures were reported.
8. Driscoll AJ, Haidara FC, Tapia MD, Deichsel EL, Samake OS, Bocoum T, Bailey JA, Fitzpatrick MC, Goldenberg RL, Kodio M, Moulton LH, Nasrin D, Onwuchekwa U, Shaffer AM, Sow SO, Kotloff KL. Antenatal, intrapartum and infant azithromycin to prevent stillbirths and infant deaths: study protocol for SANTE, a 2×2 factorial randomised controlled trial in Mali. BMJ Open. 2023;13(8): e067581. https://doi.org/10.1136/bmjopen-2022-067581.
9. Zelellw DA, Dessie G, Worku Mengesha E, Balew Shiferaw M, Mela Merhaba M, Emishaw S. A Systemic Review and Meta-analysis of the Leading Pathogens Causing Neonatal Sepsis in Developing Countries. Biomed Res Int. 2021;2021:6626983. https://doi.org/10.1155/2021/6626983.
10. The unfinished agenda of communicable diseases among children and adolescents before the COVID-19 pandemic, 1990–2019: a systematic analysis of the Global Burden of Disease Study 2019. The Lancet. 2023;402(10398):313–335. https://doi.org/10.1016/S0140-6736(23)00860-7.
11. Steer AC, Jenney AWJ, Kado J, Batzloff MR, La Vincente S, Waqatakirewa L, Mulholland EK, Carapetis JR. High burden of impetigo and scabies in a tropical country. PLoS Negl Trop Dis. 2009;3(6):e467–e467. eng. https://doi.org/10.1371/journal.pntd.0000467. Cited in: Pubmed; PMID 19547749.
12. Thean LJ, Romani L, Engelman D, Wand H, Jenney A, Mani J, Paka J, Cua T, Taole S, Silai M, Ashwini K, Sahukhan A, Kama M, Tuicakau M, Kado J, Parnaby M, Carvalho N, Whitfeld M, Kaldor J, Steer AC. Prevention of bacterial complications of scabies using mass drug administration: A population-based, before-after trial in Fiji, 2018–2020. The Lancet Regional Health – Western Pacific. 2022;22. https://doi.org/10.1016/j.lanwpc.2022.100433.
13. Laupland KB, Lyytikäinen O, Sgaard M, Kennedy KJ, Knudsen JD, Ostergaard C, Galbraith JC, Valiquette L, Jacobsson G, Collignon P, Schnheyder HC, for the International Bacteremia Surveillance C. The changing epidemiology of Staphylococcus aureus bloodstream infection: a multinational population-based surveillance study. Clin Microbiol Infect. 2013;19(5):465–71. https://doi.org/10.1111/j.1469-0691.2012.03903.x.
14. Nelson GE, Pondo T, Toews K-A, Farley MM, Lindegren ML, Lynfield R, Aragon D, Zansky SM, Watt JP, Cieslak PR, Angeles K, Harrison LH, Petit S, Beall B, Van Beneden CA. Epidemiology of Invasive Group A Streptococcal Infections in the United States, 2005–2012. Clin Infect Dis. 2016;63(4):478–86. https://doi.org/10.1093/cid/ciw248.
15. Norton R, Smith H, Wood N, Siegbrecht E, Ross A, Ketheesan N. Invasive group A streptococcal disease in North Queensland (1996–2001). Indian J Med Res. 2004;119:148–51.
16. Oluwalana C, Camara B, Bottomley C, Goodier S, Bojang A, Kampmann B, Ceesay S, D'Alessandro U, Roca A. Azithromycin in Labor Lowers Clinical Infections in Mothers and Newborns: A Double-Blind Trial. Pediatrics. 2017;139(2):e20162281. https://doi.org/10.1542/peds.2016-2281.
17. Shamim MA, Kumar J, Patil AN, Tiwari K, Sharma S, Anil A, Saravanan A, Sandeep M, Varthya SB, Singh S, Ahmed MI, Najmi A, Shamim MA, Gandhi A, Satapathy P, Sah R, Rustagi S, Gaidhane AM, Zahiruddin QS, Khatib MN, Padhi BK, Singh K, Dwivedi P. PeRinatal, neOnatal, and Maternal OuTcomEs with azithromycin prophylaxis in pregnancy and labour (PROMOTE-PROPHYLAXIS): systematic review and meta-analysis. EClinicalMedicine. 2024;73:102691. https://doi.org/10.1016/j.eclinm.2024.102691. Epub 20240621. Cited in: Pubmed; PMID 39022799. None of the authors has declared competing interests.
18. Fiji Islands. World Directory of Minorities and Indigenous Peoples: Minority rights group international <archived by UNHCR>; 12 Feb. Available from: https://webarchive.archive.unhcr.org/20230518080825/https://www.refworld.org/docid/4954ce3e53.html
19. Birth rate, crude (per 1,000 people) - Fiji. World Bank Group; 2024. The World Bank Data. Available from: https://data.worldbank.org/indicator/SP.DYN.CBRT.IN?locations=FJ. Cited 2024 12 Feb.

20. Hume-Nixon M, Ratu T, Clark S, Nguyen CD, Neal EFG, Pell CL, Bright K, Watts E, Hart J, Mulholland K, Fong J, Rafai E, Sakumeni K, Tuibeqa I, Satzke C, Steer A, Russell FM. Prevention of young infant infections using oral azithromycin in labour in Fiji (Bulabula MaPei): study protocol of a randomised control trial. BMJ Open. 2022;12(12):e061157. https://doi.org/10.1136/bmjopen-2022-061157. Epub 20221201. Cited in: Pubmed; PMID 36456016. eng. 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.
21. Eberly MD, Eide MB, Thompson JL, Nylund CM. Azithromycin in early infancy and pyloric stenosis. Pediatrics. 2015;135(3):483–8. eng. Epub 2015/02/18. https://doi.org/10.1542/peds.2014-2026. Cited in: Pubmed; PMID 25687145.
22. Ikeda AK, Prince AA, Chen JX, Lieu JEC, Shin JJ. Macrolide-associated sensorineural hearing loss: A systematic review. Laryngoscope. 2018;128(1):228–36. Epub 2017/08/05. https://doi.org/10.1002/lary.26799. Cited in: Pubmed; PMID 28771738.
23. Steer AC, Tikoduadua LV, Manalac EM, Colquhoun S, Carapetis JR, Maclennan C. Validation of an Integrated Management of Childhood Illness algorithm for managing common skin conditions in Fiji. Bull World Health Organ. 2009;87(3):173–9. Epub 2009/04/21. https://doi.org/10.2471/blt.08.052712. Cited in: Pubmed; PMID 19377712.
24. Russell FM, Carapetis JR, Balloch A, Licciardi PV, Jenney AWJ, Tikoduadua L, Waqatakirewa L, Pryor J, Nelson J, Byrnes GB, Cheung YB, Tang MLK, Mulholland EK. Hyporesponsiveness to re-challenge dose following pneumococcal polysaccharide vaccine at 12 months of age, a randomized controlled trial. Vaccine. 2010;28(19):3341–9. https://doi.org/10.1016/j.vaccine.2010.02.087.
25. Romani L, Whitfeld MJ, Koroivueta J, Kama M, Wand H, Tikoduadua L, Tuicakau M, Koroi A, Andrews R, Kaldor JM, Steer AC. Mass Drug Administration for Scabies Control in a Population with Endemic Disease. N Engl J Med. 2015;373(24):2305–13. https://doi.org/10.1056/NEJMoa1500987. Cited.In:Pubmed;PMID26650152.
26. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377–81. Epub 20080930. https://doi.org/10.1016/j.jbi.2008.08.010. Cited in: Pubmed; PMID 18929686.
27. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, McLeod L, Delacqua G, Delacqua F, Kirby J, Duda SN. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform. 2019 Jul;95:103208. eng. Declaration of interests The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. Epub 20190509. https://doi.org/10.1016/j.jbi.2019.103208. Cited in: Pubmed; PMID 31078660.
28. Stata Statistical Software. Release 18. College Station, TX: StataCorp LLC; 2023.
29. Morrell S, Lin S, Tukana I, Linhart C, Taylor R, Vatucawaqa P, Magliano DJ, Zimmet P. Diabetes incidence and projections from prevalence surveys in Fiji. Population Health Metrics. 2016 2016/11/25;14(1):45. https://doi.org/10.1186/s12963-016-0114-0.
30. Riedner G, Rusizoka M, Todd J, Maboko L, Hoelscher M, Mmbando D, Samky E, Lyamuya E, Mabey D, Grosskurth H. Single-dose azithromycin versus penicillin G benzathine for the treatment of early syphilis. N Engl J Med. 2005;353(12):1236–44.
31. Hook EW III, Behets F, Van Damme K, Ravelomanana N, Leone P, Sena AC, Martin D, Langley C, McNeil L, Wolff M. A phase III equivalence trial of azithromycin versus benzathine penicillin for treatment of early syphilis. J Infect Dis. 2010;201(11):1729–35.
32. Fiji Essential Medicines List, (4th, 2015). https://www.who.int/publications/m/item/fiji--essential-medicines-list-2015-(english).
33. Guidelines for the diagnosis, management, and prevention of typhoid fever (2010). https://www.health.gov.fj/wp-content/uploads/2014/05/Typhoid-Guideline_-Long-Version_-2010.pdf.
34. Prasad N, Jenkins AP, Naucukidi L, Rosa V, Sahu-Khan A, Kama M, Jenkins KM, Jenney AWJ, Jack SJ, Saha D, Horwitz P, Jupiter SD, Strugnell RA, Mulholland EK, Crump JA. Epidemiology and risk factors for typhoid fever in Central Division, Fiji, 2014–2017: A case-control study. PLoS Negl Trop Dis. 2018 Jun;12(6):e0006571. eng. I have read the journal's policy and the authors of this manuscript have the following competing interests: DS at present is a full time employee of GlaxoSmithKline vaccine. Epub 20180608. https://doi.org/10.1371/journal.pntd.0006571. Cited in: Pubmed; PMID 29883448.
35. Getahun Strobel A, Prasad P, Lane CR, Naidu R, Autar S, Young-Sharma T, Richards M, Suka A, Cameron D, James R, Prasad R, Buising K, Howden BP, Prasad V. The changing epidemiology of antimicrobial resistance in Fiji: a descriptive analysis of antimicrobial susceptibility and trends of endemic and emerging pathogens, 2019–2022. The Lancet Regional Health – Western Pacific. 2024;45. https://doi.org/10.1016/j.lanwpc.2024.101036.
36. Lund M, Pasternak B, Davidsen RB, Feenstra B, Krogh C, Diaz LJ, Wohlfahrt J, Melbye M. Use of macrolides in mother and child and risk of infantile hypertrophic pyloric stenosis: nationwide cohort study [Research Support, Non-U.S. Gov't]. BMJ. 2014;348:g1908. Cited in: Pubmed; PMID 24618148.
37. Abdellatif M, Ghozy S, Kamel MG, Elawady SS, Ghorab MME, Attia AW, Le Huyen TT, Duy DTV, Hirayama K, Huy NT. Association between exposure to macrolides and the development of infantile hypertrophic pyloric stenosis: a systematic review and meta-analysis [Meta-Analysis Review]. Eur J Pediatr. 2019;178(3):301–14 Cited in: Pubmed; PMID 30470884.
38. Sanyang B, de Silva TI, Camara B, Beloum N, Kanteh A, Manneh J, de Steenhuijsen Piters WAA, Bogaert D, Sesay AK, Roca A. Effect of intrapartum azithromycin on gut microbiota development in early childhood: a post hoc analysis of a double-blind randomized trial. iScience. https://doi.org/10.1016/j.isci.2024.110626.
39. Kalilani L, Mofolo I, Chaponda M, Rogerson SJ, Alker AP, Kwiek JJ, Meshnick SR. A randomized controlled pilot trial of azithromycin or artesunate added to sulfadoxine-pyrimethamine as treatment for malaria in pregnant women. PLoS One. 2007;2(11):e1166. Epub 2007/11/15. https://doi.org/10.1371/journal.pone.0001166. Cited in: Pubmed; PMID 18000538.

Publisher's Note