PeRinatal, neOnatal, and Maternal OuTcomEs with azithromycin prophylaxis in pregnancy and labour (PROMOTE-PROPHYLAXIS): systematic review and meta-analysis

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eClinicalMedicine 2024;73: 102691
Published Online xxx
https://doi.org/10.1016/j.eclinm.2024.102691

Summary

Background **Initial randomised controlled trials (RCTs) showed that prophylactic azithromycin in pregnant women improved maternal and neonatal outcomes; however, the recent evidence did not show any benefit to neonatal survival. There is conflicting evidence over the role of azithromycin prophylaxis in antenatal and intrapartum periods. We explored whether azithromycin prophylaxis in pregnant women improves maternal and neonatal outcomes.**

Methods **For this systematic review and meta-analysis registered on PROSPERO [CRD42023411093], we searched seven databases (PubMed, Scopus, Embase, Cochrane Library, EBSCOHost, ProQuest, and Web of Science) and**

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clinical trial registries until 04/23/2024, for RCTs evaluating antenatal/intrapartum azithromycin prophylaxis against placebo/routine care in pregnant women. The primary outcome was neonatal mortality. Intrapartum and antenatal administration were assessed separately. We used random-effects meta-analysis. The risk of bias was assessed using the Cochrane RoB 2 tool. The GRADE approach was used to evaluate the certainty of the evidence.

Findings Screening 2161 records retrieved 20 RCTs (56,381 participants). Intrapartum azithromycin may make little or no difference to neonatal mortality [5 RCTs, 44,436 participants; Risk Ratio (RR): 1.02, 95% CI 0.86–1.20, I^2 = 0%, very low certainty], and maternal mortality [3 RCTs, 44,131 participants, RR: 1.26, 0.65–2.42, I^2 = 0%, low certainty]. Similarly, antenatal azithromycin may have little or no effect on neonatal mortality [3 RCTs; 5304 participants; RR: 0.74, 0.35–1.56, I^2 = 43%, very-low certainty] and maternal mortality [3 RCTs; 8167 participants RR: 1.62, 0.67–3.91, I^2 = 0%, low certainty]. There is no data on long-term adverse outcomes and antimicrobial resistance.

Interpretation Low to very low certainty evidence suggests that intrapartum or antenatal azithromycin prophylaxis in pregnant women might not reduce maternal or neonatal mortality.

Funding None.

Keywords: Low birthweight; Neonatal sepsis; Surgical site infection; Maternal health; Neonatal mortality

Research in context

Evidence before this study

Several randomised controlled trials (RCTs) have provided conflicting evidence on the effect of Azithromycin prophylaxis in pregnancy. It was earlier believed that it might benefit neonatal outcomes, but some recent studies do not show beneficial effects on neonates and instead show benefits in maternal outcomes. In the face of conflicting evidence, we systematically synthesise the evidence by searching seven databases (PubMed, Scopus, Embase, Cochrane Central Register of Controlled Trials, EBSCOHost, ProQuest, and Web of Science) till September 11, 2023, for RCTs on efficacy and safety of azithromycin prophylaxis to pregnant women. We used search terms, including controlled vocabulary, for keywords about each component of this research question. We used the Risk of Bias 2 tool to assess the risk of bias. The certainty of evidence was evaluated using the GRADE framework.

Added value of this study

This systematic review and meta-analysis of 20 RCTs involving 56,381 participants found that prophylactic azithromycin therapy among pregnant women has an uncertain effect on maternal or neonatal mortality (low to very low certainty evidence). However, intrapartum azithromycin was probably associated with lesser maternal infections, endometritis, surgical site infections (SSI), and reduced antibiotic usage (low to moderate certainty evidence). In neonates, it was associated with reduced superficial skin infection, omphalitis and antibiotic use.

Implications of all the available evidence

Azithromycin prophylaxis possibly does not reduce maternal and neonatal mortality; there is probably a reduction in maternal and neonatal infections and antibiotic usage with single-dose intrapartum azithromycin prophylaxis in pregnant women. Our review supports intrapartum azithromycin prophylaxis in reducing SSI but caution is warranted, considering the lack of data on antimicrobial resistance and other long-term adverse outcomes. Future large studies should assess antimicrobial resistance, congenital anomalies, and other long-term outcomes.

Introduction

Reducing perinatal and neonatal mortality is critical to improving mother and child health and achieving sustainable development goals. The world aims to reduce the global maternal mortality ratio to below 70/100,000 live births and neonatal mortality to 12/1000 live births by 2030.[1,2] However, the current situation is far from achieving these ambitious targets. Nearly 300,000 pregnant women die annually from pregnancy-associated complications.[2] Similarly, almost 2.4 million infants die in the neonatal period. Most of these deaths are seen in low- and lower-middle-income countries. Prematurity (and low birth weight) and neonatal sepsis are the leading cause of neonatal mortality.[1,3,4] Globally, over half of neonatal deaths are attributable to prematurity and sepsis. Intrauterine infection or colonisation of the maternal genital tract is associated with preterm labour and early-onset neonatal sepsis. Therefore, antenatal and intrapartum antibiotic prophylaxis for mothers at risk of preterm labour is shown to reduce neonatal mortality.

Azithromycin is a broad-spectrum macrolide with a long half-life and high sustained placental levels. It has

antibacterial, antimalarial, and immunomodulatory activity. Hence, it has been used in antenatal and intrapartum periods to prevent malaria, reproductive tract infections, preterm labour, and caesarean section-associated wound infections.[5–8] It is effective against Group B Streptococcus, one of the most common aetiologies of neonatal sepsis.[9] There have been varying dosing schedules ranging from 500 mg single dose intravenous[10] to 9 g oral administration (one gram on three consecutive days at three different instances each) across the second and third trimesters.[11] Yet, there is no consensus on the most appropriate dose, duration, and timing of administration.

Initial randomised controlled trials (RCTs) showed that prophylactic azithromycin in the antenatal and intrapartum period was associated with improved maternal and neonatal outcomes.[5,10,12,13] Following these trials, adjunctive azithromycin prophylaxis was routinely recommended intrapartum for caesarean delivery.[14] However, recent RCTs suggest it might be ineffective in preventing neonatal mortality.[13,15,16] Instead, there are concerns about infection with azithromycin-resistant bacteria.[17,18] Animal studies have shown a link between antenatal azithromycin exposure and development concerns of multiple organ systems in fetus.[19,20] Observational studies have shown an association between antenatal azithromycin exposure and increased risk of stillbirth and congenital malformations in infants, raising serious safety concerns.[21–23] The interventions in the antenatal period can be justified if they benefit both mother and fetus or if the benefits are restricted to one of them, the other should not be harmed.

We critically appraised the existing evidence syntheses on this topic and have several concerns [Table S1]. Several recent RCTs have been conducted,[13,15,16,24–26] including some large multicentric ones.[13,15,16] Thus, we have almost four times more participants than the most comprehensive evidence synthesis on this topic.[5] Moreover, they present conflicting evidence. Hence, we aim to systematically review and update the evidence on the effect of adjuvant antenatal or intrapartum azithromycin prophylaxis on maternal, foetal, and neonatal outcomes.

Methods

Protocol registration and reporting

The pre-registered protocol is accessible at PROSPERO (CRD42023411093). This systematic review and meta-analysis (SRMA) was performed according to the Cochrane Handbook for Systematic Reviews of Interventions[27] and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)[28] 2020 guidelines.

Research question and selection criteria

This SRMA assessed whether antenatal or intrapartum adjuvant azithromycin prophylaxis to pregnant women improves neonatal, perinatal, and maternal outcomes. We answered the two research questions separately [Table S2]. The first research question is the efficacy and safety of single-dose intrapartum azithromycin administered to pregnant women during labour. The second research question deals with antenatal azithromycin administration to pregnant women, mainly during the second and third trimesters.

Studies meeting all the following criteria were considered suitable for inclusion: (i) Population: Pregnant women, (ii) Intervention: Antenatal or intrapartum prophylactic azithromycin to improve maternal or neonatal outcomes, (iii) Control: Placebo or routine care or any active comparator except other macrolides, (iv) Study design: RCT only. Studies administering azithromycin therapeutically (not prophylactically), not assessing clinical outcomes, and with a non-randomised or observational design were excluded. Our primary outcome was all-cause neonatal mortality. Major secondary outcomes included maternal (mortality, sepsis, endometritis, surgical site infection, antibiotic use, etc.), neonatal (sepsis, omphalitis, otitis, ICU admission, antibiotic use, etc.), and perinatal (low birthweight, congenital anomalies, miscarriage, etc.) outcomes (Table S4). SRMAs in this subject area routinely include multiple outcomes (a median of 52 forest plots).[29] To adjust for multiplicity,[30] we have specified all-cause neonatal mortality as the primary outcome and other outcomes as secondary outcomes in the methodology section itself.[29] In the results section, we have only included the forest plots for the primary outcome and kept the other forest plots in the supplementary, thus maintaining a distinction between the primary and secondary outcomes.[29]

Systematic search and data extraction

We systematically searched PubMed, Scopus, Embase, Cochrane Central Register of Controlled Trials, EBSCOHost, ProQuest, and Web of Science on March 25, 2023. Then, we updated the search on April 23, 2024. MAqS prepared a database-specific search strategy using MeSH/Emtree terms, truncated terms, and keywords (Table S3). Another author (JK) peer-reviewed this as per the Peer Review of Electronic Search Strategies checklist.[31] We checked clinical trial registries (Clinicaltrials.gov and World Health Organization– International Clinical Trials Registry Platform), references of selected articles, and a forward citation search to identify additional articles. We sought the opinion of subject experts to identify further studies.

After the search and deduplication, two authors (amongst MAqS, MS, KT, AA, AS, SBV, and SS) screened the records and extracted data. In case of any disagreement, the co-authors discussed amongst themselves and followed the independent reviewer's opinion (PD) if the conflict persisted. Data extraction involved a spreadsheet containing bibliographic information, study

characteristics, population details, intervention specifications, outcome data, and other key details.

Statistics

The binary and the continuous outcomes are expressed as risk ratios[32] (RR) and mean differences, respectively, with 95% confidence intervals. RR are coupled with NNT (Number needed to treat) to aid clinical decision-making. NNT was calculated using standard methodology[33] with baseline risks from the included studies and the relative risks from our meta-analysis. Considering the variability in the timing, dose, duration, and the comparator, we decided a priori to use the random-effects model for data synthesis.[31,32] The pooled estimate has been expressed using forest and drapery plots.[34] We included the intervention details, risk of bias assessment, and certainty in evidence in the forest plots for comprehensiveness and quicker interpretation.

To assess heterogeneity, we used the I-squared, Q-test, prediction interval,[35] tau and tau-squared values,[35] avoiding reliance on just a single metric.[36,37] I-squared uses a Q-test to inform what portion of the variability in results is attributed to between-study heterogeneity [Box S1]. We explored heterogeneity using subgroup analyses-based on comparator (placebo/standard of care and active antibiotics) and mode of delivery (vaginal or caesarean section). We hypothesised that there would be no significant subgroup difference between the active comparator and placebo/standard of care in the control group. If the hypothesis turned out to be true, we combined them for primary analysis (to improve generalizability), and subgroup analysis was presented separately. Meta-regression explored the effect of cumulative azithromycin dose on the outcomes. This was done only for the primary outcome and when six or more studies were available.[38] Bubble plots with the test of moderators help visualise the meta-regression.[39]

We performed a sensitivity analysis restricted to low risk of bias studies. Another post-hoc sensitivity analysis uses the Bayesian framework, which is considered superior when fewer studies are present for a given outcome[40] [Box S1].

Because of fewer studies (<10) for each outcome, we could not use funnel plots and Egger's regression. Instead, we have used Doi plots and corresponding LFK indices[41] [Box S1]. As a sensitivity analysis, we used a contour-enhanced[42] trim-and-fill[43] funnel plot for the primary outcome. All the analyses were done in R software (v4.3.0).[44]

Two authors independently performed these steps. They evaluated the risk of bias of the selected studies for individual eligible outcomes using the Risk of Bias version 2.0 tool (RoB2 tool).[45] This tool assesses each trial for bias under five domains: bias arising from the randomisation process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the measurement of the outcome and bias in the selection of the reported result. A judgement of low risk of bias, some concerns, or high risk of bias is assigned to each domain and subsequently to the overall result. We assessed the certainty of the synthesised evidence using the GRADE methodology. We have reported this for all the outcomes in the respective forest plots and Table 2.

Ethics approval

It is not applicable here since it is an SRMA of publicly available data.

Role of funding source

There was no funding source for this study.

Results

Study selection

We have identified 20 RCTs with 56,381 participants[8,10,11,13,15,16,24–26,46–56] [Fig. 1]. We excluded studies due to several reasons, including 11 articles due to inappropriate comparisons. In detail, we have listed all the excluded [Table S4] and unretrieved studies [Table S5]. We have also listed completed trials with results unavailable [Table S6] and a list of ongoing trials [Table S7].

Study characteristics

Most studies (18/20) were conducted in low- or middle-income countries, while two were from high-income countries.[10,50] Eleven studies assessed single-dose intrapartum azithromycin administration, while nine tested antenatal administration (Table 1). Among these 11 RCTs, seven and four trials focused on caesarean and vaginal delivery. Most trials (16/20) compared azithromycin against placebo or standard care. However, these four studies used active comparators like sulfapyridine,[47,54] cefazolin,[52] or chloroquine.[56] The dose of azithromycin for intrapartum administration ranged from 500 mg to 2 g. The cumulative azithromycin dose in studies on antenatal prophylaxis ranged from 1.5 g to 12 g.

Pooled estimates of single-dose intrapartum azithromycin

Compared to placebo or no treatment, intrapartum azithromycin may make little or no difference to all-cause neonatal mortality [5 RCTs; 44,436 participants with 555 events, RR: 1.02, 95% CI 0.86–1.20; 95% PI 0.78–1.33, I^2 = 0%; very low certainty of evidence] [Fig. 2A, Figure S1]. There is moderate to high certainty evidence that it reduces omphalitis [RR: 0.58, 95% CI 0.34–0.98, NNT 402], skin infections [RR: 0.48, 0.36–0.65, NNT 60], and neonatal antibiotic use [RR: 0.81, 0.71–0.93, NNT 67]. However, low to very low certainty of the evidence indicates there is little or no difference in other neonatal and perinatal outcomes

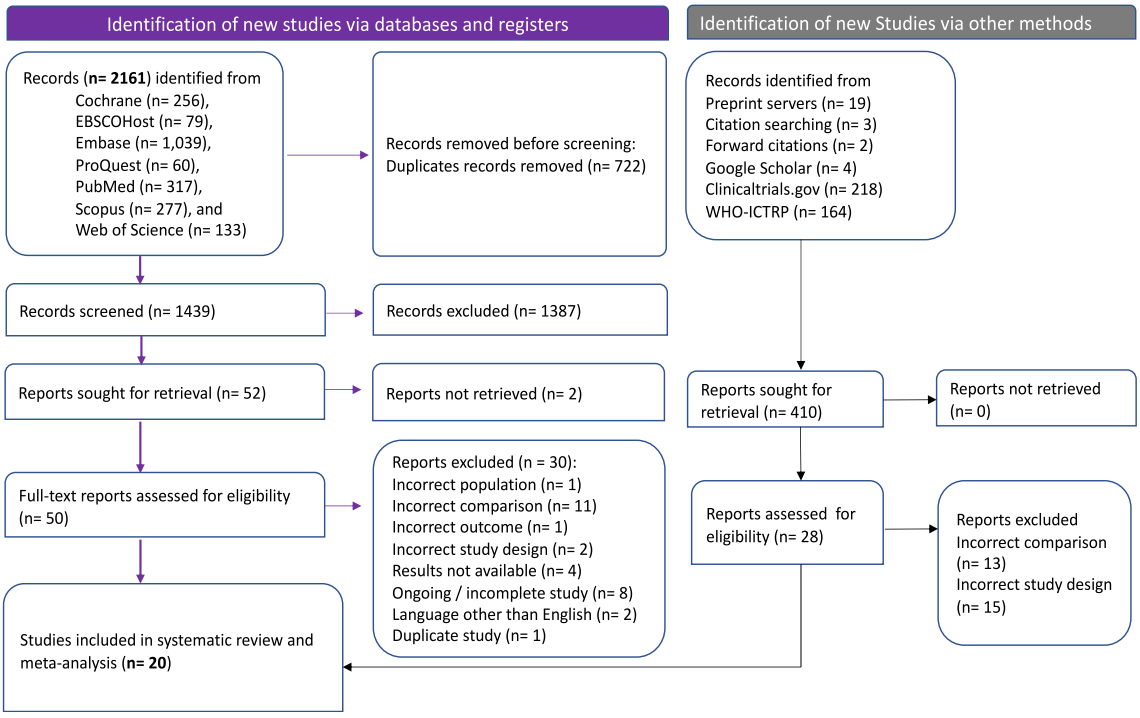

Fig. 1: **Prisma flow chart**.

including neonatal sepsis [RR: 1.02, 0.96–1.09], conjunctivitis [RR: 0.85, 0.68–1.06], otitis [RR: 0.73, 0.36–1.48], malaria [RR: 1.35, 0.25–7.20], ICU admissions [RR: 1.02, 0.94–1.10], and stillbirths [RR: 1.07, 0.76–1.51] [Table 2].

Azithromycin probably reduces endometritis [RR: 0.62, 0.53–0.73, NNT 55 (44–76)] and surgical site infections [RR: 0.41, 0.27–0.61, NNT 25 (20–38), moderate certainty evidence]. There is low to very low certainty in the evidence that azithromycin possibly reduces sepsis [RR: 0.65, 0.56–0.77, NNT 420 (327–630)], fever [RR: 0.52, 0.36–0.76, NNT 54 (40–113)], and antibiotic use [RR: 0.70, 0.55–0.89, NNT 30 (20–84)]. However, there is an uncertain effect on other maternal outcomes, including all-cause mortality [RR 1.26, 0.65–2.42], chorioamnionitis [RR 0.50, 0.22–1.18], malaria [RR 0.98, 0.45–2.11], and ICU admissions [RR 0.75, 0.31–1.81] [Table 2]. The forest plots depict the pooled estimate, mode of delivery, azithromycin dose, type of comparator, heterogeneity assessments, and certainty of the evidence for these outcomes [Figure S2].

Pooled estimates of antenatal azithromycin

Antenatal azithromycin has an uncertain effect on all-cause neonatal mortality [3 RCTs, 5304 participants with 62 events, RR 0.74, 0.35–1.56; I^2 = 43%; very low certainty of evidence] [Fig. 2B]. It may reduce the risk for low birth weight [8 RCTs; 6912 participants, RR: 0.83, 0.72–0.96, NNT 50 (30–219); low certainty of evidence] [Figure S3]. There was an uncertain effect on other neonatal and perinatal outcomes, including ICU admission [RR: 0.20, 0.03–1.59], congenital malformations [RR: 0.87, 0.51–1.48], stillbirths [RR: 1.08, 0.70–1.68], preterm births [RR: 0.88, 0.76–1.03], and miscarriages [RR: 1.01, 0.42–2.42][Table 2].

Antenatal azithromycin has an uncertain effect on other maternal outcomes, including maternal mortality [RR: 1.62, 0.67–3.91; I^2 = 0%; low certainty of evidence], endometritis [RR: 0.20, 0.01–4.16], malaria [RR: 1.15, 0.98–1.36], and readmission or prolongation of admission [RR: 0.95, 0.72–1.26].

Sensitivity analysis

We conducted a sensitivity Bayesian analysis to account for the small number of studies for many outcomes. The relative risk for all-cause neonatal mortality with single dose intrapartum azithromycin remains similar at 1.01 [95% Credible Interval (CrI) 0.70–1.42] compared to the primary estimate [RR 1.02, 95% CI 0.86–1.20] [Fig. 3A].

Another sensitivity analysis restricted each outcome to only the low-risk-of-bias studies. Since all the studies contributing to the relative risk for all-cause neonatal mortality with single-dose intrapartum azithromycin have a low risk of bias, a separate sensitivity analysis was not needed. The sensitivity analysis for other outcomes provided similar results [Figures S2 and S3].

Author (year); study site	Eligibility criteria	Participant characteristics	Intervention	Comparator	Funding/Sponsors
Single-dose intrapartum azithromycin administration					
Tita et al. (2023); Multicentric	*Inclusion criteria*: Pregnant women in labour with gestational age ≥28 weeks with a plan for vaginal delivery *Exclusion criteria*: Preterm labour undergoing management with no immediate plan to proceed to delivery, advanced stage of labour	*Intervention*: 14,590 women with a median (IQR) age of 24 years (21–28) *Comparator*: 14,688 women with a median (IQR) age of 24 years (21–28)	*Intervention*: Azithromycin *Dose*: Single 2-g oral dose *Timing*: Intrapartum	*Intervention*: Placebo *Dose*: Single 2-g oral dose *Timing*: Intrapartum	Eunice Kennedy Shriver National Institute of Child Health and Human Development; Bill and Melinda Gates Foundation.
Roca et al. (2023); Gambia and Burkina Faso	*Inclusion criteria*: Pregnant women in active labour planning for vaginal delivery *Exclusion criteria*: Known HIV infection	*Intervention*: 5802 women with a median (IQR) age of 27 years (22–31) *Comparator*: 5823 women with a median (IQR) age of 26 years (22–31)	*Intervention*: Azithromycin *Dose*: Single 2-g oral dose *Timing*: Intrapartum	*Intervention*: Placebo *Dose*: Single 2-g oral dose *Timing*: Intrapartum	UK Research and Innovation; London School of Hygiene and Tropical Medicine; Bill & Melinda Gates Foundation
Huang et al. (2022); China	*Inclusion criteria*: Pregnant women (≥37 weeks) who had rupture of membranes (spontaneous or iatrogenic) or were in labour and underwent nonelective CS (i.e., Unscheduled CS during labour, after membrane rupture). *Exclusion criteria*: Colonised/infected with GBS at 36 weeks of gestation, Maternal infection requiring additional antibiotics	*Intervention*: 121 women with a mean ± SD age of 30 ± 3.1 years *Comparator*: 121 women with a mean ± SD age of 30.4 ± 3.5 years	*Intervention*: Azithromycin + Cefuroxime *Dose*: Azithromycin (500 mg) + Cefuroxime (1500 mg) single dose *Timing*: Within 30 min before skin incision (intravenous)	*Intervention*: Placebo + Cefuroxime *Dose*: Placebo (500 mg) + Cefuroxime (1500 mg) single dose *Timing*: Within 30 min before skin incision (intravenous)	Shanghai Shenkang Hospital Development Center Clinical Science and Technology Innovation; Shanghai Municipal Health Commission
Subramaniam et al. (2021); Cameroon	*Inclusion criteria*: Pregnant women with prolonged duration of labour or PROM *Exclusion criteria*: Clinical chorioamnionitis or any other active infection at the time of randomisation; plan for elective CS before enrolment	*Intervention*: 253 women with a mean ± SD age of 27.2 ± 5.3 years *Comparator*: 250 women with a mean ± SD age of 26.0 ± 5.3 years	*Intervention*: Azithromycin *Dose*: 1-g single dose *Timing*: Intrapartum (oral)	*Intervention*: Placebo *Dose*: 1-g single dose *Timing*: Intrapartum (oral)	Merck
Mohamed et al. (2020); Egypt	*Inclusion criteria*: Women undergoing elective CS	*Intervention*: 200 women with a mean age of 25.5 years *Comparator*: 200 women with a mean age of 24.7 years	*Intervention*: Azithromycin + Cefazolin *Dose*: Azithromycin (1-g) + Cefazolin (1-g) single dose *Timing*: Two hours preoperatively	*Intervention*: Cefazolin *Dose*: Single 1-g dose *Timing*: Two hours preoperatively	Not reported
Jyothi et al. (2019); India	*Inclusion criteria*: Pregnant women planned for a CS *Exclusion criteria*: Chorioamnionitis, Infection warranting antimicrobial use, Prolonged or obstructed labour, PROM.	*Intervention*: 100 women with a mean ± SD age of 26.42 ± 2.7 years *Comparator*: 100 women with a mean ± SD age of 27.39 ± 3.0 years	*Intervention*: Azithromycin + Cefazolin *Dose*: Azithromycin (500 mg) + Cefazolin (2-g) single dose *Timing*: 15–20 min before the skin incision (intravenous)	*Intervention*: Placebo + Cefazolin *Dose*: Placebo (500 mg) + cefazolin (2-g) single dose *Timing*: 15–20 min before the skin incision (intravenous)	None
Oluwalana et al. (2017); Gambia	*Inclusion criteria*: Pregnant women in labour or undergoing emergency CS (98% underwent vaginal delivery). *Exclusion criteria*: Known HIV infection or antibiotic intake in the previous week.	*Intervention*: 414 women with a median (IQR) age of 26 years (22–30) *Comparator*: 415 women with a median (IQR) age of 25 years (22–30)	*Intervention*: Azithromycin *Dose*: Azithromycin (2-g) *Timing*: In labour	*Intervention*: Placebo *Dose*: Placebo (2-g) *Timing*: In labour	Medical Research Council UK
Tita et al. (2016); United States of America	*Inclusion criteria*: Pregnant women with a gestational age ≥24 weeks who were undergoing nonelective CS during labour or after membrane rupture *Exclusion criteria*: Chorioamnionitis or other infection requiring postpartum antibiotic therapy (patients receiving antibiotics for GBS were eligible)	*Intervention*: 1019 women with mean ± SD age of 28.2 ± 6.1 years *Comparator*: 994 women with mean ± SD age of 28.4 ± 6.5 years	*Intervention*: Azithromycin + Cefazolin *Dose*: Azithromycin (500 mg) single dose + cefazolin (as per protocol) *Timing*: Up to 1 h before incision (intravenous)	*Intervention*: Placebo + Cefazolin *Dose*: 500 mg single dose + Cefazolin (as per protocol) *Timing*: Up to 1 h before incision (intravenous)	Eunice Kennedy Shriver National Institute of Child Health and Human Development; Drug provided by Pfizer Inc (New York, NY)

(Table 1 continues on next page)

Author (year); study site	Eligibility criteria	Participant characteristics	Intervention	Comparator	Funding/Sponsors
(Continued from previous page)					
Mohan et al. (2013); India	*Inclusion criteria*: Pregnant women planned for CS *Exclusion criteria:* Signs of obvious infection; recently received antibiotics	*Intervention*: 35 women, age range of 16–30 years *Comparator*: 35 women, age range of 16–30 years	*Intervention*: Azithromycin *Dose*: 500 mg *Timing*: Single-dose half an hour before CS	*Intervention*: Cefazolin *Dose*: (1 g; single dose) *Timing*: Single-dose half an hour before CS	Not reported
Ogasawara et al. (1999); United States of America	*Inclusion criteria:* Pregnant women with gestational age between 22 and 34 weeks with either preterm labour or preterm PROM *Exclusion criteria:* Maternal or fetal condition requiring immediate delivery	*Intervention*: 32 women with a mean ± SE age of 23.6 ± 1.1 years *Comparator*: 27 women with a mean ± SE age of 27.3 ± 1.1 years	*Intervention*: Azithromycin + Ampicillin *Dose*: Azithromycin (1-g) + Ampicillin (2 g) *Timing*: Azithromycin: single dose at enrolment Ampicillin: 2-g 6 hourly till the group B streptococcus culture results were available, followed by a 7-day course and intravenous ampicillin during labour	*Intervention*: Placebo + Ampicillin *Dose*: Placebo (1-g) + Ampicillin (2 g) *Timing*: Placebo: single dose at enrolment Ampicillin: 2-g 6 hourly till the group B streptococcus culture results were available, followed by a 7-day course and intravenous ampicillin during labour	Drug provided by Pfizer Inc (New York, NY)
Antenatal azithromycin administration					
Lingani et al. (2023); Burkina Faso	*Inclusion criteria:* Pregnant women in the antenatal period between 12 and 24 weeks of gestation *Exclusion criteria*: Cotrimoxazole prophylaxis for HIV	*Intervention*: 496 women with mean ± SD age of 26 ± 6 years *Comparator*: 496 women with mean ± SD age of 25 ± 6 years	*Intervention:* Azithromycin + Sulfadoxine-Pyrimethamine (SP) *Dose*: Azithromycin (1-g daily x 2 days) + SP (1500/75 mg monthly) *Timing*: Second and third trimesters of pregnancy	*Intervention:* Sulfadoxine-Pyrimethamine *Dose:* SP (1500/75 mg monthly) *Timing*: Second and third trimesters of pregnancy	Clinical Research Unit of Nanoro, Burkina Faso; Belgian Universities Cooperation for the Development
Hallamaa et al. (2023); Malawi	*Inclusion criteria:* Pregnant women with ultrasound-confirmed gestational age of 14–26 weeks	*Intervention*: 443 women with mean ± SD age of 25 ± 6 years *Comparator*: 441 women with mean ± SD age of 25 ± 7 years	*Intervention*: Azithromycin + Sulfadoxine-pyrimethamine (SP) *Dose*: Azithromycin (1-g) + SP (1500/75 mg) *Timing*: Azithromycin: at enrolment and a visit between 28 and 34 weeks of gestation SP: At enrolment and monthly after that until 37 weeks	*Intervention:* Placebo + Sulfadoxine-pyrimethamine *Dose*: SP (1500/75 mg) *Timing*: Placebo: At enrolment and a visit between the 28th–34th weeks SP: At enrolment and monthly after that until 37 weeks	Academy of Finland; Foundation for Pediatric Research in Finland; Tampere University Hospital. Drug provided by Pfizer Inc (New York, NY)
Madanitsa et al. (2023); Malawi, Tanzania, and Kenya	*Inclusion criteria*: Pregnant women with viable singleton pregnancy between 16 and 28 weeks *Exclusion criteria:* Known HIV infection	*Intervention*: 1558 women with a mean ± SD age of 24.9 ± 6 years *Comparator*: 1561 women with mean ± SD age of 25.1 ± 6.1 years	*Intervention:* Dihydroartemisinin–piperaquine (DHP) + Azithromycin *Dose:* Azithromycin (1-g) + DHP (120/960 mg–200/1600 mg as per body weight) *Timing:* Azithromycin: at enrolment and next day (total two doses) DHP: at enrolment and next two days (total three doses)	*Intervention:* Dihydroartemisinin–piperaquine (DHP) + Placebo *Dose:* DHP (120/960 mg–200/1600 mg according to body weight) + Placebo (1-g) *Timing*: DHP: at enrolment and next two days (total three doses)	Medical Research Council; Wellcome; Bill & Melinda Gates Foundation
Ahmed et al. (2023); Egypt	*Inclusion criteria*: Pregnant women who had vaginal cerclage *Exclusion criteria:* Bacterial vaginal infection detected on high vaginal swab before cerclage	*Intervention*: 25 women with a mean ± SD age of 30.0 ± 4.8 years *Comparator*: 25 women with a mean ± SD age of 29.7 ± 3.9 years	*Intervention:* Azithromycin *Dose:* 1-g *Timing:* Three days in 14th, 24th and 32nd weeks each (total nine days)	Routine antenatal care	None
Akinyotu et al. (2019); Nigeria	*Inclusion criteria:* Pregnant HIV-positive women with gestational age ≥16 weeks	*Intervention*: 60 women with a mean ± SD age of 33.20 ± 4.9 years *Comparator*: 63 women with a mean ± SD age of 32.17 ± 5.6 years	*Intervention*: Azithromycin + Sulfadoxine-pyrimethamine (SP) *Dose*: Azithromycin (500 mg) + SP (1500/75 mg) *Timing*: Azithromycin: at enrolment and next two days (total three doses) SP: at enrolment and next two months (total three doses)	*Intervention*: Sulfadoxine-pyrimethamine (SP) *Dose*: SP (1500/75 mg) *Timing*: SP: at enrolment and next two months (total three doses)	None

(Table 1 continues on next page)

Author (year); study site	Eligibility criteria	Participant characteristics	Intervention	Comparator	Funding/Sponsors
(Continued from previous page)					
van den Broek et al. (2009); Malawi	*Inclusion criteria:* Pregnant women with gestational age <24 weeks	*Intervention*: 1149 women with a mean ± SD age of 22.8 ± 5.1 years *Comparator*: 1148 women with mean ± SD age of 23.0 ± 5.2 years	*Intervention:* Azithromycin *Dose:* Azithromycin (1-g) *Timing:* One each at both 16–24 and 28–32 weeks of gestation	*Intervention:* Placebo *Dose:* Single 1-g dose *Timing:* One each at both 16–24 and 28–32 weeks of gestation	Wellcome Trust; Drug provided by Pfizer Inc (New York, NY)
Abdus-salam et al. (2016); Iran	*Inclusion criteria:* Pregnant women in the second trimester *Exclusion criteria:* History of previous intermittent preventive treatment for malaria in index pregnancy	*Intervention*: 115 women with mean ± SD age of 31.24 ± 4.7 years *Comparator*: 115 women with a mean ± SD age of 31.07 ± 4.2 years	*Intervention:* Azithromycin *Dose:* Azithromycin (500 mg) *Timing:* At enrolment and next two days (total three doses)	*Intervention:* Sulphadoxime + Pyrimethamine (SP) *Dose:* SP (1500/75 mg) *Timing*: At enrolment, followed by repeat dose 4 weeks later	None
Sivasankari et al. (2016); India	*Inclusion criteria:* Pregnant women with ≥37 weeks of gestation and planned for CS *Exclusion criteria:* Administration of antibiotics within a week before the delivery	*Intervention*: 302 women with mean ± SD age of 27.59 ± 4.4 years *Comparator*: 296 women with a mean ± SD age of 27.28 ± 4.7 years	*Intervention:* Azithromycin + Cefazolin *Dose:* Azithromycin (500 mg) + Cefazolin (1–2 g) single dose *Timing*: 1 h before the skin incision (intravenous)	*Intervention:* Placebo + Cefazolin *Dose:* Placebo (500 mg) + cefazolin (1–2 g) single-dose *Timing*: 1 h before the skin incision (intravenous)	Christian Medical College, Vellore, India
Unger et al. (2015); Papua New Guinea	*Inclusion criteria:* Pregnant women presenting for their first antenatal visit at ≤26 weeks gestational age	*Intervention*: 1393 women with mean ± SD age of 24.4 ± 5.5 years *Comparator*: 1382 women with mean ± SD age of 24.5 ± 5.4 years	*Intervention*: Azithromycin + Sulfadoxine-pyrimethamine (SP) *Dose*: Azithromycin (1-g) + SP (1500/75 mg) *Timing*: Three courses (one at enrolment, the second minimum four weeks later, the third minimum four weeks after that)	*Intervention*: Chloroquine (CQ) + Sulfadoxine-pyrimethamine (SP) *Dose*: CQ (450–600 mg) + SP (1500/75 mg) *Timing*: One course of SP and three days of CQ, followed by placebo equivalent for the next courses	Bill & Melinda Gates Foundation; Pregvax Consortium (EU & Spanish Government); Drug provided by Pfizer Inc (New York, NY)
Kalilani et al. (2007); Malawi	*Inclusion criteria*: Pregnant women (14–26 weeks) with peripheral parasitaemia (Plasmodium falciparum) *Exclusion criteria:* Antimalarial drugs within 28 days before enrolment	*Intervention*: 47 women with a median (IQR) age of 20 years (18–23) *Comparator*: 47 women with a median (IQR) age of 20 years (18–24)	*Intervention*: Azithromycin + Sulfadoxine-pyrimethamine (SP) *Dose*: Azithromycin (1-g) + SP (1500/75 mg) *Timing*: First course at enrolment with SP on day 1 and azithromycin (1 g/day) on days 1 and 2 The second course at least four weeks later	*Intervention*: Sulfadoxine-pyrimethamine (SP) *Dose*: SP (1500/75 mg) *Timing*: First course at enrolment with SP on day 1 The second course at least four weeks later	Centers for Disease Control and Prevention

Abbreviations: CS: Caesarean section, CQ: Chloroquine; DHP: Dihydroartemisinin-piperaquine; GBS: Group B streptococci; HIV: Human Immunodeficiency Virus; IQR: Interquartile range; PROM: Prolonged rupture of membranes; SD: Standard Deviation; SE: Standard Error; SP: Sulfadoxine-pyrimethamine.

Table 1: **Summary of randomised controlled trials reporting the effect of azithromycin on pregnancy outcomes (N = 20).**

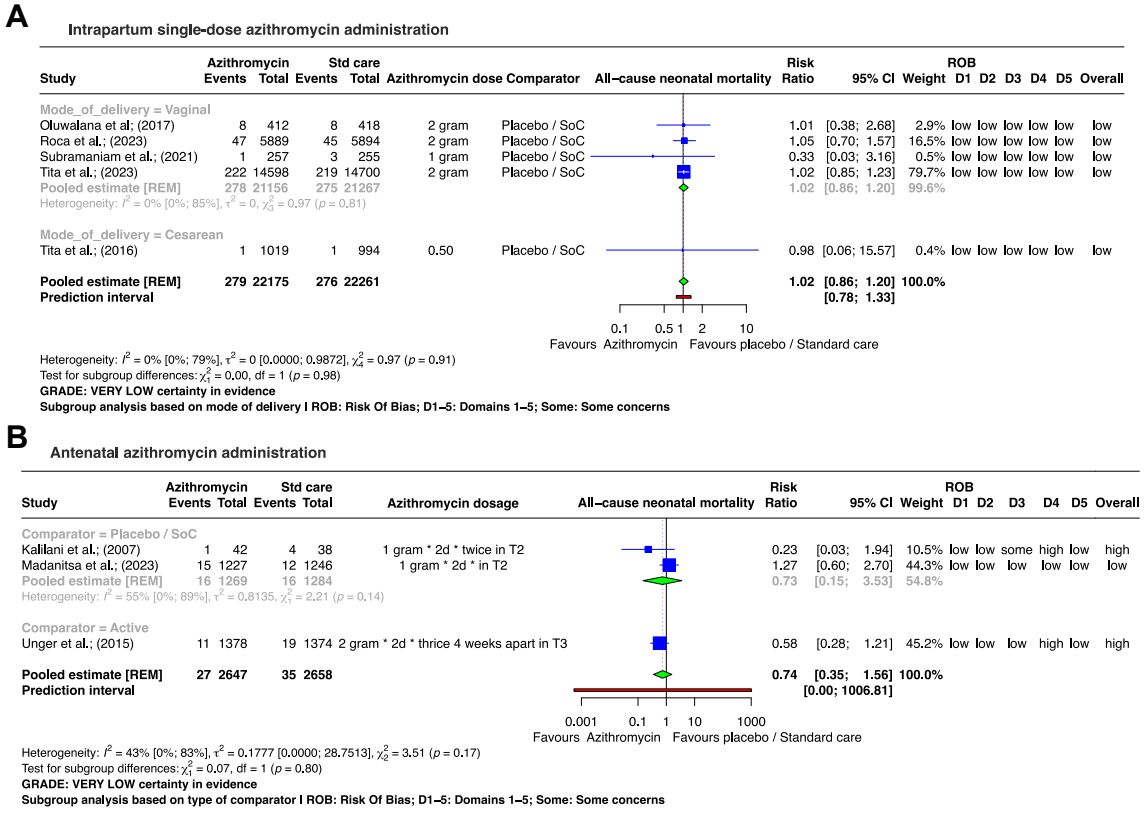

Fig. 2: Forest plot showing the relative risk, risk of bias assessment, and certainty in evidence of all-cause neonatal mortality with [A] ipntrapartum single dose and [B] antenatal azithromycin administration. REM: Random Effects Model; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations.

Exploring heterogeneity

We explored heterogeneity using subgroup analyses based on the mode of delivery and the type of comparator. The relative risk for all-cause neonatal mortality with single dose intrapartum azithromycin did not vary based on the mode of delivery [vaginal delivery: RR 1.02, 0.86–1.21; caesarean delivery: RR 1.01, 0.40–2.52; test for subgroup differences: p = 0.91] [Fig. 2]. All these studies used a passive comparator; hence, another subgroup analysis based on the type of comparator was not required. Though these subgroup analyses help summarise the effect better, the inference could be limited in some cases due to very few studies within each subgroup for different outcomes [Figures S2 and S3].

Risk for all-cause neonatal mortality with single-dose intrapartum azithromycin did not depend on the dose (p = 0.52) [Fig. 3B]. Most outcomes, except maternal fever, did not show a dose- response relationship [Figures S2 and S3]. The relative risk for maternal fever with single-dose intrapartum azithromycin decreased with an increase in the dose (p = 0.04) [Figure S2]. Similarly, the risk for preterm birth decreased (p = 0.04) with increased antenatal azithromycin dose [Figure S3].

Risk of bias

Most of the included studies had an overall low risk of bias. All the studies reporting all-cause neonatal mortality with single-dose intrapartum azithromycin are at a low risk of bias. For other outcomes, some studies had some concerns or a high risk of bias. Two studies have serious concerns with outcome ascertainment.[55,56] One of which[55] also has some concerns with missing outcome data. The outcome-wise risk of bias assessments for each study contributing to each outcome are given in the individual forest plots for better interpretation [Figures S2 and S3].

Publication bias

The Doi plot for all-cause neonatal mortality with single dose intrapartum azithromycin is asymmetric, has low heterogeneity, is overloaded on the left limb, and has an LFK index of –5.09 (<–1) [Figure S1B]. It suggests potential publication bias in favour of studies reporting a lower relative risk of all-cause neonatal mortality with the administration of single-dose intrapartum azithromycin. We constructed a sensitivity funnel plot too [Figure S1B]. There is no asymmetry–visually (inspection of the funnel plot) and statistically (Egger's

Outcome(s)	Participants (studies)	Pooled Estimates (RR/MD) (with 95% CI), I^2	Sensitivity BayesianEstimates (RR/MD) (with 95% CrI)	Anticipated absolute effects		Certainty of the evidence (GRADE)
				Risk with comparator	RD with azithromycin (with 95% CI)	
Single-dose intrapartum azithromycin administration						
All-cause neonatal mortality	44,436 (5 RCTs)	1.02 (0.86–1.2), I^2 = 0%	1.01 (0.7–1.42)	9 per 1000	0 more per 1000 (1 fewer to 2 more)	⨁◯◯◯ Very low[a,b]
Neonatal sepsis	44,573 (6 RCTs)	1.02 (0.96–1.09), I^2 = 0%	1.02 (0.83–1.24)	27 per 1000	1 more per 1000 (1 fewer to 3 more)	⨁◯◯◯ Very low[a,b]
Omphalitis	12,626 (2 RCTs)	0.58 (0.34–0.98), I^2 = 0%	0.66 (0.32–1.51)	6 per 1000	2 fewer per 1000 (4 fewer to 0 fewer) **NNT 402** (257–11,145)	⨁⨁⨁◯ Moderate[c]
Conjunctivitis	12,626 (2 RCTs)	0.85 (0.68–1.06), I^2 = 0%	0.86 (0.51–1.43)	48 per 1000	7 fewer per 1000 (15 fewer to 3 more)	⨁⨁◯◯ Low[a]
Skin infection	12,626 (2 RCTs)	0.48 (0.36–0.65), I^2 = 0%	0.54 (0.31–1.08)	32 per 1000	17 fewer per 1000 (21 fewer to 11 fewer) **NNT 60** (48–88)	⨁⨁⨁◯ Moderate[c]
Otitis	12,626 (2 RCTs)	0.73 (0.36–1.48), I^2 = 0%	0.8 (0.37–1.74)	4 per 1000	1 fewer per 1000 (3 fewer to 2 more)	⨁⨁◯◯ Low[a]
Neonatal malaria	12,626 (2 RCTs)	1.35 (0.25–7.2), I^2 = 0%	1.12 (0.38–3.32)	0 per 1000	0 more per 1000 (0 fewer to 2 more)	⨁⨁◯◯ Low[a]
Neonatal antibiotic use	12,626 (2 RCTs)	0.81 (0.71–0.93), I^2 = 5%	0.84 (0.41–1.34)	79 per 1000	15 fewer per 1000 (23 fewer to 5 fewer) **NNT 67** (43–193)	⨁⨁⨁⨁ High
Readmission or prolongation [Neonatal]	31,459 (3 RCTs)	1.06 (0.95–1.18), I^2 = 0%	1.05 (0.77–1.66)	75 per 1000	4 more per 1000 (4 fewer to 13 more)	⨁⨁◯◯ Low[a]
ICU admission [Neonatal]	31,297 (3 RCTs)	1.02 (0.94–1.1), I^2 = 9%	1 (0.74–1.36)	100 per 1000	2 more per 1000 (6 fewer to 10 more)	⨁⨁◯◯ Low[a]
Apgar score at 1 min	412 (2 RCTs)	MD: 0.56 (−0.03 to 1.15), I^2 = 96%	MD 0.44 (−0.63 to 1.35)	–	MD 0.56 higher (0.03 lower to 1.15 higher)	⨁⨁◯◯ Low[a]
Stillbirth	30,815 (3 RCTs)	1.07 (0.76–1.51), I^2 = 0%	1.06 (0.6–1.86)	6 per 1000	0 more per 1000 (1 fewer to 3 more)	⨁⨁◯◯ Low[a]
All-cause maternal mortality	44,131 (3 RCTs)	1.26 (0.65–2.42), I^2 = 0%	1.18 (0.58–2.36)	1 per 1000	0 more per 1000 (0 fewer to 1 more)	⨁⨁◯◯ Low[a]
Maternal sepsis	44,190 (5 RCTs)	0.65 (0.56–0.77), I^2 = 0%	0.69 (0.47–1.16)	7 per 1000	2 fewer per 1000 (3 fewer to 2 fewer) **NNT 420** (327–630)	⨁⨁◯◯ Low[c,d]
Maternal infections	15,879 (6 RCTs)	0.5 (0.41–0.61), I^2 = 3%	0.52 (0.39–0.7)	49 per 1000	24 fewer per 1000 (29 fewer to 19 fewer) **NNT 41** (35–53)	⨁⨁◯◯ Low[c,d]
Endometritis	32,532 (5 RCTs)	0.62 (0.53–0.73), I^2 = 23%	0.58 (0.38–0.78)	48 per 1000	18 fewer per 1000 (23 fewer to 13 fewer) **NNT 55** (44–76)	⨁⨁⨁◯ Moderate[b]
Surgical site infections	3306 (4 RCTs)	0.41 (0.27–0.61), I^2 = 15%	0.46 (0.29–0.82)	68 per 1000	40 fewer per 1000 (49 fewer to 27 fewer) **NNT 25** (20–38)	⨁⨁⨁◯ Moderate[d]
Chorioamnionitis	29,781 (2 RCTs)	0.5 (0.22–1.18), I^2 = 0%	0.65 (0.28–1.58)	4 per 1000	2 fewer per 1000 (3 fewer to 1 more)	⨁⨁◯◯ Low[a]
Maternal malaria	12,454 (2 RCTs)	0.98 (0.45–2.11), I^2 = 24%	0.99 (0.47–2.19)	5 per 1000	0 fewer per 1000 (3 fewer to 5 more)	⨁⨁◯◯ Low[a]
Maternal fever	15,240 (6 RCTs)	0.52 (0.35–0.77), I^2 = 52%	0.56 (0.36–0.89)	38 per 1000	19 fewer per 1000 (25 fewer to 9 fewer) **NNT 54** (40–113)	⨁⨁◯◯ Low[d,e]

(Table 2 continues on next page)

Outcome(s)	Participants (studies)	Pooled Estimates (RR/MD) (with 95% CI), I^2	Sensitivity BayesianEstimates (RR/MD) (with 95% CrI)	Anticipated absolute effects		Certainty of the evidence (GRADE)
				Risk with comparator	RD with azithromycin (with 95% CI)	
(Continued from previous page)						
Maternal antibiotic use	44,388 (6 RCTs)	0.7 (0.55–0.89), I^2 = 87%	0.7 (0.51–0.93)	110 per 1000	33 fewer per 1000 (50 fewer to 12 fewer) **NNT 30** (20–84)	⨁◯◯◯ Very low[b,f]
Readmission or prolongation [Maternal]	32,308 (4 RCTs)	0.81 (0.46–1.41), I^2 = 55%	0.8 (0.51–1.57)	20 per 1000	4 fewer per 1000 (11 fewer to 8 more)	⨁◯◯◯ Very low[a,e]
ICU admission [Maternal]	31,235 (2 RCTs)	0.75 (0.31–1.81), I^2 = 26%	0.83 (0.35–1.63)	9 per 1000	2 fewer per 1000 (6 fewer to 7 more)	⨁⨁◯◯ Low[a]
Antenatal azithromycin administration						
All-cause neonatal mortality	5305 (3 RCTs)	0.74 (0.35–1.56), I^2 = 43%	0.8 (0.4–1.6)	21 per 1000	5 fewer per 1000 (13 fewer to 12 more)	⨁◯◯◯ Very low[a,g]
Readmission or prolongation [Neonatal]	2752 (1 RCTs)	1.1 (0.78–1.54), I^2 = NA	1.05 (0.45–2.14)	44 per 1000	4 more per 1000 (10 fewer to 24 more)	⨁◯◯◯ Very low[a,g]
ICU admission [Neonatal]	50 (1 RCT)	0.2 (0.03–1.59), I^2 = NA	0.69 (0.21–2.44)	200 per 1000	160 fewer per 1000 (195 fewer to 118 more)	⨁◯◯◯ Very low[a,h]
Neonatal infections	6526 (3 RCTs)	0.94 (0.66–1.34), I^2 = 0%	0.95 (0.57–1.57)	16 per 1000	1 fewer per 1000 (6 fewer to 5 more)	⨁◯◯◯ Very low[a,g]
Congenital malformations	5534 (2 RCTs)	0.87 (0.51–1.48), I^2 = 0%	0.91 (0.45–1.9)	10 per 1000	1 fewer per 1000 (5 fewer to 5 more)	⨁⨁◯◯ Low[a]
Low birth weight	6912 (8 RCTs)	0.83 (0.72–0.96), I^2 = 0%	0.84 (0.68–1.03)	119 per 1000	20 fewer per 1000 (33 fewer to 5 fewer) **NNT 50** (30–219)	⨁⨁◯◯ Low[c,d]
Apgar score at 1 min	289 (2 RCTs)	MD: −0.07 (−0.58 to 0.45), I^2 = 87%	MD: −0.09 (−1.21 to 0.78)	–	MD 0.07 lower (0.58 lower to 0.45 higher)	⨁◯◯◯ Very low[a,f,g]
Apgar score at 5 min	289 (2 RCTs)	MD: −0.07 (−0.28 to 0.14), I^2 = 38%	MD: −0.09 (−0.65 to 0.54)	–	MD 0.07 lower (0.28 lower to 0.14 higher)	⨁◯◯◯ Very low[a,g]
Preterm birth	8617 (8 RCTs)	0.88 (0.76–1.03), I^2 = 14%	0.9 (0.72–1.16)	91 per 1000	11 fewer per 1000 (22 fewer to 3 more)	⨁◯◯◯ Very low[a,b]
Stillbirth	6827 (6 RCTs)	1.08 (0.7–1.68), I^2 = 5%	1.05 (0.6–1.71)	15 per 1000	1 more per 1000 (5 fewer to 10 more)	⨁◯◯◯ Very low[a,b]
Miscarriage	6677 (5 RCTs)	1.01 (0.42–2.42), I^2 = 31%	1.03 (0.47–2.22)	5 per 1000	0 more per 1000 (3 fewer to 7 more)	⨁◯◯◯ Very low[a,b,e,g]
All-cause maternal mortality	8167 (3 RCTs)	1.62 (0.67–3.91), I^2 = 0%	1.36 (0.59–3.09)	2 per 1000	1 more per 1000 (1 fewer to 5 more)	⨁⨁◯◯ Low[a]
Maternal infections	5870 (2 RCTs)	0.75 (0.41–1.39), I^2 = 0%	0.81 (0.4–1.66)	8 per 1000	2 fewer per 1000 (5 fewer to 3 more)	⨁⨁◯◯ Low[a]
Endometritis	992 (1 RCT)	0.2 (0.01–4.16), I^2 = NA	0.8 (0.23–2.81)	4 per 1000	3 fewer per 1000 (4 fewer to 13 more)	⨁◯◯◯ Very low[a,g]
Maternal malaria	4856 (3 RCTs)	1.15 (0.98–1.36), I^2 = 0%	1.12 (0.57–1.62)	95 per 1000	15 more per 1000 (2 fewer to 35 more)	⨁⨁◯◯ Low[a]
Maternal fever	50 (1 RCT)	0.5 (0.05–5.17), I^2 = NA	0.86 (0.26–2.88)	80 per 1000	40 fewer per 1000 (76 fewer to 333 more)	⨁◯◯◯ Very low[a,h]
Readmission or prolongation of admission [Maternal]	2752 (1 RCT)	0.95 (0.72–1.26), I^2 = NA	0.96 (0.44–1.94)	68 per 1000	3 fewer per 1000 (19 fewer to 18 more)	⨁◯◯◯ Very low[a,g]
Fetal body weight [gram]	3833 (5 RCTs)	MD: 17.4 (−12.9 to 47.8), I^2 = 66%	MD 0.08 (−1.86 to 2.03)	Mean fetal body weight was 2902.84	MD 17.4 higher (12.9 lower to 47.8 higher)	⨁◯◯◯ Very low[a,f]

Abbreviations: CI: Confidence Intervals; CrI: Credible Intervals; MD: Mean difference; NA: Not applicable; NNT: Number Needed to Treat; RCT: Randomised controlled trial; RD: Risk difference; RR: Risk Ratio. Explanations: a. Downrated two levels for imprecision: The point estimate suggests one direction, but the CI includes the possibility of an important effect in the opposite direction.b. Downrated one level for publication bias: Asymmetrical Doi plot and deranged LFK index indicate potential publication bias.c. Downrated one level for imprecision: Optimal information size not achieved.d. Downrated one level for quality due to some quality concerns or concerns over varying definitions and subjective assessment.e. Downrated one level for inconsistency: There is unexplained variation in the estimates from different studies for this outcome.f. Downrated two levels for inconsistency: There is substantial unexplained variation in the estimates from different studies for this outcome.g. Downrated two levels for study quality: High-quality studies and overall estimates differ and point in the opposite direction.h. Downrated three levels for imprecision: The point estimate suggests one direction, but the CI includes the possibility of an important effect in both directions.

Table 2: **Summary of findings table for azithromycin prophylaxis (antenatal or intrapartum) in pregnancy for neonatal, perinatal, and maternal outcomes.**

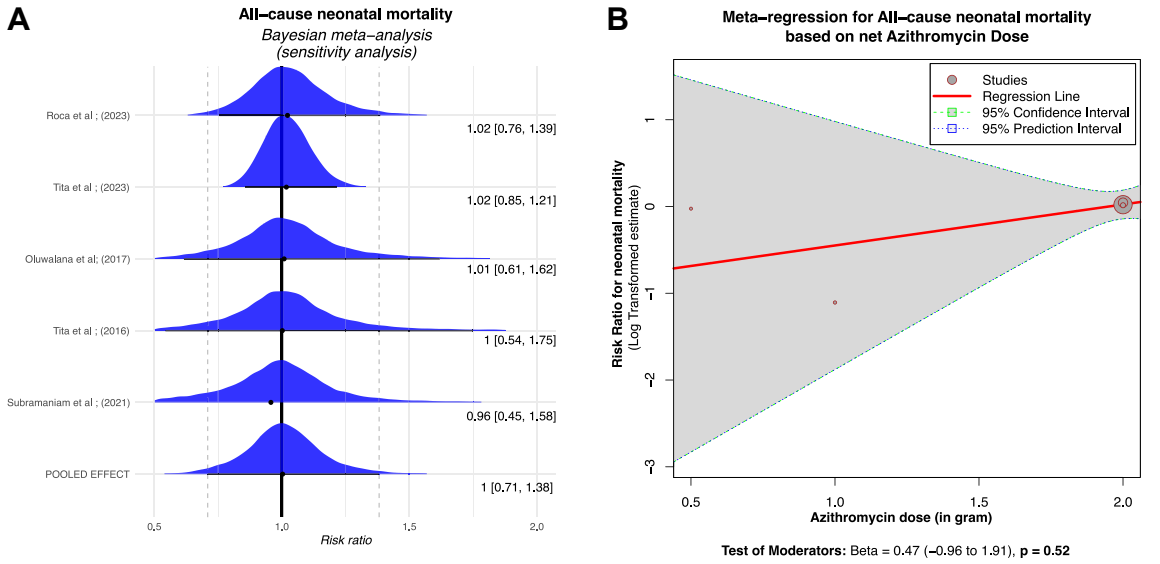

Fig. 3: A. Bayesian sensitivity analysis for the relative risk of all-cause neonatal mortality with intrapartum single-dose azithromycin administration. B. Bubble plot to visualise meta-regression for the relative risk of all-cause neonatal mortality with intrapartum single-dose azithromycin administration based on dose.

regression: p = 0.33). However, the test is underpowered, and trim-and-fill imputing for two study estimates. Hence, the lack of evidence of publication bias (from the funnel plot) should be interpreted cautiously. Similarly, neonatal sepsis, endometritis, and maternal antibiotic use also have concerns over publication bias [Figure S2].

Discussion

This SRMA of 20 RCTs involving 56,381 participants evaluated the evidence of the role of adjuvant azithromycin prophylaxis among pregnant women. This review's findings suggest that prophylactic azithromycin use in pregnant women possibly has little or no effect on maternal and neonatal mortality (low to very-low certainty evidence). However, single-dose intrapartum azithromycin prophylaxis possibly reduces maternal infections, including systemic sepsis, endometritis, surgical site infections (SSI) (low to moderate certainty evidence), and antibiotic usage. In neonates, its effect was limited to a reduction in superficial skin infection and omphalitis but not on systemic sepsis. Neonatal antibiotic use was also reduced (high certainty evidence). Antenatal azithromycin prophylaxis possibly has little or no effect on chorioamnionitis and preterm births (very-low certainty evidence). There was probably a reduction in the risk of low birth weight. Limited evidence suggests that it may or may not increase the risk of stillbirths, miscarriage, and congenital anomalies. Most outcomes did not show any evidence of a dose–response relationship. However, the risk of maternal fever is reduced with a higher dose of intrapartum azithromycin. Similarly, the risk of preterm birth is reduced with a higher net dose of antenatal azithromycin. None of the included trials studied long-term neurodevelopmental outcomes. There was no data from clinical trials to support or refute the emergence of multidrug resistance with prophylactic azithromycin.

Azithromycin is a broad-spectrum, longer-acting macrolide initially used to treat reproductive tract infections (RTI) among pregnant women.[57] It also has an immunomodulatory and antimalarial action. Maternal infections (RTI, intraamniotic inflammation) and genital tract colonisation with Ureaplasma, Mycoplasma, and Chlamydia are associated with preterm birth in mothers with preterm premature rupture of membrane (P-PROM)/cervical insufficiency. Azithromycin reduces infection by its antibacterial action and inflammation by downregulating the expression of proinflammatory transcription factors.[22] It is also one of the most potent macrolides with antimalarial activity and has been used for intermittent prophylaxis against malaria in pregnancy in African and Asian countries.[5] Malaria in pregnancy also predisposes to preterm labour and, hence, the complications related to prematurity. It was explored for its role in preventing preterm births by these properties. Initial trials showed that antenatal azithromycin use was associated with reduced preterm delivery, improved neonatal survival, and better weight gain (less incidence of low birth weight).[58] We did not observe these effects except for low birth weight. In malaria-endemic countries, azithromycin intermittent prophylaxis in the antenatal period was associated with

reduced prematurity and low birth weight.[5] However, it is unclear whether these effects were due to treatment of the underlying infection, which themselves can lead to adverse neonatal outcomes, or were direct effects of the immunomodulatory action of azithromycin.

Subsequent trials from high-income countries where the prevalence of untreated RTIs and malaria was low in pregnancy failed to show beneficial effects on foetal and neonatal well-being.[15,16,24] Instead, they consistently showed that single-dose intrapartum azithromycin prophylaxis was associated with reduced SSIs, endometritis, and maternal mortality.[10,13,15] Hence, recently, the focus has shifted from neonatal to maternal outcomes. American College of Obstetrics and Gynecology recommends azithromycin prophylaxis to reduce SSI in pregnant women undergoing elective caesarean section.[14] Our review further supports these recommendations and probably extends its use among women planning for elective vaginal delivery too. However, we must acknowledge here that there are concerns over the increased risk of miscarriage, stillbirths, congenital anomalies, cerebral palsy, and childhood asthma with azithromycin use during pregnancy.[5,23,57,59,60] These associations were mainly from the population-based observational cohort or retrospective[60] studies. In the index review, there is no increase in the incidence of miscarriage, stillbirths, or congenital anomalies. However, these rare events might not have been adequately represented in RCTs, so caution is warranted until further studies[61,62] are done on this aspect. Since the beneficial effects are seen chiefly with single-dose intrapartum prophylaxis, which is unlikely to be associated with either of these outcomes. However, considering the uncertainty over adverse outcomes, clinicians should make informed decisions about using intrapartum azithromycin.

This is the most up-to-date comprehensive evidence synthesis on azithromycin prophylaxis among pregnant women and is done per standard guidelines. However, there are some limitations. There was wide variation in the timing of administration, dosing schedule, and co-interventions. Though we explored these via appropriate subgroup analyses and meta-regression for the dose–response relationship, the number of studies for each outcome was less than enough to draw robust conclusions. There is heterogeneity in the definitions used for neonatal and maternal sepsis, with much subjectivity. We adjusted for the same while assessing evidence certainty. The reporting of follow-up periods is different in different studies and hence might not provide true estimates of neonatal mortality (up to 28 days) and maternal mortality (up to 42 days). The rare adverse events like congenital malformations might not have been captured. Hence, the interpretation of safety should be taken with caution. None of the trials followed infants for long-term adverse outcomes and antimicrobial resistance. Most RCTs on antenatal azithromycin use are done in low and lower-middle-income countries with inadequate representation from high-income countries. We detected potential publication bias favouring studies reporting a benefit on neonatal mortality with antenatal azithromycin, further lowering our confidence in the estimate. For most outcomes, the evidence of certainty is low to very-low, making it difficult to draw firm conclusions.

Considering these limitations, there is a need for further well-conducted, adequately powered trials on this aspect. Further trials should also focus on safety aspects, including adequate follow-up of infants for antimicrobial resistance and long-term outcomes.

Low to very low certainty evidence suggests that intrapartum or antenatal azithromycin prophylaxis in pregnant women might not reduce maternal or neonatal mortality. However, single-dose intrapartum azithromycin might reduce maternal infections, mainly surgical site infections and endometritis, as well as antibiotic usage. It also reduces superficial skin infection, omphalitis, and antibiotic usage among neonates. There is a need for data on adverse events, including congenital malformations, antimicrobial resistance, and long-term neurodevelopmental outcomes among neonates.

Contributors

MAqS: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Writing—original draft.

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The lead author (MAqS) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as initially planned (and if relevant, registered) have been explained.

MAqS and JK have complete access to and have verified the underlying data.

All authors read and approved the final version of the manuscript.

Data sharing statement

All data has been made available here and in the annexures.

Declaration of interests

None of the authors has declared competing interests.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102691.

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