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SYSTEMATIC REVIEW

Intrapartum azithromycin to prevent maternal and neonatal sepsis and deaths: A systematic review with meta-analysis

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Abstract

Objectives: A systematic review with met-analysis was performed to summarise the evidence on the effect of intrapartum azithromycin on maternal and neonatal infections and deaths.

Search strategy: PubMed, Scopus and Web of Science databases were searched in March 2023.

Selection criteria: Randomised controlled trials comparing intrapartum single-dose of azithromycin with placebo.

Data collection and analysis: Maternal infections, maternal mortality, neonatal sepsis, neonatal mortality. We used the random-effects Mantel–Haenszel method to calculate risk ratios (RR) with 95% confidence intervals (95% CI). We assessed risk of bias of the included studies and estimated the evidence certainty using the GRADE approach.

Main results: After screening 410 abstracts, five studies with 44 190 women and 44 565 neonates were included. The risk of bias was low in four and had some concerns in one of the studies. The risk of endometritis was 1.5% in the azithromycin group and 2.3% in the placebo group (RR 0.64, 95% CI 0.55–0.75), and the evidence certainty was high. The respective risk for chorioamnionitis was 0.05% and 0.1% (RR 0.50, 95% CI 0.22–1.18; evidence certainty moderate). The wound infection rate was lower in the azithromycin group (1.6%) than in the placebo group (2.5%), RR 0.52 (95% CI 0.30–0.89; moderate certainty evidence). The maternal sepsis rate was 1.1% in the azithromycin group and 1.7% in the placebo group (RR 0.66, 95% CI 0.56–0.77; evidence certainty high). Mortality rates did not show evidence of a difference (0.09% versus 0.08%; RR 1.26, 95% CI 0.65–2.42; moderate certainty evidence). The neonatal mortality rate was 0.7% in the azithromycin group and 0.8% in the placebo group (RR 0.94, 95% CI 0.76–1.16; moderate certainty evidence). The neonatal sepsis rate was 7.6% in the azithromycin group and 7.4% in the placebo group (RR 1.02, 95% CI 0.96–1.09; moderate certainty evidence).

Conclusions: Intrapartum administration of azithromycin to the mother reduces maternal postpartum infections, including sepsis. Impact on maternal mortality remains undecided. Azithromycin does not reduce neonatal sepsis or mortality rates.

KEYWORDS
azithromycin, meta-analysis, mortality, perinatal outcomes, sepsis

Protocol registration: This review has been registered in PROSPERO – CRD42023412194.

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1 | INTRODUCTION

Although the burden of maternal and neonatal mortality has been decreasing, these rates are still high in Sub-Saharan Africa and South Asia.[1] Thus, effective interventions to reduce the burden of mortality are needed.[2] Overall previous studies have shown that prophylactic antibiotics during caesarean sections reduce the maternal infection burden.[3,4] Studies have assessed the effect of intrapartum maternal azithromycin on maternal and neonatal outcomes and found both positive and null results.[5–7] Prophylactic azithromycin has been promising, especially against maternal infections after caesarean sections.[7,8] The most recent guideline from the American College of Obstetricians and Gynecologists recommended a single dose of, for example, first-generation cephalosporin in elective caesarean section, and addition of azithromycin in non-elective caesarean section.[9]

A previous Cochrane review suggested that prophylactic antibiotics in operative vaginal delivery may reduce postpartum maternal infections.[10] However, the evidence in spontaneous vaginal deliveries has not been previously well summarised. Furthermore, most previous studies have been mainly designed to estimate maternal infections and have been underpowered to estimate neonatal outcomes.[5,7] However, two large-scale randomised controlled trials were recently published which analysed both mothers and neonates and found benefits for mothers but not for neonates.[11,12] These were both conducted in low-income settings. Although the previous studies have been large, they have still been underpowered to estimate maternal mortality, and thus a systematic review with meta-analysis could have the power to detect possible effects.

The aim of this systematic review with meta-analysis is to summarise the evidence on the effect of intrapartum azithromycin on maternal and neonatal infections and deaths.

2 | METHODS

2.1 | Search

We searched systematically PubMed, Scopus and Web of Science databases on 8 March 2023 (search strategy in Appendix S1). We did not use any time filter in the search. Two authors performed the title and full-text screening process independently and blinded. Mutual consensus was used in conflicting assessments. Covidence software was used in the screening process.

2.2 | Inclusion and exclusion criteria

We included randomised controlled trials where the intervention was intrapartum azithromycin administration to the mother regardless of the delivery mode, and the control intervention was placebo. We did not have any criteria regarding the study setting (country or hospital status). We excluded non-English reports and all studies that did not present original data (editorials, reviews, commentaries, etc.). We did not search the grey literature.

2.3 | Outcome measures

We had four main outcomes: maternal infections and mortality, neonatal sepsis and mortality rates within 60 days of the delivery. We included both confirmed and suspected cases of neonatal sepsis. We assessed the following maternal infections: endometritis, chorioamnionitis, wound infections and sepsis. We used the definition used in the original studies of these conditions. We also analysed maternal adverse outcomes and neonatal pyloric stenosis detections.

2.4 | Risk of bias

Risk of bias of the included studies was assessed using the Cochrane RISK OF BIAS 2.0 tool.[13] Risk of bias was visualised using Robvis shinyapp.[14] Risk of bias assessments were made by two authors and cases of discrepancy were resolved by mutual consensus.

2.5 | Data extraction

One author extracted the data and another author validated the extracted data to reduce potential extraction errors. The following information was extracted from each study: authors, journal, country, study period, publication year, funding, competing interests, intervention, control, inclusion criteria, exclusion criteria, number of participants (mothers and neonates) in intervention and control groups, cohort characteristics in both groups, maternal outcomes (number of infections and deaths), neonatal outcomes (number of suspected and confirmed sepsis, neonatal deaths).

2.6 | Statistics

We used the random-effects Mantel–Haenszel method, as suggested by the Cochrane handbook in cases of low outcome rate, to calculate pooled risk ratios (RR) with 95% confidence intervals (95% CI).[15] We expected heterogeneity in the patient populations and outcome definitions, and thus used a random effects model. We assessed statistical heterogeneity based on the variation, interpreted as an I^2 statistic. However, this did not have an effect on the model choice, and instead was used as a part of the GRADE assessment. We planned to perform subgroup analysis based on the delivery mode (vaginal, elective caesarean section, non-elective caesarean section) and on study country (low-income versus higher income countries). Publication bias was assessed by funnel plots.[16] We preplanned sensitivity analyses, where studies with high risk of bias would be excluded. Furthermore, we decided to conduct leave-one-out

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sensitivity analysis to assess how much impact an individual study had on effect estimates. Additional sensitivity or meta-regression analyses were not planned. Adverse outcomes had a high heterogeneity in the reporting; these were not pooled and instead are presented separately in the text. Evidence certainty for all main outcomes was assessed according to GRADE methodology.[17,18] This study has been reported according to preferred reporting items in systematic reviews and meta-analyses (PRISMA) 2020 guidelines.[19] The completed PRISMA checklist is provided as a supplementary file.

2.7 | Core outcome set

This study did not utilise any core outcome sets.

2.8 | Patient involvement

No patients were involved in the study process.

2.9 | Protocol registration

This review has been registered in PROSPERO: CRD42023412194. Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023412194.

3 | RESULTS

Initially, we assessed 410 abstracts: 13 full reports were further evaluated, and finally 5 studies included.[5–7,11,12] (Figure 1) All of the included studies were double-blinded and placebo-controlled (Table 1). Azithromycin dose varied between 500 mg and 2 g, and four studies gave it orally and one intravenously. The risk of bias was low in all studies (Figure 2). Studies were conducted in Africa, Asia, USA and Latin America (Table 1). One study focused only on caesarean deliveries and one focused on attempted vaginal deliveries. Elective caesarean deliveries were excluded in all of the included studies. The non-elective caesarean delivery rate varied between 1.8% and 33% (Table 1). The inclusion criteria and exclusion criteria were rather similar between the included studies (Table S1). Risk of bias was low in four and had some concerns in one of the included studies (Figure 2). The study by Oluwalana et al. was downgraded due to some concerns because the clinical outcomes were not reported in the original protocol and thus the results reported represented a post-hoc analysis.[6,20]

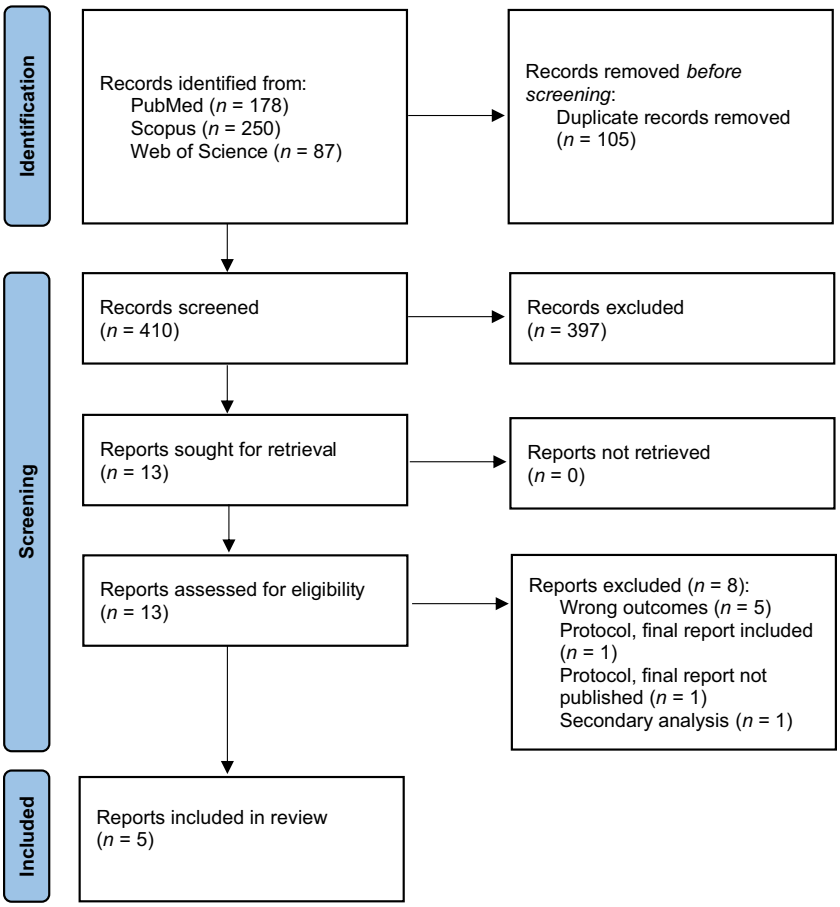

FIGURE 1 Flow chart of the study selection process.

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TABLE 1 Characteristics of the included studies.

Study	Country	Study period	Intervention	Control	Blinding	No. of participants	Delivery mode		
							Elective CS	Vaginal delivery	Non-elective CS
Oluwalana et al. 2017	Gambia	2013–2014	Azithromycin 2 g per os	Placebo	Double	829	Excluded	814 (98.2%)	15 (1.8%)
Roca et al. 2023	Gambia and Burkina Faso	2017–2021	Azithromycin 2 g per os	Placebo	Double	11 625	Excluded	11 392 (98.0%)	233 (2.0%)
Subramaniam et al. 2021	Cameroon	2018–2020	Azithromycin 1 g per os	Placebo	Double	503	Excluded	337 (67%)	166 (33%)
Tita et al. 2016	USA	2011–2014	Azithromycin 500 mg intravenous	Placebo	Double	2013	Excluded	0	2013 (100%)
Tita et al. 2023	Africa Asia Latin America		Azithromycin 2 g per os	Placebo	Double	29 163	Excluded	25 069 (86.0%)	4094 (14.0%)

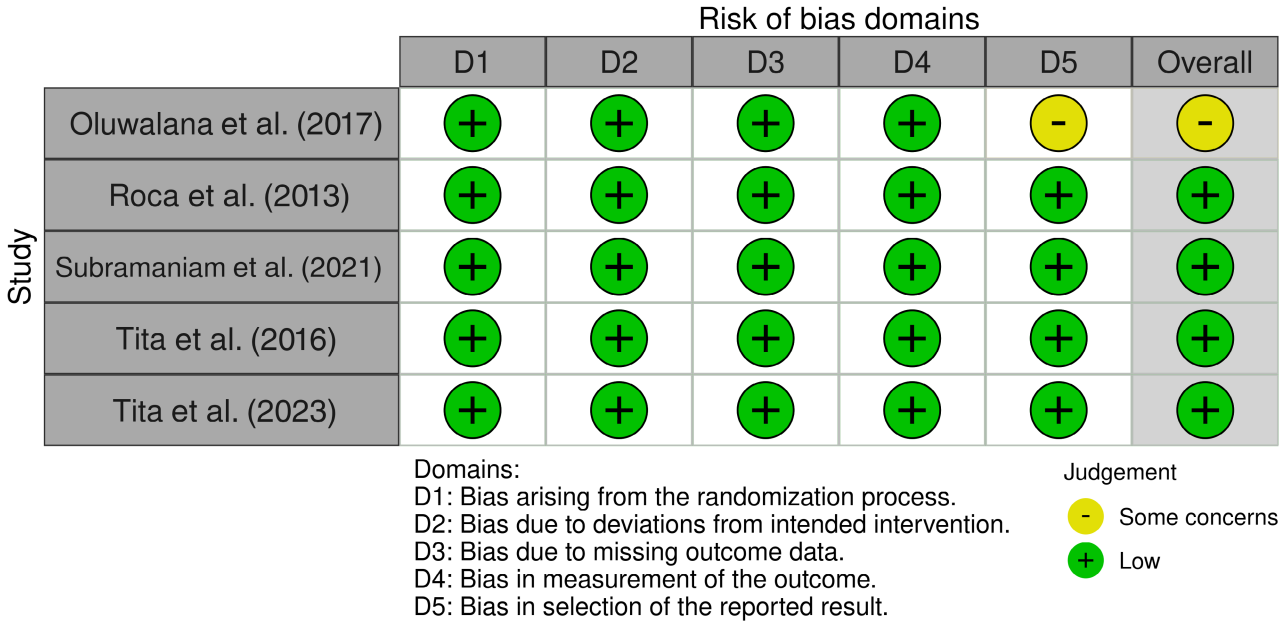

FIGURE 2 Risk of bias of the included studies.

3.1 | Maternal outcomes

The risk for chorioamnionitis (2 studies,[5,12] 29 781 parturients) was 0.05% and 0.1% (RR 0.50, 95% CI 0.22–1.18; Figure 3; evidence certainty moderate; Table 1). The risk of endometritis (3 studies,[5,7,12] 31 753 parturients) was 1.5% in the azithromycin group and 2.3% in the placebo group (RR 0.64, 95% CI 0.55–0.75; Figure 3), with high evidence certainty (Table 1). Wound infection (3 studies,[5,7,12] 31 728 parturients) rate was lower in the azithromycin group (1.6%) than in the placebo group (2.5%) (RR 0.52 (95% CI 0.30–0.89; Figure 3); evidence certainty was ranked as moderate (Table 2). The maternal sepsis rate was assessed in five studies[5–7,11,12] (44 190 parturients). The rate was 1.1% in the azithromycin group and 1.7% in the placebo group (RR 0.66, 95% CI 0.56–0.77; Figure 3; evidence certainty high; Table 2). Five studies[5–7,11,12] analysed mortality rates and did not show evidence of a difference (0.09% versus 0.08%; RR 1.26, 95% CI 0.65–2.42; Figure 3). Evidence certainty was ranked as moderate (Table 2). We did not detect signs of publication bias (Figure S1). A sensitivity analysis was performed where the study conducted in a high-income country (USA) was removed; this did not notably change the effect estimates (Figure S2). The similar sensitivity analysis also meant that the study which included only caesarean deliveries and only intravenous administration was excluded, and thus this estimated also the impact of azithromycin in cases of trial of labour and only oral administration. In the leave-one-out

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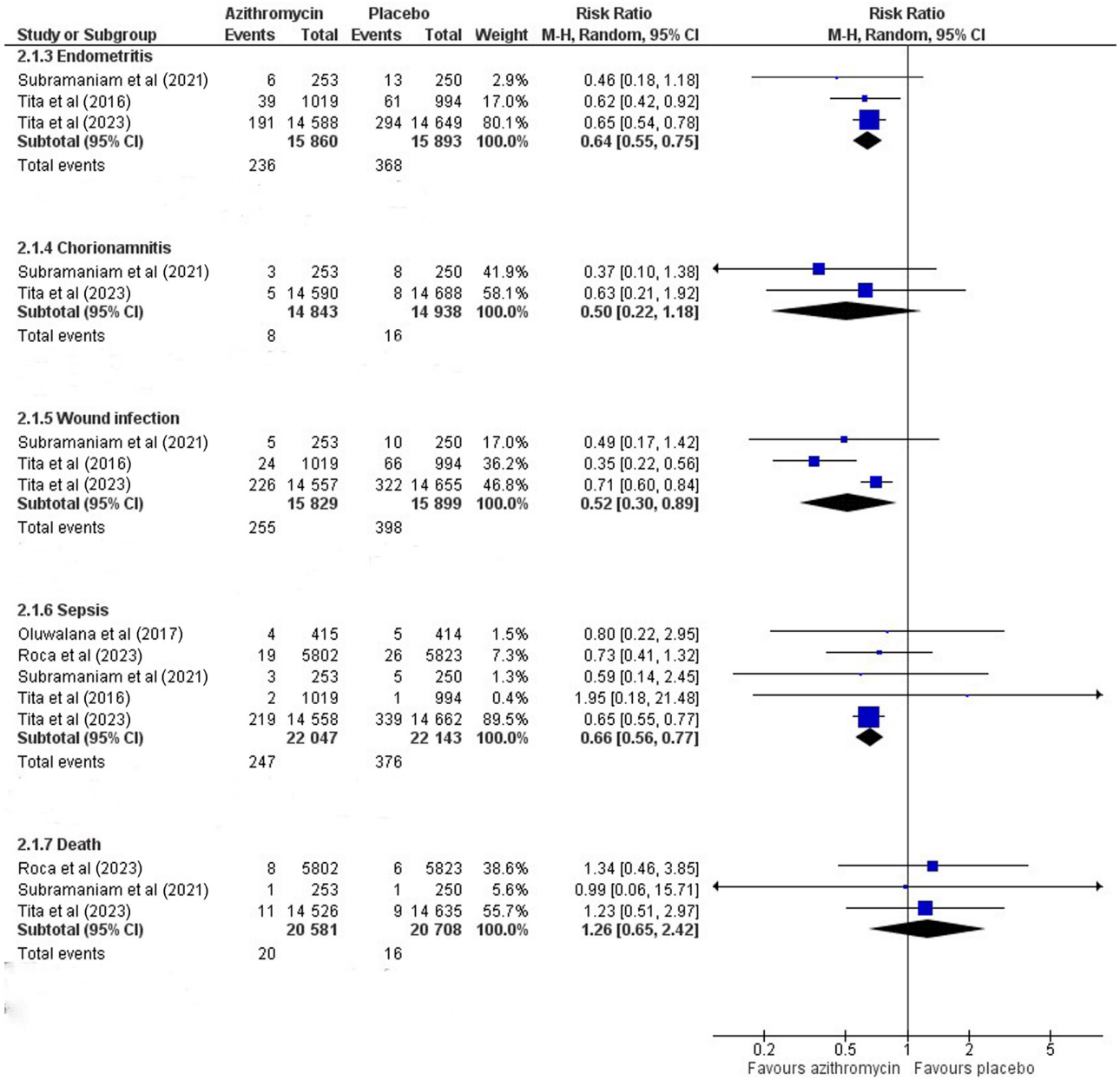

FIGURE 3 Forest plot of the main maternal outcomes (maternal postpartum infections and death). The random-effects Mantel–Haenszel method was used to calculate risk ratios with 95% confidence intervals.

sensitivity analysis (which analysed the impact of an individual study on pooled effect estimate), the dropping of the largest trial[12] changed the estimate of maternal sepsis to RR 0.75 (95% CI 0.46–1.23) and thus the finding was now imprecise. Other maternal estimates remained nearly unchanged (Figure S3).

3.2 | Neonatal outcomes

Neonatal death was assessed in five studies[2–6] (44 565 neonates). The absolute risk was 0.7% in the azithromycin group and 0.8% in the placebo group (RR 0.94, 95% CI 0.76–1.16; Figure 4). We ranked the evidence certainty as moderate (Table 2). Neonatal sepsis was assessed in five studies.[2–6] The absolute risk was 7.6% in the azithromycin group and 7.4% in the placebo group (RR 1.02, 95% CI 0.96–1.09; Figure 4), with evidence certainty ranked as moderate (Table 2). We did not detect publication bias in the funnel plot (Figure S4). A sensitivity analysis was performed where the study conducted in a high-income country (USA) was removed and the study which only included caesarean deliveries; this did not change notably the effect estimates (Figure S5). In the leave-one-out sensitivity analysis, the removal of any individual study did not change the effect estimates (Figure S6).

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TABLE 2 Summary of findings and evidence certainty of main outcomes assessed according to GRADE methodology.

Outcome	No. of studies (no. of participants)	Absolute risk		Relative effect (risk ratio)	Absolute anticipated effect	GRADE
		Azithromycin group	Placebo group			
Maternal outcomes						
Postpartum infections						
Endometritis	3 (31 753)	15 per 1000	23 per 1000	0.64 (95% CI 0.55–0.75)	8 fewer per 1000 (10 fewer to 6 fewer)	High
Chorioamnionitis	2 (29 781)	0.5 per 1000	1 per 1000	0.50 (95% CI 0.22–1.18)	0.5 fewer per 1000 (0.8 fewer to 0.2 more)	Moderate[a]
Wound infection	3 (31 728)	16 per 1000	25 per 1000	0.52 (95% CI 0.30–0.89)	12 fewer per 1000 (18 fewer to 3 fewer)	Moderate[b]
Sepsis	5 (44 190)	11 per 1000	17 per 1000	0.66 (95% CI 0.56–0.77)	6 fewer per 1000 (8 fewer to 4 fewer)	High
Mortality	3 (41 289)	0.9 per 1000	0.8 per 1000	1.26 (95% CI 0.65–2.42)	0.2 more per 1000 (0.3 fewer to 1.1 more)	Moderate[a]
Neonatal outcomes						
Neonatal death	5 (44 565)	7 per 1000	8 per 1000	0.94 (95% CI 0.76–1.16)	0.5 fewer per 1000 (2 fewer to 1 more)	Moderate[c]
Neonatal sepsis	5 (44 565)	76 per 1000	74 per 1000	1.02 (95% CI 0.96–1.09)	1 fewer per 1000 (3 fewer to 7 more)	Moderate[c]

[a]Downgraded due to imprecision.
[b]Downgraded due to inconsistency.
[c]Downgraded due to risk of bias.

3.3 | Adverse events

Oluwalana et al.[6] reported that no serious adverse events were detected related to azithromycin in their study but without further specifying these. Roca et al.[11] reported that vomiting (10.1% versus 6.1%) and oedema (4.2% versus 3.2%) were more common in the azithromycin group mothers. Subramaniam et al.[5] reported vomiting in 1.6% versus 1.2% of mothers. Maternal and neonatal adverse event rates did not differ in the study by Tita et al.[7]

Roca et al.[11] did not detect pyloric stenosis in either group. Tita et al.[12] reported pyloric stenosis in eight neonates (0.05%) in the azithromycin group and three neonates (0.02%) in the placebo group.

4 | DISCUSSION

4.1 | Main findings

In this systematic review and meta-analysis, we found high-quality evidence that addition of single dose intrapartum azithromycin reduces postpartum infections (endometritis, wound infections and sepsis). However, moderate-quality evidence suggests that azithromycin does not have an impact on maternal mortality. Furthermore, we found high-quality evidence that intrapartum administration of azithromycin does not reduce neonatal deaths nor suspected neonatal sepsis diagnoses.

4.2 | Maternal outcomes

The risk for endometritis and wound infections was reduced by a single dose of azithromycin during labour. The reduced risk for wound infections was more evident after caesarean section,[7,12] which is not surprising, as caesarean sections, especially unplanned caesarean section, are associated with increased risk for postpartum infections.[9] Our results are consistent with a previous meta-analysis that included only caesarean sections.[8] In addition, receiving azithromycin during labour seemed to reduce the risk of maternal sepsis. This association was mostly derived from a multinational study of Tita et al.,[12] where azithromycin reduced the risk for sepsis after caesarean and vaginal deliveries. However, azithromycin benefitted more women in Africa than in Asia.[12] Among the other three studies from Africa, no clear evidence of a difference between the groups was seen in the individual studies. There was a tendency towards fewer sepsis infections in the azithromycin group, but these trials were notably smaller in size.[5,6,11] Chorioamnionitis has been associated with neonatal sepsis, but the association between chorioamnionitis and maternal sepsis is inconclusive.[21] Chorioamnionitis was a rare event and was reported in only two studies. Our results suggest that adding azithromycin may help prevent chorioamnionitis but the results need cautious interpretation, due to the small number of events. The use of other prophylactic antibiotics during delivery (for B

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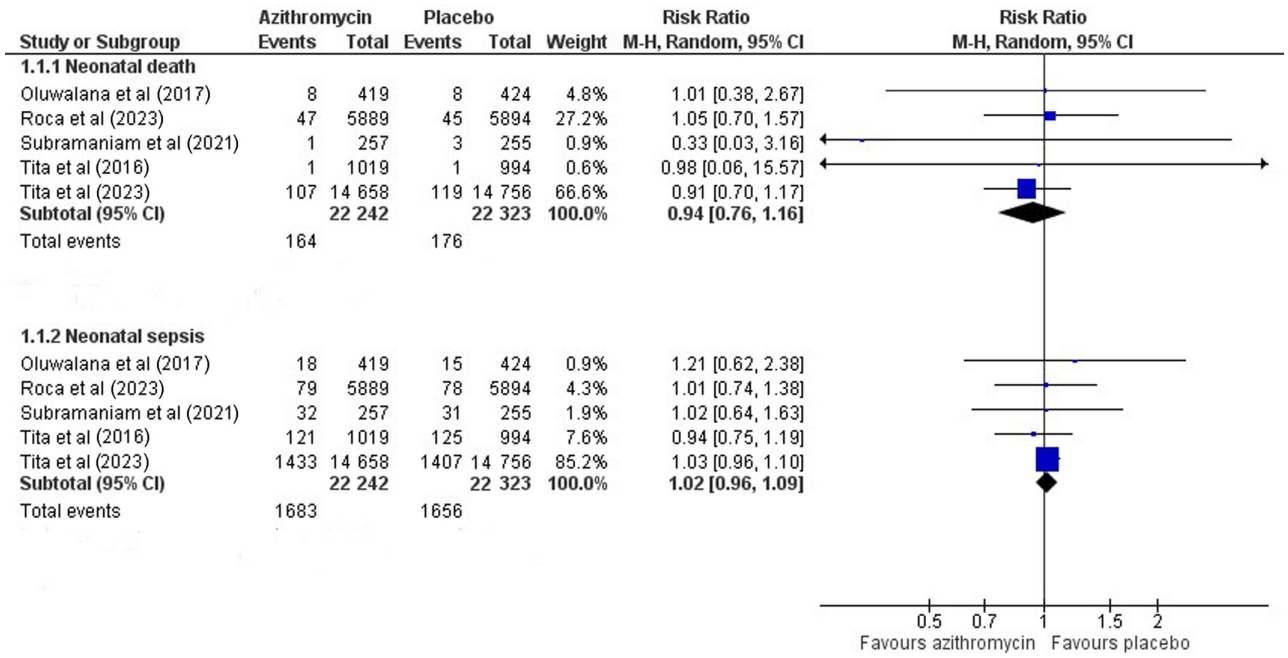

FIGURE 4 Forest plot of the main neonatal outcomes (neonatal death and neonatal sepsis). The random-effects Mantel–Haenszel method used to calculate risk ratios with 95% confidence intervals.

streptococcus, prolonged rupture of membranes, caesarean section) and the caesarean section rate varied between study populations, which causes heterogeneity of results. The included studies did not reveal any notable concern about acute adverse events for mothers in relation to azithromycin.

4.3 | Neonatal outcomes

Based on these findings the neonates did not benefit from maternal intrapartum azithromycin. Intrapartum antibiotics in women with carriage of B streptococcus have been shown to decrease the neonatal sepsis rates and are currently recommended in guidelines.[9,22] However, previous studies have shown that intrapartum antibiotics also may increase sepsis diagnoses due other pathogens.[23,24] Intrapartum antibiotics have been shown to affect offspring microbiota notably and these changes persist during infancy.[25–28] Retrospective register studies have associated intrapartum antibiotic exposure with increased odds of developing asthma, atopic dermatitis or allergic rhinitis, and a higher body mass index in childhood.[29–31] Furthermore, the ORACLE II trial found that the rate of any functional impairment at the age of 7 years was higher among children whose mothers were exposed to erythromycin before spontaneous preterm labour. Both erythromycin and amoxicillin-clavulanate acid were associated with increased rates of cerebral palsy.[32] A large register study found an association between macrolide use during pregnancy and childhood epilepsy and cerebral palsy. This was not seen for antibiotics other than macrolides.[33] Thus, it should be kept in mind that, although the results suggest a clear benefit of intrapartum azithromycin for maternal infections, the addition of azithromycin could impose potential long-term harm to neonates. However, this remains speculative, as there are no studies currently that would have assessed the intrapartum azithromycin and health in later childhood. A recent study from Burkina Faso analysed neonatal azithromycin exposure and early infancy growth up to 6 months, and found no evidence that azithromycin could reduce growth.[34] This study also concluded that single-dose azithromycin in neonatal period does not have an impact on infant mortality.[35] Azithromycin has been associated with increased odds of pyloric stenosis if administered within 14 days after birth, and thus the impact of intrapartum administration on pyloric stenosis should be analysed.[36,37] Two of the included studies did report pyloric stenosis rates but as it is such a rare outcome, these studies were underpowered to analyse it as an outcome.[11,12]

4.4 | Future research and implications to clinical practice

Currently these results are mostly adaptable to low-income settings, where the maternal infection burden is highest, and thus the benefits of azithromycin would be the highest as well. On the basis of our results, the adoption of azithromycin would reduce maternal infection burden and maternal sepsis rates in low-income countries. However, there are still many unanswered questions which need further assessment. Further studies should be conducted in different settings to make the results more generalisable. Although the largest trial included nearly 30 000 women, it was still underpowered to estimate the effect on maternal mortality. Furthermore, as maternal mortality was assessed in

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only three studies, this meta-analysis was not sufficient to provide a precise effect estimate on maternal mortality. Future studies are still needed to analyse rare outcomes. As in general, antibiotic stewardship is also needed for this indication, and future studies should aim to help identify which parturient groups would benefit most from azithromycin administration, for example, only focusing on non-elective caesarean sections. This would allow focusing of resources and would reduce the likelihood of azithromycin resistance. Furthermore, optimal dosing and the administration route also need to be addressed in the future. Four studies used the oral route, which seemed to be effective.

Based on these results, neonates are unlikely to benefit from maternal azithromycin. However, future studies should also assess neonatal outcomes as well long-term outcomes in these children, as intrapartum antibiotics have previously been recognised to affect the neonatal gut microbiome[25,26] and thus may have long-standing effects on child health.[38]

An interesting option would be to study the administration of azithromycin immediately after clamping of umbilical cord, as this would prevent exposure of the neonate; in theory, this would still provide maternal benefits as prophylaxis, but avoid the neonatal harms. Although previous evidence in caesarean sections has indicated it may not be equally effective against maternal infections, these studies were not conducted with azithromycin.[39]

4.5 | Strengths and limitations

The main strength of our systematic review and meta-analysis is the quality of the included studies, as four of the five studies were at low risk of bias and one study had some concerns only due to post-hoc reporting. Evidence quality was downgraded for the maternal death outcome due to imprecision, as the confidence intervals included both clear benefit and harm, which means that the current trials were underpowered to estimate such a rare outcome. However, although we also had confidence intervals that overlapped 1 in neonatal mortality and sepsis outcomes, we did not downgrade these due to imprecision, as the confidence interval margins were not that wide.[40] Furthermore, we feel rather confident that azithromycin does not reduce the rates of suspected neonatal sepsis cases or mortality. A further limitation is that only one of the included studies was designed to focus only on neonates as primary outcome, whereas the others mainly focused on mothers. We did have one protocol deviation, as initially we planned to perform subgroup analysis for outcomes by the delivery mode; however, the outcomes were not reported in enough detail in the original publications to enable completely assessment of these. This must be seen as a clear limitation, and this furthermore causes heterogeneity of our results and reduces the generalisability of our results in practice. The trials were mainly designed to analyse the effect of azithromycin in attempted vaginal deliveries, which should be noted when interpreting the results. We performed a sensitivity analysis by removing the study which only included caesarean deliveries, but this did not change the effect estimates notably. A further limitation was that the studies had notable imbalance in the sample sizes, and thus the results were dominated in the meta-analysis by the biggest trials. The studies were also conducted geographically in varying settings, which causes heterogeneity of the results. It should be noted, therefore, that these results may not be widely generalisable. We performed leave-one-out sensitivity analysis to control for this and the only estimate that changed was the maternal sepsis estimate. As stated already in this discussion, even with large studies being pooled together, there was still not enough data to detect meaningful changes in maternal chorioamnionitis and mortality outcomes.

5 | CONCLUSION

Intrapartum administration of azithromycin to the mother does reduce maternal postpartum infections in low-income countries. The impact on maternal mortality showed both clear benefit and substantial harm, and thus conclusions as to the effect of azithromycin on maternal mortality remains undecided. Azithromycin does not reduce neonatal adverse outcomes. Further studies are needed in different settings and countries to better estimate the implication of this finding in each region before introducing it into wider use.

AUTHOR CONTRIBUTIONS

IK and MR had the initial idea. IK and MR screened the search results. IK was incharge of the data-analysis. MR and MK participated in interpreting the results. IK wrote the initial draft. MK and MR commented and critically revised the manuscript. All authors have approved the final version to be submitted.

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FUNDING INFORMATION

None.

CONFLICT OF INTEREST STATEMENT

None to report.

DATA AVAILABILITY STATEMENT

All necessary data to replicate the analysis can be found in this article.

ETHICS APPROVAL

Not requires due to study design.

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