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Research Paper

A Systematic Review and meta-analysis of the effect of administration of azithromycin during pregnancy on perinatal and neonatal outcomes

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ABSTRACT

Background: Currently there are trials in Africa and Asia investigating whether prophylactic azithromycin during pregnancy reduces infection-related neonatal morbidity and mortality. We undertook a systematic review and meta-analysis to determine the effect of azithromycin during pregnancy on perinatal and neonatal outcomes.

Methods: We identified articles between January 1990 and 13th June 2021 by searching five electronic databases. Randomised control trials (RCTs) that included pregnant women administered azithromycin alone or in combination with other medications, and that reported outcomes of low birthweight (LBW), prematurity, stillbirth, and neonatal deaths, infections, and admissions, were eligible. Fixed effects meta-analyses were used for primary analysis. Quality appraisal was performed using Cochrane's Risk of Bias 2 tool. This review was registered with PROSPERO, CRD42019127099.

Findings: The search generated 5777 studies, of which 14 studies were included involving 17,594 participants. Most studies investigated azithromycin as Intermittent Preventive Treatment in Pregnancy (IPTp) for malaria. More than 50% of the studies had low risk of bias for all outcomes, except for LBW and neonatal admissions. Fixed-effects meta-analyses found that azithromycin reduced the risk of LBW (seven studies, Pooled RR 0·79; 95% CI 0·68-0·93; I^2 = 0·00%), and prematurity compared to controls (eight studies, Pooled RR 0·87; 95% CI 0·78-0·98; I^2 = 23·28%). There was no strong evidence of any effect on neonatal mortality, infections and admissions. There was an increase in stillbirth but the 95% CI crossed the null value (seven studies, Pooled RR 1·39; 95% CI 0·94 – 2.07; I^2=0·00%). However this review was limited by differences in the types of intervention and study populations, and inconsistency in outcome reporting between studies.

Interpretation: Prophylactic azithromycin during pregnancy reduces LBW and prematurity. However, as azithromycin has been investigated as part of IPTp, it is unclear whether it would improve perinatal and neonatal outcomes in non-malaria endemic settings. The potential harm on stillbirth rates needs further investigation.

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1. Introduction

Reducing perinatal and neonatal mortality is essential to improving child and maternal health globally. In 2019, 47% of all under-5 deaths worldwide occurred in the newborn period, [1,2] and in 2020 there were 1·9 million stillbirths [3]. Globally, neonatal infections cause approximately 21% of 2·4 million neonatal deaths each year [2,4]. Neonatal infections can be transmitted vertically, from mother to infant through the placenta or vagina during delivery, or horizontally, for example via close contact during breastfeeding. Vertical transmission of potentially pathogenic bacteria, including Group B Streptococcus (GBS), *Escherichia coli* and those associated with sexually transmitted infections (STIs), increases the risk of preterm delivery [5,6], early onset neonatal sepsis, and newborn death [7]. Infections, including syphilis, are amongst the most common causes of stillbirth worldwide, and there are much higher rates of stillbirth in low-income compared with high-income settings [8].

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Panel: Research in context

Evidence before this study

There is evidence on use of azithromycin during pregnancy for various indications including intermittent preventive treatment in pregnancy (IPTp) of malaria, treatment of sexually transmitted infections, and Caesarean section wound infection prophylaxis. However we found no systematic reviews synthesizing the results of these studies, particularly for neonatal outcomes such as prematurity, low birth weight (LBW), and neonatal infection, admission and mortality, although there have been systematic reviews and meta-analyses looking at macrolide prescribing during pregnancy and the risk of malformation, miscarriage, stillbirth and pyloric stenosis.

Added value of this study

This study showed that treatments containing azithromycin administered during pregnancy lowered the risk of LBW and prematurity compared to controls. However there was little evidence for these treatments on neonatal mortality, infections and admissions. Stillbirths was the only outcome for which the pooled effect estimate showed a potentially harmful effect of azithromycin, however the 95% CIs crossed the null value as the number of cases was small.

Implications of all the available evidence

Our findings showing a reduced risk of LBW and prematurity were largely from studies where azithromycin was used either alone, or in combination for IPTp in malaria, and therefore cannot be used to generally support use of azithromycin during pregnancy where malaria is not endemic. However, it may support recommending azithromycin combination treatments for IPTp in contexts where IPTp is implemented, and demonstrates the importance of further research in this area.

Azithromycin is an inexpensive, broad-spectrum macrolide antibiotic with bacteriostatic activity against many gram-positive and gram-negative bacteria [9]. Azithromycin has a prolonged half-life and high-sustained antibiotic levels in placental tissues [10], and is therefore potentially an ideal antibiotic to prevent and treat serious perinatal and neonatal infections. In pregnancy, it has been specifically used to treat STIs [11], as intermittent preventive treatment in pregnancy (IPTp) for malaria [12,13], and to prevent Caesarean section wound infections [14,15]. In 2015, an individual randomised control trial (RCT) in the Gambia found that a single-dose of oral azithromycin administered during labour reduced GBS, *Staphylococcus aureus* (SA) and *Streptococcus pneumoniae* (SPN) carriage, and also reduced maternal and infant infections up to two months post-delivery [16,17]. Additionally, a multi-country cluster RCT (cRCT) in Malawi, Niger, and Tanzania found that azithromycin reduced child mortality by 13·5% (95% CI 6·7 to 19·8) with the greatest effect in children aged 1 to 5 months [18]. This decrease in mortality was thought to be due to reductions in respiratory infections, diarrhoea, and malaria, because of azithromycin's action against SPN, gastrointestinal pathogens, and *Plasmodium falciparum* [18].

Given the potential for azithromycin administered during pregnancy to reduce important causes of perinatal and neonatal mortality, particularly in low and middle-income countries (LMICs), the aim of this systematic review and meta-analysis is to determine the effect of prophylactic administration of azithromycin during pregnancy on perinatal and neonatal outcomes, and explore whether the effect is dependent on the timing of administration during pregnancy.

2. Methods

2.1. Search strategy and selection criteria

For this systematic review with meta-analyses, studies were eligible if they included pregnant women of any gestation randomised to receive azithromycin, and collected data on perinatal and/or neonatal outcomes including neonatal deaths, stillbirths, admission to neonatal intensive or special care unit, neonatal infections, low birthweight (LBW), and/or prematurity. In addition, eligible studies that administered azithromycin alone or in combination with other medications, in any dosing regime, in any trimester of pregnancy including during labour and delivery were included. RCTs as well as cRCTs, published in English between 1990 to 13 June 2021 were included. To be eligible studies needed a comparison group of pregnant women who received no intervention, placebo, or an alternative treatment. Observational studies, qualitative studies, case reports, and reviews were excluded. Additionally, studies were excluded if the comparison treatment was another macrolide (eg. erythromycin).

Five electronic databases were searched including MEDLINE (including Cochrane Library), EMBASE, Emcare, Global Health, and Web of Science. Grey literature was searched, but restricted to using key terms on the .who domain, and clinical trial registration databases (ClinicalTrials.gov and International Clinical Trials Registry Platform) looking for trials relevant to this review at any stage of completion. For studies still recruiting, or where recruitment status was unclear, authors were contacted and requested to provide study results related to the systematic review's outcomes of interest. Reference lists in review articles identified during this search and the final included articles were checked to identify additional potentially eligible studies.

The search strategy contained terms related to the intervention, azithromycin and administration during pregnancy (see supplements 1 and 2 for full search strategy). This included terms related to common uses of azithromycin during pregnancy including IPTp and treatment of STIs. The search strategy also contained terms related to pregnancy, and related to neonates, perinatal mortality, LBW, and adverse events. This search was limited to studies in English only, and studies published between January 1990 and June 2021.

2.2. Data analysis

Two reviewers (MHN and AQ) screened articles independently, first by title and abstract, then by full-text, to determine eligibility for final inclusion. At each stage of screening any differences between reviewers were discussed, and a consensus decision for eligibility and inclusion was made for all articles. In cases where multiple publications were associated with the same RCT, a key paper for each RCT was selected, and then the other associated publications were used for supplementary information during the data extraction process. MHN performed data extraction from the final selection of articles using an extraction table. All data items were checked by a second reviewer (RR or AQ).

Quality appraisal was conducted using the Cochrane risk of bias (ROB) 2 tool for each full-text article [19]. Quality appraisal was supported where possible by supplementary documents including other papers from the same RCT, such as protocols and information from clinical trial registries. A separate risk of bias assessment was performed for every outcome reported by each individual study, as some of the signalling questions in the ROB 2 tool were specific to a single outcome [19].

Outcomes selected for pooled analyses differed based on timing of azithromycin administration in pregnancy for each study so as to account for the plausible biological effects of azithromycin treatment at different stages of pregnancy on neonatal outcomes. For studies where azithromycin was administered in any trimester throughout pregnancy, data were extracted for the outcomes of stillbirth, LBW, prematurity, and neonatal death, admission, and infection. Data extracted were raw frequencies of outcomes in neonates of mothers from the azithromycin group and in neonates of mothers from the control group for each outcome. Only data for stillbirth, and neonatal death, admission, and infection were extracted for studies where azithromycin was administered at delivery only, as azithromycin administered at this time is unlikely to have any effect on LBW and prematurity. For the outcome of neonatal admissions, studies either specified admissions to a Neonatal Intensive Care Unit (NICU) or baby unit or alternatively stated 'admissions'.

For the outcome of stillbirth, the denominator used was the total number of births reported by the study. The denominator for the outcomes of neonatal death, admission, and infection was the number of live births, and where possible this was the denominator used for the outcomes of LBW and prematurity. However, when studies did not measure these outcomes for all infants, the denominators used were those reported in the papers. For the two studies where there were three trial arms [12,20], only one control arm was included in the analysis and this was determined by the similarity in the frequency of dosing or medications co-administered, so as to minimise heterogeneity between treatment and control arms.

For all outcomes, risk ratios (RR) were used as the summary measure. The RR and 95% confidence intervals (CI) were calculated based on the extracted frequencies and denominators described earlier, with the RR being the ratio of azithromycin over control. Results were pooled using fixed effects meta-analysis using the Mantel-Haenszel method for primary analyses. For sensitivity analyses that included the cRCT, a random effects model using the REML estimator was used, which included the cluster-adjusted variance estimates from the cRCT. A random effects model was used to allow the true intervention effect to be different across the studies given that in the cRCT identified for final inclusion, the entire community was given azithromycin as part of STI prophylaxis as opposed to the individual randomised trials where the intervention was given to pregnant women only. For this reason cRCTs were excluded from primary analyses. Studies where there were no events in both arms for a specific outcome were excluded from the meta-analysis as per Cochrane handbook recommendations [21]. Heterogeneity of the pooled studies was assessed using both the test of homogeneity of study-specific effect sizes and the I^2 statistic, in addition to visual confirmation from forest plots. Negative I^2 values were treated as zero as per Higgins et al 2003 [22], and were interpreted in terms of heterogeneity between studies as per the Cochrane Handbook recommendations [21]. Subgroup analyses were conducted to explore the effect of treatment administered throughout trimesters of pregnancy compared to administered at delivery. Low and moderate risk of bias outcomes for studies were included in sensitivity analyses for all outcomes, excluding studies with outcomes assessed as having a 'high' risk of bias. cRCTs were included in subgroup analyses using reported effect estimates and CIs that accounted for the effect of clustering. All analyses were performed using Stata 16·0 [23]. For studies where there were no events in one arm Stata added a fixed value of 0·5 to all cells of the 2×2 table where this occurred when using the Mantel-Haenszel method [24].

This review is registered with PROSPERO, CRD42019127099. We followed PRISMA reporting guidelines [25].

2.3. Role of the funding source

There was no funding source for this study.

3. Results

The search identified 5777 articles, and an additional 26 articles were identified by checking references of papers identified during screening. After 2425 duplicates were removed, 3378 articles were screened with 3304 excluded at the title/abstract screening stage as they were not eligible. This left 74 full-text articles that were assessed for eligibility, 14 of which met criteria for final inclusion (Figure 1).

In total, there were 17,594 participants. The largest study included was a cRCT in which 3867 pregnant women received the intervention or control (Table 1) [26]. The largest RCT was a multi-country study involving 2891 participants [27], while the smallest had 60 participants [28]. Of the 14 eligible studies, two studies were undertaken in the United States of America [14,28], nine in Africa, [12,17,20,26,27,29-32] three in Asia or Oceania, two in Papua New Guinea [13,33], and one in India [15]. The follow-up period varied, with the longest being eight weeks after delivery [17]. Three studies recorded no follow-up after delivery [13,28,30].

The timing and frequency of azithromycin administration in pregnancy varied between studies. Six studies administered azithromycin as a once-off dose [14,15,17,26,28,32], most commonly given at delivery [14,15,17,28,32], but in one study this was given as a once-off dose at any gestation after enrolment [26]. The remaining eight studies administered azithromycin at different trimesters of pregnancy. [12,13,20,27,29-31,33] Seven studies gave either azithromycin or azithromycin-containing combinations for IPTp [12,13,20,27,29,30,33], with five studies giving azithromycin in combination with another antimalarial drug; three studies administered it with sulfadoxine-pyrimethamine [12,20,33], piperaquine [13], or chloroquine [27]. In five studies,[17,28-31] azithromycin was administered alone, and in three studies it was co-administered with an antibiotic for either caesarean section wound infection prophylaxis or empiric STI treatment [14,15,26]. For all studies in which azithromycin or azithromycin containing combinations were given for IPTp, the control group received sulfadoxine-pyrimethamine either alone or in combination with other antimalarial drugs. The other studies compared azithromycin to either placebo alone,[17,28,31,32] placebo co-administered with an antibiotic for peripartum or caesarean section wound infection prophylaxis [14,15,32], or to vitamins [26].

Eight of the nine studies in which azithromycin was given throughout pregnancy reported on outcomes related to prematurity, [13,20,26,27,29-31,33] and LBW (Table 2) [12,13,20,26,27,29,30,33]. For prematurity, half of these studies had a low risk of bias, [20,27,29,31] three had a high risk of bias [26,30,33], and one was assessed as having some concerns of bias [13]. Of those reporting on LBW, three had a high risk of bias [12,20,26], three had some concerns of bias [13,30,33], and two had a low risk of bias [27,29]. For neonatal deaths half of studies (five out of ten) and for stillbirth more than half of studies (five out of nine) were assessed as having low risk of bias (Tables 2 and 3). Eight studies reported on outcomes related to infections, with six studies reporting on overall frequency of neonatal infections [14,15,17,27,32,33], and two studies reporting on specific infections only [26,28]. These studies were not included in the quality appraisal as their outcomes (specific infections) were reported in a way that was not comparable with how infection was reported in the included studies in this review. For the remaining six articles, three had low risk of bias.

Studies where azithromycin was administered throughout any trimester of pregnancy were included in meta-analyses for LBW and prematurity. The pooled results from seven studies reporting on LBW favoured this intervention, demonstrating a 21% reduction in LBW (Pooled RR 0·79; 95% CI 0·68-0·93) with little evidence of heterogeneity between studies (I^2 = 0·00%, p-value = 0·79) (Figure 2). Similarly pooled results for prematurity favoured the intervention, showing a 13% decrease in prematurity in the azithromycin group compared to controls (8 studies; Pooled RR 0·87; 95% CI 0·78-0·98) with some

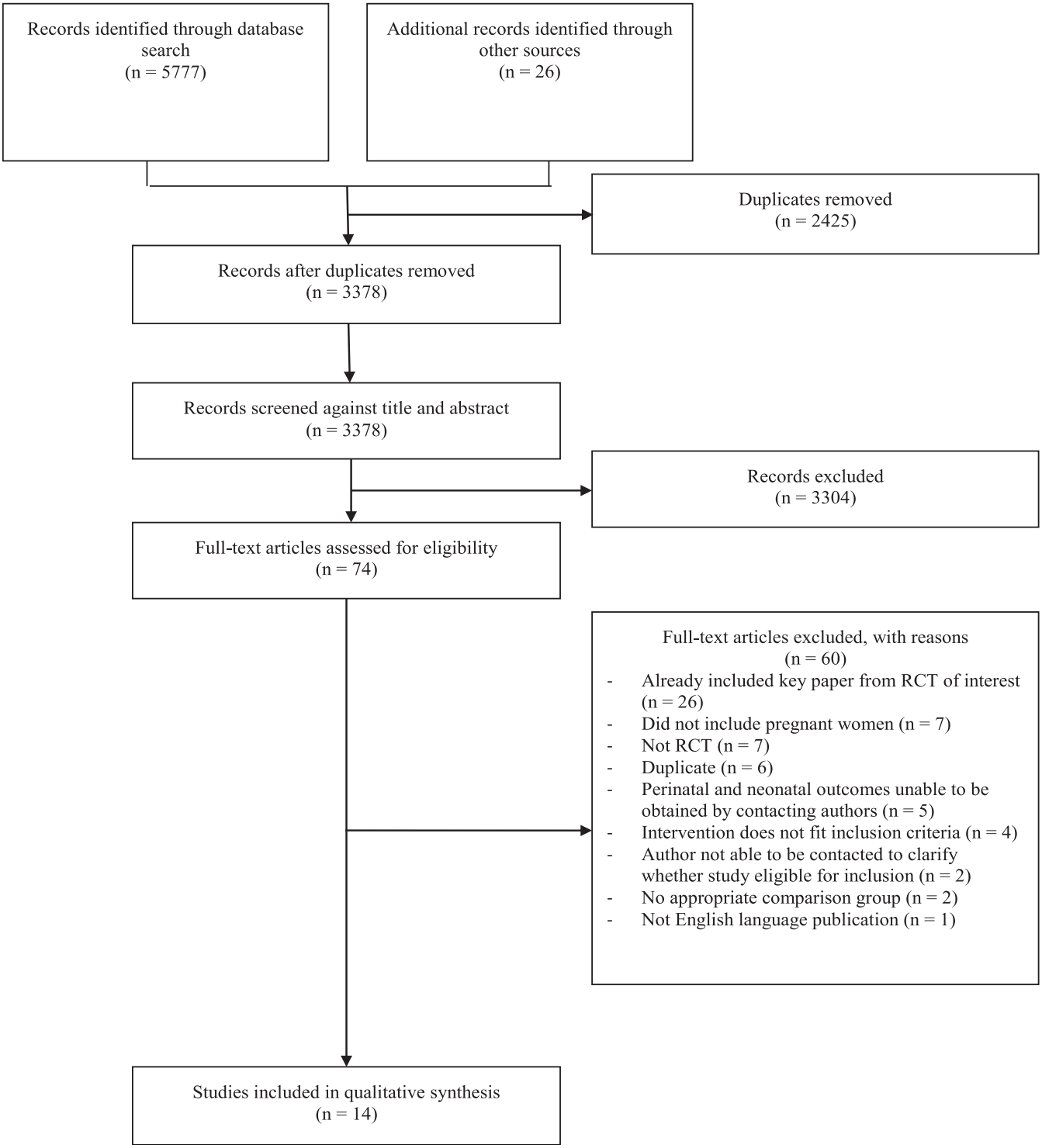

Figure 1. Flow chart of search results (adapted from PRISMA 2009 Flow Diagram). Moher et al. [25]

heterogeneity between studies (See Figure 3). The result for LBW remained robust when sensitivity analysis for bias was performed (Supplementary Figure S1), however the evidence for the effect of the intervention on prematurity became weak when studies with a high risk of bias were excluded (Pooled RR 0·95; 95% CI 0·82-1·10) (Supplementary Figure S3).

For outcomes of stillbirth, neonatal death, infection, and admissions, results from all studies were pooled, irrespective of when azithromycin was administered. Pooled results from seven studies showed an increased risk of stillbirth of 39% (Pooled RR 1·39; 95% CI 0·94 – 2.07) (Figure 4) when azithromycin was administered throughout pregnancy. However, the 95% CI crossed the null value. This was the only outcome for which azithromycin was shown to be potentially harmful, and in contrast, the intervention reduced the risk of neonatal deaths by 16% (Pooled RR 0·84; 95% CI 0·57-1·23) (Figure 5) albeit with weak evidence. The evidence for this effect on

Table 1
Study characteristics table for included individual and cluster RCTs

Author, year, study design	Country	Year(s)	Rural/ urban	Total no of participants	No of participants assigned to intervention, received intervention	No of participants assigned to receive control, received control	Comparison treatment	AZI dose, route of administration	AZI dosing schedule	Timing of dosing (weeks gestation)	Total no of courses	Follow-up period (post-partum)	Primary outcome	Loss to follow-up
Studies where AZI was given throughout trimesters of pregnancy														
Abdus-Salam 2016[29] RCT	Nigeria	Jan 2012-Sep 2012	Urban	200	100	100	SP: 3 tabs 500mg sulfadoxine & 25mg pyrimethamine per tab	500mg PO	OD for 3d	1st dose of SP or AZI given after foetal movement perceived in the 2nd T. Second dose 4w after 1st dose in SP group	2	None following delivery	To determine the occurrence of malaria infection – parasitaemia in the participants during pregnancy and at delivery; placental and cord blood malaria parasite of the newborn at delivery.	166/200 (83%) completed study, and 34/200 (17%) lost to FU. 86/100 (86%) in the SP group & 80/100 (80%) in AZI group completed the study.
Akinyotu 2019[30] RCT	Nigeria	Sep 2015- Aug 2016	Urban	123	Assigned: 70 Received: 60	Assigned: 70 Received: 63	SP 500mg/25mg	500mg, PO	OD for 3d	Given from enrolment & randomisation (gestational age of 16w or greater) as a monthly dose for 3m	3	None following delivery	Peripheral maternal malaria infection (microscopic) at delivery	123/140 (87•9%) completed study. 17/140 participants (12•1%) lost to FU.
Gray 2001[26] cRCT	Uganda	1994 - Jan 1998 (Trial discontinued)	Rural	Consented: 4036 Received 3867	Assigned: 2072 Received: 1962	Assigned: 1964 Received: 1905	Iron/folate & low-dose multivitamin*	1000mg PO (with cefixime 400mg, & metronidazole 2g)*	Once-only	Varying gestations (whenever time of enrolment & randomisation of cluster)	1	2w†	Incidence of HIV-1 infection	Post-partum visits achieved for 94·5% of mothers in intervention group and 92·7% in control group
Kalilani 2007[12] RCT	Malawi	Sep 2003- Sep 2004	Rural	141	1st dose: 47 2nd dose: 42	Two non-AZI groups: 1) SP Only: 1st dose: 47; 2nd dose: 40 2) SP & Artesunate: 1st dose: 47; 2nd dose: 39	1) SP: 3 tabs 500mg sulfadoxine & 25mg pyrimethamine per tab 2) SP & Artesunate: 200mg artesunate with 3 tabs SP	1g (with 3 tabs SP) PO	OD for 2d	1st dose at enrolment (between 14-26 weeks), second dose at least 4w after 1st dose	2	-1w & 4w visits -6m	1) To determine the tolerability of SP-artesunate & SP-azithromycin. 2) To compare the parasite clearance times & fever clearance times of SP, SP-artesunate, & SP-azithromycin.	118/141 (83·7%) completed FU. 23/141 lost to FU (16·3%). 38/47 in SP group; 42/47 in SP-Azithromycin group; 38/47 in SP-Artesunate group
Kimani 2016[27] RCT	Multi-country Sub-Saharan Africa (Benin, Kenya, Malawi, Tanzania, & Uganda)	Oct 2010-Nov 2013	Mostly urban	2891	1446	1445	1500/75mg SP	1000mg (with 620mg Chloroquine CQ), PO	3 courses of AZCQ at 4-8 week intervals: Each course - OD for 3d	-1st course 14-26w -Subsequent courses at 4-8w intervals -3rd course administered prior to or during 36w	3	Day 28 post- delivery (time window: day 28 to 42)	The primary endpoint was the proportion of participants with suboptimal pregnancy outcomes†	119/2891 (4·1%) lost to FU. 68/1446 in AZCQ group (4·7%), 51/1445 (3·5%) in SP group
Luntamo 2010[20] RCT	Malawi	Dec 2003-Oct 2006	Rural	1320	443	Two non-AZI groups: 1) SP Twice: 436 2) Monthly SP: 441	SP twice or Monthly SP SP: Three tabs each containing 500mg sulfadoxine and 25mg pyrimethamine	1g (in combination with monthly SP), PO	Twice during pregnancy	At enrolment visit & between 28-34w	2	1m	Incidence of preterm delivery	Data available for 99·7% of participants for length of gestation, and from 91% of birth weights within two days of delivery. Similar between groups (SP twice: 92%; monthly SP 89%; AZI-SP: 91%)
Moore 2019[13] RCT	PNG	Nov 2014- Mar 2016	Not stated	122	61	61	SP: 4,500 mg sulfadoxine & 225 mg pyrimethamine	1 g AZI (plus 960 mg PQ), PO	OD for 3d	On enrolment between 14-32w	1	After delivery	Evaluate the tolerability & prophylactic efficacy of AZI plus PQ in	92/122 (75·4%) had delivery outcome data. Equal in both groups (46/61).

(*continued on next page*)

Table 1 (*Continued*)

Author, year, study design	Country	Year(s)	Rural/ urban	Total no of participants	No of participants assigned to intervention, received intervention	No of participants assigned to receive control, received control	Comparison treatment	AZI dose, route of administration	AZI dosing schedule	Timing of dosing (weeks gestation)	Total no of courses	Follow-up period (post-partum)	Primary outcome	Loss to follow-up
													pregnant women in PNG	
Unger 2015[33] RCT	PNG	Nov 2009- Feb 2013	Mostly rural	2775[‡]	Assigned: 1393 Receiving: 1st Rx: 1370 2nd Rx: 1254 3rd Rx: 1034 4th Rx: 5	Assigned: 1382 Receiving: 1st Rx: 1365 2nd Rx: 1223 3rd Rx: 999 4th Rx: 2	SP (3 tabs, 500/25mg) & CQ (3 or 4 tabs of 150mg)	1g (with SP), PO	BD for 2d	At enrolment, then given monthly	3	Delivery & 4-6w	To compare efficacy of IPTp with SPAZ with a single treatment course of SPCQ to prevent LBW	2247/2775 (81·0%) had birth outcome information collected, & 2021/2775 (72·8%) had BW included in primary outcome analysis. 1013 BW analysed in intervention group, & 1008 birthweights analysed in control group
Van den Broek 2009[31] RCT	Malawi	Feb 2004- Sep 2005	Rural & peri-urban	2297	Assigned: 1149 Received: 1048	Assigned: 1148 Received: 1056	Placebo	1g, PO	Twice during pregnancy	16-24w, & 28-32w gestation	2	1w & 6w	Incidence of preterm delivery, defined as <37 weeks.	Primary outcome known for 2183 (95·0%). 1744 (75·9%) followed-up until 6w postpartum. 876/1149 assessed at 6w postnatally in AZI group, & 868/1148 in placebo group.
Studies where AZI was administered at delivery														
Jyothi 2019[15] RCT	India	Not stated.	Urban	200	100	100	Placebo IV normal saline (+ Cefazolin 2g IV)	500mg in 250mL of saline, IV (+ Cefazolin 2g IV)	Once-only	Given to woman undergoing elective or emergency caesarean section prior to skin incision	1	1w & 6w	Evaluating the effect of prophylaxis efficacy of azithromycin as an add on in routine cefazolin for caesarean deliveries for surgical site infections	All delivery outcomes for woman in both arms collected – no loss to FU
Ogasawara 1999[28] RCT	USA	Jun 1995-Jan 1996	Urban	60	32	27	Placebo[¶]	1g, PO	Once-only	Given when presenting for delivery with preterm labour or preterm premature rupture of membranes between 22 & 34w	1	None following delivery (included postpartum endometritis)	To determine if azithromycin is effective in reducing lower genital colonisation of *Ureaplasma urealyticum* in women with preterm labour or PPROM	Delivery information available on 54/60 (90%) patients. 3/27 (11%) in the control group & 2/32 (6%) in the intervention group were lost to FU.
Oluwalana 2017[17] RCT	Gambia	Apr 2013- Apr 2014	Peri-urban	829	414	415	Placebo	2g, PO	Once only	In labour	1	For 8w after delivery	Prevalence of SA, GBS, or SPN in NP swab sample of the newborn at day 6.	Outcome data available 828/829 (99·9%) -1 loss to FU in AZI group
Subramaniam 2021[32] RCT (abstract only)	Cameroon	2018-2020	NR	756	Arm 1 (AZI/Placebo): 253 Arm 2 (AZI/AMOX): 253	Arm 3 (Placebo/Placebo): 250	Arm 1&3: Placebo Arm 2: AMOX 2g PO All groups received 'usual care' including ABx given at provider discretion	1g PO	Once-only	During labour for those with prolonged labour >18 hrs or ROM >8 hrs	1	6w	Effectiveness of a single dose AZI ± AMOX vs placebo on composite maternal peripartum infection/death up to 6w postpartum.	6w follow-up for 739/756 (98%). Even across arms: 98% in Arm 1&2, 97% in Arm 3.
Tita 2016[14] RCT	USA	May 2011- Dec 2015	Mostly urban	2013	Assigned: 1019 Received: 1018	Assigned: 994 Received: 992	Saline placebo (IV) (+standard prophylaxis (cefazolin) according to	500mg in 250mL of saline, IV (+std prophylaxis)	Once only	Up to 1 hr before caesarean section incision	1	-6w postpartum visit. -Telephone contact at 3m to identify infant	Composite of endometritis, wound infection, or other infections	-Neonatal outcome data available for all patients at time of

(*continued on next page*)

Table 1 (*Continued*)

Author, year, study design	Country	Year(s)	Rural/ urban	Total no of participants	No of participants assigned to intervention, received intervention	No of participants assigned to receive control, received control	Comparison treatment	AZI dose, route of administration	AZI dosing schedule	Timing of dosing (weeks gestation)	Total no of courses	Follow-up period (post-partum)	Primary outcome	Loss to follow-up
							the protocol at each trial centre)					deaths & adverse events.	(abdominopelvic abscess, maternal sepsis, pelvic septic thrombophlebitis, pyelonephritis, pneumonia, or meningitis) occurring up to 6w after surgery.	hospital discharge -Postpartum FU within 6w available for 1961/ 2013 (97·4%) AZI group: 25 did not have 6w maternal FU, 54 did not have 3m child FU. In control: 27 did not have 6w maternal FU, 55 did not have 3m child FU

Antibiotic acronyms/abbreviations: ABx, Antibiotics; AMOX, Amoxycillin; AZI, Azithromycin; SP, Sulphadoxine-pyrimethamine; CQ, Chloroquine; PQ, Piperaquine; SPAZ, SP plus azithromycin
Route of administration abbreviations: PO, oral administration; IV, Intravenous
Microorganisms: GBS, Group B Streptococcus; SA, *Staphylococcus aureus*; SPN, *Streptococcus pneumoniae*
Other acronyms/abbreviations: BD, Twice daily; cRCT, cluster randomised controlled trial; d, days; FU, Follow-up; hr, hour; m, months; NP, nasopharyngeal; NR, not reported; OD, Once daily; PNG, Papua New Guinea; PPROM, preterm premature rupture of membranes; ROM, rupture of membranes; RCT, randomised controlled trial; std, standard; T, Trimester; USA, United States of America; w, weeks

* In intervention group: Women with positive syphilis serologic factors received intramuscular penicillin G benzathine (2·4 million IU). Control arm subjects with positive syphilis serology were offered their results in confidence and referred to government clinics for free treatment. Symptomatic control arm subjects were provided with syndromic STD treatment at the time of the survey.

† In addition, infants of HIV positive mothers received follow-up visits at 4-6 weeks of life for repeat blood samples

‡ A composite endpoint comprising live-borne neonates with low birth weight [<2,500 g], premature birth [<37 weeks], still birth [>28weeks], abortion [< or equal to 28 weeks], lost to follow-up prior to observation of pregnancy outcome, or missing birth weight.

§ 2793 women randomised and then 18 excluded due to incomplete consent forms, leaving 2775 in the intention-to-treat cohort at baseline.

¶ Note that all patients received intravenous ampicillin 2g every 6 hours until the GBS culture results were available as per institutional standard for preterm labour or PPROM.

Table 2
Summary of findings for effect of azithromycin administered throughout pregnancy on perinatal and neonatal outcomes

Author, Year	Outcome											
	Neonatal deaths				LBW				Prematurity			
	No in AZI	No in control	RR	RoB 2	No in AZI	No in control	RR	RoB 2	No in AZI	No in control	RR	RoB 2
Abdus-Salam 2016[29]	0/79	0/89	-	+	5/79	9/89	0·63 (0·22-1·79)†	+	13/79‡	9/89	1·63 (0·74-3·60)†	+
Akinyotu 2019[30]	NR				6/60	3/63	2·22 (0·53-9·32)	?	4/60	4/63	1·05 (0·25-4·42)	-
Gray 2001[26]	48/1888	51/1754	0·83 (0·71-0·97)*	-	131/1438§	136/1236	0·68 (0·53-0·86)*	-	141/1438¶	145/1228	0·77 (0·56-1·05)*	-
Kalilani 2007[12]	1/38	SP only: 4/37 SP & Artesunate 3/34	SP: 0·24 (0·03-2·08)†; SP & Artesunate: 0·30 (0·03-2·73)†	-	6/38	SP only: 8/37 SP & Artesunate: 6/34	SP: 0·73 (0·28-1·90)†; SP & Artesunate: 0·89 (0·32-2·51)†	-	NR			
Kimani 2016[27]	25/1140	22/1190	1·19 (0·67-2·09)†	-	57/1140‖	68/1190	0·88 (0·62-1·23)†	+	47/1140‖	45/1190	1·09 (0·73-1·63)†	+
Luntamo 2010[20]	NR				32/406**	SP twice: 52/402 Monthly SP: 36/394	SP twice: 0·61 (0·40-0·93) Monthly SP: 0·86 (0·55-1·36)	-	52/440**	SP twice: 78/435 Monthly SP: 68/441	SP twice: 0·66 (0·48-0·91) Monthly SP: 0·77 (0·55-1·07)	+
Moore 2019[13]	0/46‡	0/46	-	+	3/46‡	4/46	0·75 (0·18-3·17)†	?	7/46‡	10/46	0·70 (0·29-1·68)†	?
Unger 2015[33]	11/1098***	19/1096***	0·58 (0·28-1·21)†	?	130/1013	175/1008	0·74 (0·60-0·91)	?	44/668	69/652	0·62 (0·43-0·89)	-
van den Broek 2009[31]	NR				Not available – only a few women gave birth in facilities‡				184/1096	189/1087	0·97 (0·80-1·16)†	+

Author, Year	Outcome											
	Stillbirth				Admissions to NICU/Special baby unit				Neonatal Infections			
	No in AZI	No in control	RR	RoB 2	No in AZI	No in control	RR	RoB 2	No in AZI	No in control	RR	RoB 2
Abdus-Salam 2016	2/81****	0/89	-	+	2/79‡	2/89	1·13 (0·16-7·81)†	+	Data not collected‡			
Akinyotu 2019	NR				NR				NR			
Gray 2001	70/1993*****	50/1850	1.25 (0·70-1·83)*	-	No NICUs in this rural area of Uganda				Infant ocular gonorrhoea: 6/1022****** Infant ocular chlamydia: 6/1022 Infant gonorrhoea or chlamydia: 12/1022	Infant ocular gonorrhoea: 17/1008 Infant ocular chlamydia: 11/1008 Infant gonorrhoea or chlamydia: 28/1008	Infant ocular gonorrhoea: 0·34 (0·19-0·62)* Infant ocular chlamydia: 0·44 (0·18-1·10)* Infant gonorrhoea or chlamydia: 0·37 (0·20-0·70)*	
Kalilani 2007	0/42	SP only: 1/38 SP & Artesunate 4/38	0	-	NR				NR			
Kimani 2016	17/1164	17/1211	1·04 (0·53-2·03)†	+					32/1140*******	35/1190	0.95 (0·60-1.53)†	-
Luntamo 2010	NR				NR				NR			
Moore 2019	3/49‡	1/47	2·88 (0·31-26·69)†	+	0/46‡	2/46	0	-	Not available as study end-point time of delivery‡			
Unger 2015	25/1128	15/1119	1.65 (0.88-3.12)†	?	67/1098	61/1096	1·10 (0·78-1·54)†	?	37/1098********	42/1100	0·88 (0·57-1·36)†	?
van den Broek 2009	NR				No data collected‡				Data not collected‡			

Risk of bias (RoB) 2 symbols used: + low risk; ? some concerns; - high risk
Abbreviations/acronyms: AZI, Azithromycin; NICU, Neonatal Intensive Care Unit; NR, Not reported; SP, Sulphadoxine-pyrimethamine
* Cluster-adjusted RR
† Effect estimate calculated using STATA 15·0 (StataCorp LLC, Lakeway Drive College Station,TX, USA)
‡ Data provided by author
§ Based on proxy used in study for LBW – chest circumference <30 cm, and denominator those tested
¶ Based on Ballard score, and denominator those tested
‖ Numerator calculated from data in paper
** Denominator for birth weight excluded those who had birth weight not measured within two days of birth, and for BW & gestational age those who moved away
*** Denominator calculated by subtracting outcomes of miscarriage, stillbirth, and molar pregnancy from those with delivery information in each arm
**** Included stillbirths and intrauterine foetal deaths
***** Denominator used was pregnancies with postpartum follow-up
****** Denominator: n tested
******* Numerator taken from 'Total infections and infestations', including neonatal infection, pneumonia, and sepsis neonatal
******** Type of infections not specified

Table 3
Summary of findings for effect of azithromycin administered at delivery on perinatal and neonatal outcomes

Author, Year	Outcome															
	Neonatal deaths				Admissions to NICU/Special baby unit				Neonatal Infections				Stillbirth			
	No in AZI	No in control	RR	RoB 2	No in AZI	No in control	RR	RoB 2	No in AZI	No in control	RR	RoB 2	No in AZI	No in control	RR	RoB 2
Tita 2016[14]	1/1016	1/993	0•98 (0•06-15•60)[†]	+	171/1016	169/993	0•99 (0•81-1•20)[†]	?	120/1016[**]	124/993	0•95 (0•75-1•20)[†]	+	3/1019	1/994	2•93 (0•30-28•09)	?
Oluwalana 2017[17]	8/412	8/418	1•01 (0•38-2•68)[†]	+	Admissions to neonatal ward not reported.				76/412[†,***]	101/418	0•76 (0•59-0•99)[†]	+	7/419	6/424	1•18 (0•40-3•48)[†]	+
Jyothi 2019[15]	0/100	0/100	-	+	4/100	9/100	0•44 (0•14-1•40)[†]	+	5/100[****]	7/100	0•71 (0•23-2•18)[†]	+	0/100[*]	0/100[*]	-	+
Ogasawara 1999[28]	NR				NR				NR	"One case of GBS sepsis [in] a control patient"			NR			
Subramaniam 2021[32] (abstract only)	Arm 1 (AZI/Placebo): 1/253	Arm 3 (Placebo/Placebo): 3/250	Arm 1: 0.33 (0.03-3.15)[†]	-	NR				Arm 1 (AZI/Placebo): 18/253	Arm 3 (Placebo/Placebo): 18/250	Arm 1: 0.99 (0.53-1.85)[†]	-	NR			
	Arm 2 (AZI+AMOX): 3/253		Arm 2: 0.99 (0.20-4.85)[†]						Arm 2 (AZI+AMOX): 14/253[****]		Arm 2: 0.77 (0.39-1.51)[†]					

Abbreviations/acronyms: AMOX: Amoxycillin; AZI: Azithromycin; GBS: Group B Streptococcus; NR: Not reported
Risk of bias (RoB) 2 symbols used: + low risk; ? some concerns; - high risk
† Effect estimate calculated using STATA 15•0 (StataCorp LLC, Lakeway Drive College Station,TX, USA)
§ Taken from 'any infection' including skin infection, umbilical infection, conjunctivitis, otitis, oral infection, sepsis, meningitis, pneumonia
* Data provided by author
** Suspected neonatal sepsis (need for sepsis work-up)
*** Included all neonatal infections: Skin infection, umbilical infection, conjunctivitis, otitis, oral infection, clinical sepsis, meningitis, and pneumonia
**** Neonatal sepsis

neonatal deaths was increased when Gray 2001, a cRCT, was included in the analysis (Pooled RR 0·83; 95% CI 0·72-0·96) (Supplementary Figure S7). The intervention also reduced the overall risk of infection by 12% (Pooled RR 0·88; 95% CI 0·76-1·02) (Figure 6), however there was no reduction in risk of neonatal admission (Pooled RR 0·99; 95% CI 0·84-1·17) (Supplementary Figure S13). Based on I^2 there was little evidence of variability between studies due to heterogeneity rather than random error for all these outcomes. Results for outcomes of stillbirth, neonatal infections and admissions were robust with sensitivity analysis for bias, and subgroup analyses did not find any additional benefit in administering azithromycin throughout pregnancy compared to only at delivery for these outcomes (See Supplementary Figures S8-S15).

4. Discussion

Our systematic review and meta-analyses found supportive evidence that azithromycin administered during pregnancy reduces LBW and prematurity, although the evidence for preventing prematurity was weak when studies with a high risk of bias were excluded. We did not find any reduction in neonatal deaths, infections, or admissions. Subgroup analyses did not find any strong evidence for an additional benefit in administering azithromycin throughout pregnancy compared to only at delivery for these outcomes. The meta-analysis for stillbirths was the only outcome for which the pooled effect estimate showed a potentially harmful effect of azithromycin, however this crossed the null value which may have been due to the small number of cases included in this analysis.

A limitation of our findings was that many of the included studies used azithromycin in combination with other anti-malarial agents and compared this to IPTp regimes using alternative drugs, making it difficult to determine whether our findings were due to azithromycin alone. This is particularly challenging given that there is evidence that sulfadoxine-pyrimethamine has non-malarial effects on pregnancy outcomes such as birthweight [34] Furthermore, as malaria is associated with preterm birth and LBW [35,36], these pooled results may be attributed to azithromycin's effect on malaria, making it difficult to extrapolate to malaria non-endemic areas. However, the majority of included studies in this review found no difference in either peripheral and/or placental malaria parasitaemia at delivery between azithromycin and control groups suggesting the effects of the study were unlikely to be due to anti-malarial effects, [12,13,20,29-31] with the exception of two studies that showed decreased parasitaemia in the azithromycin group. One of these studies had increased frequency of IPTp administration in the intervention group compared to controls, which may explain this finding, and the other study found this effect at 36-38 weeks gestation so this is unlikely to be relevant to the outcomes of LBW and prematurity. The additional benefits of azithromycin combination treatments for IPTp compared to alternatives on LBW and prematurity suggested by this review may support recommending this intervention in malaria endemic areas, although this also needs to be considered in terms of cost implications, and bacterial resistance patterns.

Another explanation for azithromycin reducing LBW and prematurity, is that azithromycin is effective against the common bacteria causing STIs. STIs increase the likelihood of these LBW and prematurity [37]. However the three included studies that compared the prevalence of STIs between intervention groups found inconclusive results. Two studies found decreased *Neisseria gonorrhoeae* rates in the azithromycin group [27,33], but neither of the two studies reporting on *Chlamydia trachomatis* rates found a difference between treatment arms [20,27]. These results suggest that azithromycin may reduce the risk of LBW and prematurity through pathways other than treatment of malarial and reproductive tract infections. In LMICs, these infections may be key causes of inflammation in pregnancy, which is an independent risk factor for small-for-gestational

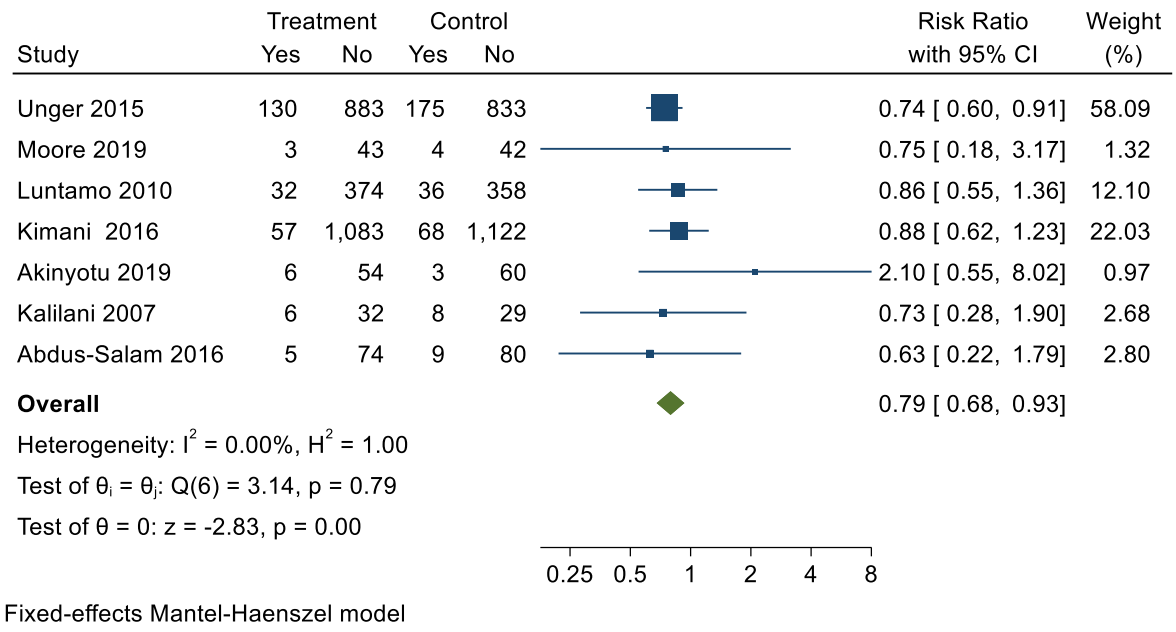

Figure 2. Risk ratio of the effect of azithromycin compared to control on LBW for studies where azithromycin was administered throughout trimesters of pregnancy

age and premature birth [38,39], potentially through dysregulation of placental angiogenesis [40]. In addition to anti-bacterial properties, azithromycin also has immunomodulatory effects [41], with a recent study showing that women treated with ITPp containing azithromycin had lower inflammatory markers at delivery, suggesting that this intervention may reduce inflammation and thereby improve pregnancy outcomes such as LBW and prematurity [40].

Although we did not find any strong evidence for a beneficial effect of azithromycin on neonatal infection, admission, or neonatal death, it is important to consider that because many of the included studies were not designed to specifically record these outcomes, and neonatal death was a rare event, and this may have affected our findings. Of note when additional results from the cRCT were included in the meta-analysis a small benefit for neonatal deaths was demonstrated. Furthermore there are biologically plausible mechanisms for how azithromycin may improve these outcomes. Preterm birth and LBW are risk factors for neonatal sepsis [42], and therefore reducing these outcomes may indirectly reduce neonatal infections,

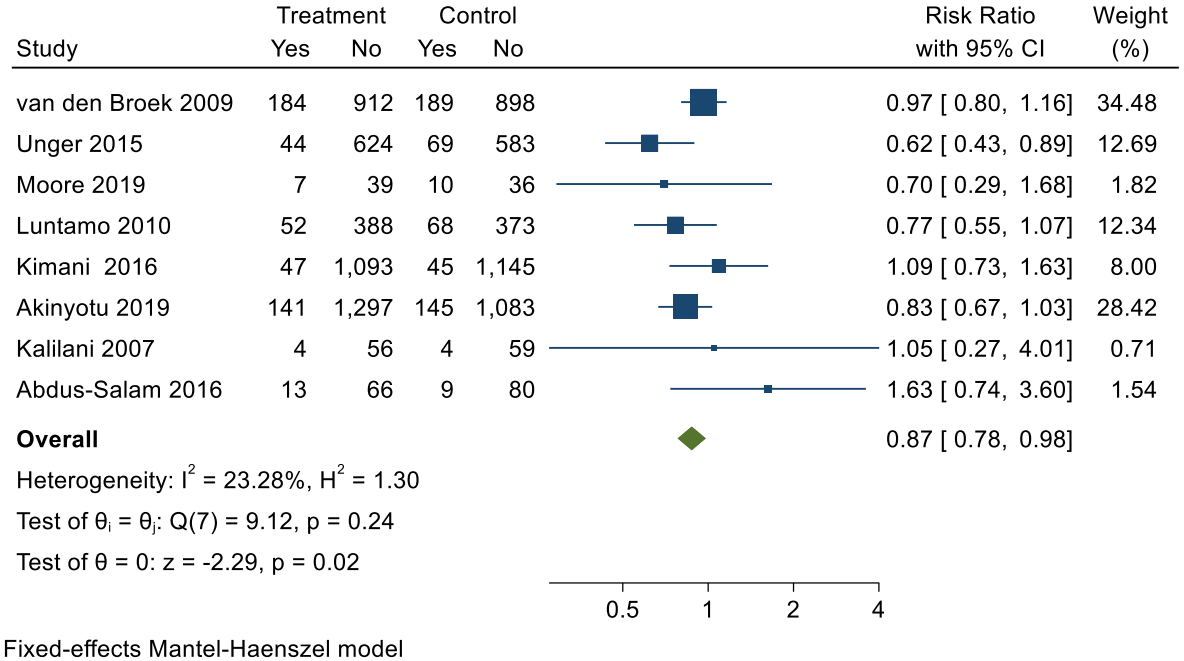

Figure 3. Risk ratio of the effect of azithromycin compared to control on prematurity for studies in which azithromycin was administered throughout trimesters of pregnancy

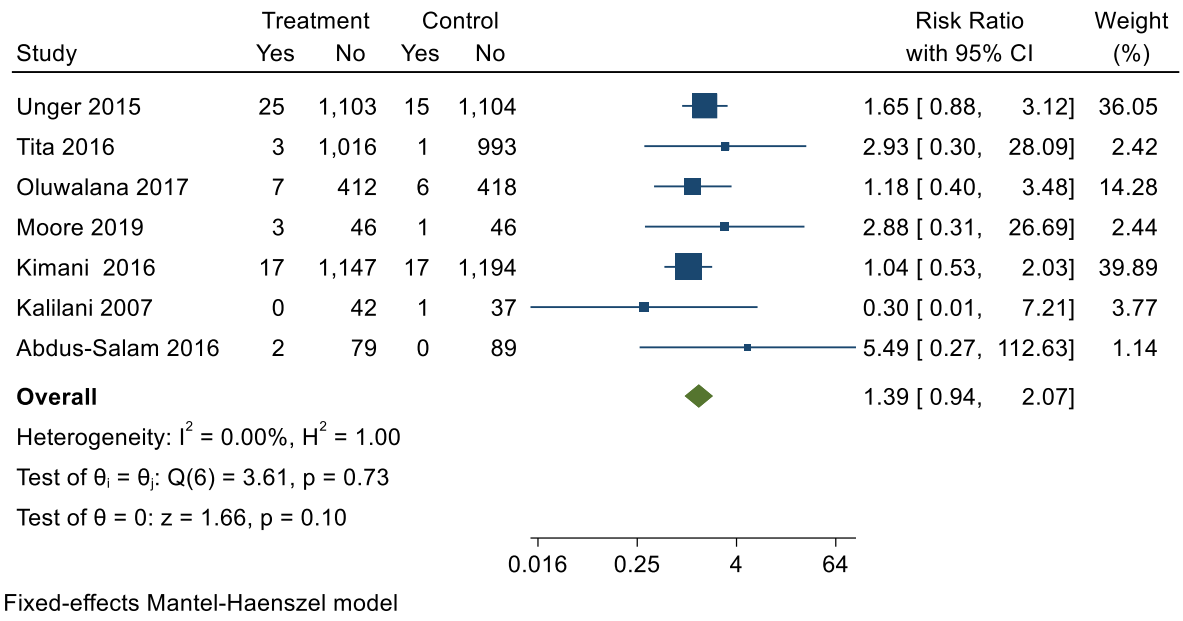

Figure 4. Risk ratio of the effect of azithromycin administered at any time throughout trimesters of pregnancy and/or at delivery compared to control on stillbirths

admissions and deaths. The antimicrobial activity of azithromycin also may have direct impact on reductions in neonatal infections, and therefore admissions and deaths, through disruption of vertical transmission of pathogenic organisms. This includes common organisms causing chorioamnionitis such as *Ureaplasma urealyticum* and GBS that are susceptible to macrolides, and STIs causing neonatal conjunctivitis and pneumonia like *Chlamydia trachomatis*.

Prevention of vertical transmission may be maximised when azithromycin is administered at delivery as opposed to during pregnancy, to avoid reinfection with STIs or recolonization of the vaginal tract occurring prior to delivery. Only three of the included studies administered azithromycin during delivery [14,15,17], and two of these studies looked at this in the context of caesarean section wound prophylaxis [14,15]. Infants born to mothers undergoing caesarean section may not be exposed to potential pathogens in the vaginal tract, and this may reduce the benefit of azithromycin in this group in comparison to those delivering vaginally. This is supported by results from one of the studies where azithromycin was administered during delivery, where 98-99% of participants had a vaginal delivery and there was a 13% decrease in infant infections in the azithromycin group compared to controls [17].

We found a potentially harmful effect of azithromycin on stillbirth, although this was a rare event and the confidence intervals contained the null value, and therefore our results are inconclusive. Lack of comparability in the definition of stillbirth used may have contributed to this effect, as some studies used a lower gestational age cut-off for defining stillbirth than the WHO definition [13,33,8]. Consequently some fetal deaths may have been reported as stillbirths

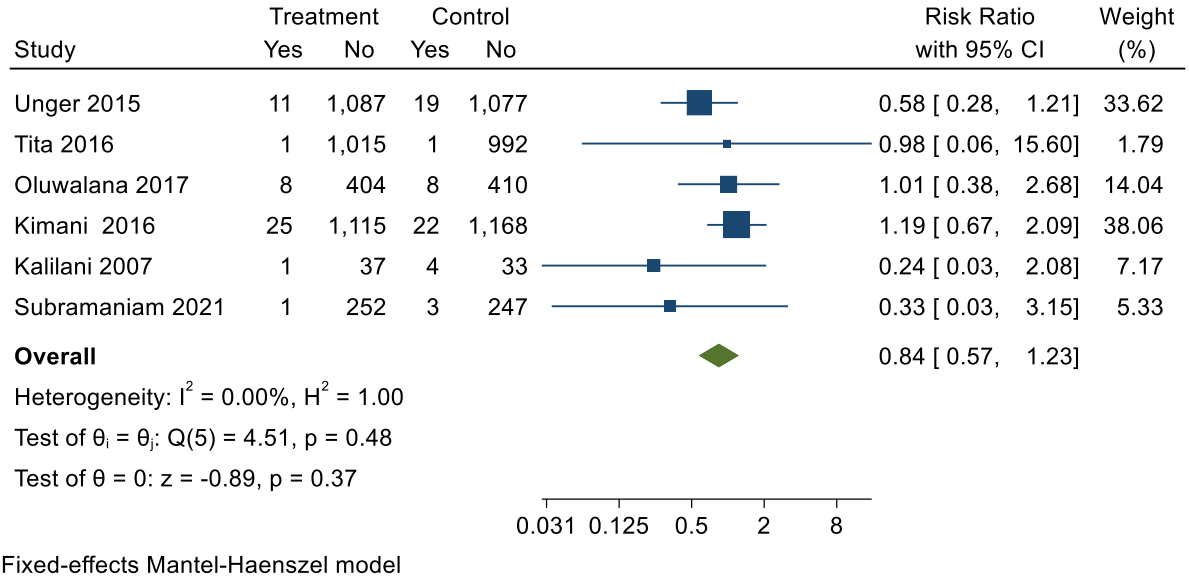

Figure 5. Risk ratio of the effect of azithromycin administered at any time throughout trimesters of pregnancy and/or at delivery compared to control on neonatal deaths

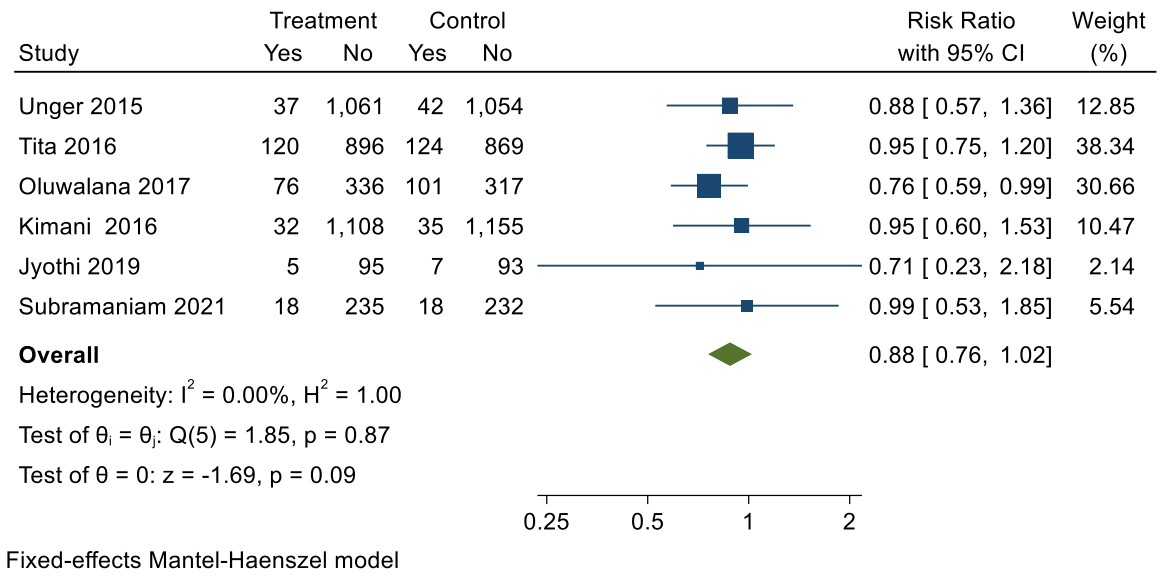

Figure 6. Risk ratio of the effect of azithromycin administered at any time throughout trimesters of pregnancy and/or at delivery compared to control on neonatal infections

that would have met the WHO definition of miscarriage. This may be particularly important as a recent systematic review found that macrolides administered during pregnancy were associated with an increased risk of miscarriage and gastrointestinal malformations compared to other antibiotics, but found no evidence of an adverse effect on other malformations, stillbirth or neonatal death [43]. A subsequent large cohort study observed that prescriptions of macrolides during the first trimester were associated with an increased risk of major malformations compared with penicillin [44]. However, this study did not report on stillbirths and did not perform specific subanalyses for azithromycin because of few events. The authors hypothesized that macrolides may lead to fetal cardiac arrhythmia and short term fetal hypoxia, based on animal models, and that this could be associated with malformations associated with short term fetal hypoxia [44]. Other systematic reviews looking at perinatal macrolide use found an increased risk of pyloric stenosis in infants but these studies did not report on other perinatal or neonatal outcomes [45,46]. Given that major congenital malformations are associated with an increased risk of stillbirth [47], it cannot be excluded that azithromycin may be associated with stillbirth, and further research is required in this area.

A strength of this systematic review was that it used a comprehensive search strategy, particularly for specific possible uses of azithromycin in pregnancy, including for IPTp and treatment of STIs. However, this systematic review was limited by the lack of literature on this topic, such that subgroup analyses were unable to be performed for certain important intervention and contextual characteristics including dosing regimen during pregnancy and geographical setting. In particular, as IPTp was a common reason for azithromycin use during pregnancy, it may be beneficial in future to examine the impact of malaria burden on the effect of IPTp on neonatal outcomes. Variation in dosing regimes of azithromycin in the included studies made it difficult to assess any dose-related effects as azithromycin's immunomodulatory effects and its potential effect on LBW and prematurity when administered throughout pregnancy may be dose-related [48]. Reporting of follow-up period differed between studies, with some studies reporting no follow-up after delivery, and therefore could not fulfil the WHO definition of neonatal mortality [49].

While our review found that azithromycin administered during pregnancy reduces LBW and prematurity, most evidence was from studies of IPTp in malaria, limiting support for recommendations of azithromycin use in pregnancy to improve maternal and neonatal outcomes beyond malaria endemic areas. There are at least four clinical trials underway that will involve almost 150,000 participants in total [50-53], that are investigating the effectiveness of azithromycin given during pregnancy and labour on stillbirth, maternal and neonatal infection and neonatal mortality. These studies may provide further evidence to guide future recommendations about preventative use of azithromycin during pregnancy in low and middle-income settings.

5. Contributors

MHN performed the search, and was the first reviewer for article screening, and for data extraction and quality appraisal. AQ was the second reviewer for article screening, and for some data extraction and quality appraisal. RR was the main second reviewer for data extraction and quality appraisal. This extracted data was used for meta-analyses performed, and MHN was responsible for this data that was used to perform the statistical analysis and wrote the first draft of the manuscript with input from FR and AS. CN reviewed the manuscript and gave input on the statistical analysis, including having access to summarised data from included studies used for meta-analyses. All authors provided input on the writing of the manuscript.

Data Sharing statement

All data used for the study has been included in the manuscript and supplementary material.

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None

Declaration of Competing Interest

MHN's PhD stipend is funded by MCRI. All other authors declare no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2021.101123.

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