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Antenatal interventions to reduce risk of low birth weight related to maternal infections during pregnancy

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A B S T R A C T

Background: Maternal infections during pregnancy have been linked to increased risk of adverse birth outcomes, including low birth weight (LBW), preterm birth (PTB), small for gestational age (SGA), and stillbirth (SB).

Objectives: The purpose of this article was to summarize evidence from published literature on the effect of key interventions targeting maternal infections on adverse birth outcomes.

Methods: We searched MEDLINE, Embase, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and CINAHL Complete between March 2020 and May 2020 with an update to cover until August 2022. We included randomized controlled trials (RCTs) and reviews of RCTs of 15 antenatal interventions for pregnant women reporting LBW, PTB, SGA, or SB as outcomes.

Results: Of the 15 reviewed interventions, the administration of 3 or more doses of intermittent preventive treatment in pregnancy with sulphadoxine–pyrimethamine [IPTp-SP; RR: 0.80 (95% CI: 0.69, 0.94)] can reduce risk of LBW compared with 2 doses. The provision of insecticide-treated bed nets, periodontal treatment, and screening and treatment of asymptomatic bacteriuria may reduce risk of LBW. Maternal viral influenza vaccination, treatment of bacterial vaginosis, intermittent preventive treatment with dihydroartemisinin–piperaquine compared with IPTp-SP, and intermittent screening and treatment of malaria during pregnancy compared with IPTp were deemed unlikely to reduce the prevalence of adverse birth outcomes.

Conclusions: At present, there is limited evidence from RCTs available for some potentially relevant interventions targeting maternal infections, which could be prioritized for future research.

Keywords: low birth weight, preterm birth, small for gestational age, stillbirth, antenatal care, pregnancy, maternal infections, low- and middle-income countries

Introduction

Low birth weight (LBW) is a major public health problem associated with increased neonatal and childhood mortality, morbidity, developmental delays, long-term disability, and chronic health conditions in adulthood. Globally, an estimated 15% of all births, or over 20 million newborns annually have LBW, i.e., birth weight of <2500 g. LBW results from either preterm birth (PTB, birth at <37 wk completed gestation) or fetal growth restriction, often resulting in a small for gestational age infant (SGA, less than the 10th centile of weight to gestational age), or both. The highest proportion of LBW births occurs in low- and middle-income countries (LMICs) [1,2]. Reduction of LBW is considered a public health priority, and the international community has adopted a global target of 30% reduction in the number of babies born with LBW between 2010 and 2025 [3].

Abbreviations: ANC, antenatal care; ASB, asymptomatic bacteriuria; BV, bacterial vaginosis; DP, dihydroartemisinin–piperaquine; ES, effect size; Hib, *Haemophilus influenzae* type b; HIC, high-income country; IPTp, intermittent preventive treatment in pregnancy; IST, intermittent screening and treatment; ITN, insecticide-treated bed nets; LBW, low birth weight; LMIC, low- and middle-income countries; PTB, preterm birth; RCT, randomized controlled trial; SB, stillbirth; SGA, small for gestational age; STI, sexually transmitted infection; SP, sulphadoxine–pyrimethamine; SRMA, systematic review and meta-analysis; TB, tuberculosis.

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There are several known risk factors for LBW. Maternal infections, alongside maternal nutritional issues, remain major risk factors for LBW and related adverse birth outcomes [4,5]. Bacterial, viral, parasitic, and fungal infections can lead to LBW either by infecting the fetus (vertical transmission) or by compromising the health of the pregnant woman. Vertical transmission during pregnancy occurs when the pathogen either crosses the placental barrier or ascends the cervix, infecting and sometimes breaching the fetal membranes. Infections that threaten pregnancy by compromising maternal health include malaria, respiratory viruses, bacterial sepsis, and systemic inflammation, which can be caused by local infections, such as urogenital infections and periodontal disease [6]. Although it is uncertain whether changes that occur to the immune system during pregnancy result in increased susceptibility to infection, there is evidence that the duration and severity of certain illnesses is increased with influenza being the most documented example [7]. There is considerable evidence that maternal infections contribute to a high prevalence of LBW. In 2019, it was estimated from 33 moderate-to-high transmission countries in Africa that 12 million pregnant women were infected with malaria resulting in 822,000 LBW infants [8]. Therefore, maternal infections constitute a significant public health and economic burden [9,10] that requires comprehensive prevention strategies to effectively address the high prevalence of both infection and LBW, particularly in LMICs.

Over the years, several strategies to prevent maternal and neonatal infections before, during, and after pregnancy have been implemented globally. Currently, the WHO recommends malaria preventive chemotherapy, tetanus vaccination, HIV screening and management with antiretroviral therapy, screening and treatment of syphilis, asymptomatic bacteriuria (ASB), urinary tract infections, and tuberculosis (TB) to prevent maternal and neonatal infection. However, it is not known whether some of these interventions also reduce the prevalence of LBW and related outcomes. Therefore, it is important to evaluate whether there is any emerging evidence on the protective effect on pregnancy and birth outcomes for established interventions. Screening and treatment of bacterial vaginosis (BV), chlamydia, gonorrhea, trichomonas, and other STI is not currently recommended but may have the potential to reduce LBW [11]. Due to the size of the global burden of LBW, any intervention with proven efficacy has the potential for impact. Addressing infections during pregnancy is considered a feasible strategy to reduce LBW. There is, however, a lack of reviews that would concomitantly summarize evidence from multiple infection control and prevention interventions during pregnancy. This poses a challenge because it is important to have an overview of the evidence regarding what does or does not reduce LBW to inform planning for improved antenatal care (ANC). Hence, this review aimed to summarize evidence from randomized controlled trials (RCTs) of interventions targeting maternal infections during pregnancy to report the evidence of their effect on reducing risk of LBW, PTB, SGA, and stillbirth (SB).

Methods

This work was part of a larger evidence synthesis that aimed to determine whether some ANC interventions to prevent LBW could be done differently or in addition to what is currently recommended. The interventions were selected as part of a prioritization exercise by an international group of experts working in maternal and child health in low- and middle-income countries (LMIC) [12]. The current review reports 15 antenatal interventions out of 46, targeting infections during pregnancy and their effect on adverse birth outcomes. Interventions related to maternal nutrition, psychosocial interventions, and environmental exposures, and the full list of the 46 reviewed interventions are reported elsewhere in this supplement [12–15].

For the literature search, study selection, and evidence synthesis, we used a recently described novel method, the modular review, that allows concomitant review of multiple interventions [16]. The modular review consists of a streamlined process to evaluate, synthesize, summarize, and categorize evidence optimized to inform decision making, policy making, and program planning. The modular review methodology allowed us a landscape view of the efficacy of several interventions on adverse birth outcomes concurrently and provided statements related to the likelihood that the intervention improves birth outcomes in at least some contexts. Although the design of the method, particularly its ability to review multiple interventions simultaneously, precluded the registration of the study in prospective registers of systematic reviews of single interventions, an a priori protocol was used, and the method was published in detail [16].

Full details of the method are provided in the **Supplementary Methods**. In brief, we performed 8 systematic searches in MEDLINE (OvidSP), Embase (OvidSP), Cochrane Database of Systematic Reviews (Wiley Cochrane Library), Cochrane Central Register of Controlled Trials (Wiley Cochrane Library), and CINAHL Complete (EbscoHOST) between 3 March, 2020 and 27 March, 2020 without language or time limitations.

We included English language studies that were relevant to population, intervention, study design, and outcomes. The population of interest was pregnant females, irrespective of gestational age. The interventions were selected by a panel of experts in global maternal and newborn health based on their ability or potential to address maternal infections that contribute to a high burden of adverse birth outcomes as well as maternal and neonatal mortality, particularly in low resource settings (Table 1) [17–33]. Association studies show increased rates of LBW and PTB from maternal infections such as malaria, urinary tract infections, and periodontal diseases [34–36]. Some of the interventions are already recommended in WHO ANC guidelines [11] based on their reduction of the incidence of maternal disease and perinatal transmission; this review sought to summarize evidence on their impact on adverse birth outcomes to recommend prioritization and scale up of these interventions. The detailed definitions of interventions and search terms are listed in Supplementary Data 1–15.

As study designs, we included RCTs and reviews of RCTs. The included studies had to report at least one of the following outcomes: LBW, PTB, SGA, or SB. Although LBW was the starting point of our project, PTB and SGA indicate the 2 main pathways that lead to it, and SB is an extreme outcome that often results from the same processes that limit fetal growth or shorten the duration of pregnancy. Thus, all 4 outcomes can be partially attributed to the same antecedents [37].

For each intervention, we sought the best estimate of the effect size (ES) from the included studies. ES documents consisted of the most recent quantitative evidence, with reviews of reviews (umbrella reviews, meta-reviews, reviews of (systematic) reviews) constituting the highest level of evidence. The next level consisted of reviews from the Cochrane collaboration followed by high-quality systematic reviews with or without meta-analyses. If there were no reviews available, we used peer-reviewed published RCTs to estimate the combined ES. Statistical analyses were conducted using Meta-essentials [38] and R version 3.4.4. The graphs in the supplementary information were created with "forestplot" package [39]. In addition to identifying the latest reviews as ES documents, we identified RCTs published after the

TABLE 1
Reviewed interventions, risk factors, prevalence, and mechanism to address the risk

Intervention	Risk factor	Prevalence of the risk factor in LMIC	Assumed mechanism of action for the intervention
Malaria in pregnancy			
Provision of insecticide-treated bed nets in pregnancy	Malaria	Approximately 35% (11.6 million) pregnancies were exposed to malaria infection in SSA in 2019 [8].	Insecticide-treated nets are used as a personal protective barrier against malaria infection in communities living in malaria-endemic areas. Insecticides such as pyrroles and pyrethroids that are used for treating bed nets prevent entry into the house and repel or kill malaria-spreading mosquitoes when they come into contact with the nets [17].
Intermittent preventive treatment (IPTp)	Malaria		Intermittent preventive treatment (IPTp) refers to the administration of an antimalarial drug at routine ANC visits during pregnancy—regardless of whether the woman is infected with malaria. IPTp with sulphadoxine—pyrimethamine (SP) is currently recommended by the WHO and used in malaria prevention programs.Pregnant women are vulnerable to malaria infections and their consequences such as anemia. SP clears or suppresses existing malaria infections in the placental and peripheral blood of pregnant women and provides a prophylactic effect by preventing new infections for several weeks after each dose. Additionally, SP also acts as a broad-spectrum antibiotic effective against other infections such as STIs, which are prevalent in malaria-endemic areas, and may also resolve these infections consequently improving adverse birth outcomes [18].Due to parasite resistance, different types of antimalarial drugs such as dihydroartemisinin–piperaquine, amodiaquine, mefloquine, and chloroquine–azithromycin have been tested as potential alternatives to IPTp-SP [19].
Respiratory infections			
Influenza virus vaccination	Viral influenza	The incidence of laboratory confirmed influenza ranged between 0.10 and 486 per 10,000 pregnant women (all HICs) [20].	Maternal influenza vaccination involves vaccinating pregnant women with an inactivated virus early in pregnancy to maximize the maternal antibody response and passive antibody transfer to the growing fetus. Maternal vaccination thus decreases the onset and severity of influenza in both pregnant women and their infants [21].
Haemophilus influenzae type b (Hib) vaccination	Bacterial influenza	The incidence of invasive Hib reported as 2.98/100,000 woman-years) in a HIC setting [22]. Global incidence of 142 (130–232) cases of Hib disease per 100,000 children (1–59 mo) in 2015 [23].	Pregnant women and infants have an increased risk of acquiring influenza infections. Vaccinating pregnant women with bacterial vaccine in early pregnancy protects both pregnant women and infants by passive antibody transfer to the growing fetus. Maternal vaccination thus decreases the onset and severity of influenza in both pregnant women and their infants [52].
Screening of Tuberculosis (TB)	TB	Globally, 21 (18–24) cases of active TB per 1000 pregnant women (2011) [25].	Untreated TB or TB-treated late may cause severe consequences to pregnant women and infants. Antenatal care presents a good opportunity to screen and treat women found to be TB positive, thus preventing associated obstetric complications [25].
Maternal genitourinary infections and sexually transmitted infections			
Screening and treatment of asymptomatic bacteriuria (ASB) in pregnancy	ASB in pregnancy	ASB occurs in 2%–7% of pregnant women [26].	Untreated ASB usually develops into pyelonephritis, which is associated with perinatal complications, such as low birth weight, and preterm birth. Screening pregnant women using urine cultures or other available methods allows early detection and treatment with antibiotics, thus reducing the incidence of pyelonephritis

(*continued on next page*)

TABLE 1 (*continued*)

Intervention	Risk factor	Prevalence of the risk factor in LMIC	Assumed mechanism of action for the intervention
			during pregnancy and associated complications [27].
Antibiotic treatment with clindamycin or metronidazole treatment of pregnant women with current bacterial vaginosis (BV) Antibiotic treatment with Clindamycin or metronidazole treatment in pregnant women with current BV and previous PTB	BV	The median prevalence of maternal BV was 20.9% among pregnant women in studies in LMICs [9].	Early detection and treatment of BV with antibiotics reduces the growth of genitourinary pathogens and prevents inflammation, thus reducing risk of obstetric complications and adverse birth outcomes [28].
Screening and treatment of STI other than HIV and syphilis	Sexually transmitted infections	*Trichomonas vaginalis* mean prevalence in SSA (6.8%–24.6%) (highest), Asia (13.6%) and Latin America (3.9%). *Neisseria gonorrhoeae* mean prevalence in SSA (2.3%–4.6%) (highest); Asia 2.8%; Latin America 1.2%. *Chlamydia trachomatis* mean prevalence in Latin America 11.2%) (highest); SSA (4.2%–7.15%); Asia 0.8% [30].	Several STIs are associated with adverse pregnancy outcomes such as miscarriages, premature birth, low birth weight, premature rupture of membranes, and chorioamnionitis. Early detection and treatment of STIs reduces risk of obstetric complications and adverse birth outcomes [29].
Oral and other infections			
Treatment of periodontal disease Treatment of documented deep caries or periapical periodontal disease during pregnancy	Periodontal disease/deep caries or periapical periodontal disease	Several studies report various prevalence rates of periodontitis ranging from 0% to 61% during pregnancy [31].	Periodontal treatments reduce inflammation by minimizing the amount of plaque and calculus levels. It is thought that the resolution of this inflammation/infection may be an important outcome for preventing adverse birth outcomes [32].
Tetanus toxoid vaccination	Tetanus	No formal reporting of maternal tetanus cases but maternal tetanus is estimated to be responsible for ≥5% of maternal death [33].	Maternal tetanus immunization includes a series of vaccinations during pregnancy and subsequent doses after pregnancy. As a long-standing intervention recommended by the WHO, women who are fully immunized with tetanus toxoid vaccine remain protected against maternal tetanus throughout their childbearing years. Newborns born to vaccinated women are also protected from neonatal tetanus by transplacental transfer of maternal antitetanus antibody. The evidence on whether maternal tetanus vaccination has an effect on other birth outcomes is unknown despite its routine use in antenatal care.

HIC, high-income country; LMIC, low- and middle-income countries; PTB, preterm birth; SSA, sub-Saharan Africa; STI, sexually transmitted infection.

review as ES documents. In such cases, results from the more recent RCTs were reported separately. In reporting the ES, we used RR or OR with 95% or 90% CIs, stating the number of randomly assigned participants.

In assessing the quality of evidence, we primarily accepted the assessment given in the Summary of Findings tables of the utilized ES documents that were reviews. Typically, the tables are produced according to the Grading of Recommendations Assessment, Development, and Evaluation process, and they provide the quality of evidence rating for each outcome [40]. In the older ES documents, the assessment was typically described to indicate the "quality" of evidence, whereas in the newer documents it was marked as the "certainty" of evidence. For RCTs used as ES documents, we assessed risk of bias for individual studies. This was converted into an assessment of the quality of evidence (detailed in Supplementary Methods).

To interpret the impact of the interventions on each outcome, we sorted our findings into 5 categories based on the calculated ES, 95% or 90% CI, the number of studies, and the quality of evidence. Each intervention was given a standardized statement in relation to its effect on each outcome, accompanied by a color code (Table 2).

For reporting the results, we applied the PRISMA 2020 checklist [41]. For each intervention, we report quantitative estimates on the size of the effect of the intervention on LBW, PTB, SGA, and SB with an assessment of the quality of evidence.

Due to the magnitude of the evidence synthesis project including the 46 interventions, the review process, data processing, and consolidation of results took ~24 mo, resulting in a time gap between the original searches and published reports. To ensure the timeliness and relevance of our evidence synthesis, we conducted additional searches that covered the period between our original searches and the time of the updated ones, i.e., between 3 March, 2020 and 31 August, 2022. For the updated searches, we used the same search strategies as the previous searches but conducted the searches only in One database (Embase). Like our original searches, One researcher conducted the

TABLE 2
Summary of categorization of the evidence

Color	Interpretation	Criteria
Green	The intervention likely reduces risk of the adverse outcomes.	• At least 2 moderate-to-high quality RCTs in a meta-analysis/IPD analysis, with 95% CI of the point estimate of the RR entirely below 1.
Yellow	The intervention may reduce risk of the adverse outcomes.	• At least 2 RCTs in a meta-analysis/IPD analysis, where either the 95% CI of the point estimate of the RR is entirely below 1 but the quality of the evidence is low or the quality is moderate to high and the 90% CI of the point estimate of the RR entirely below 1. • One moderate-to-high quality RCT, with 95% CI of the point estimate of the RR entirely below 1.
Red	The intervention is not likely to reduce risk of the adverse outcomes.	• Situations that do not meet the requirements for other categories, including meta-analysis results suggestive of harm. In other words, there is sufficient evidence to conclude that the intervention is unlikely to have a positive effect on the outcome.
Gray	Inconclusive published research on the intervention's effect on the outcome.	• At least 2 RCTs, 95% CI of the point estimate of the RR ranges from <0.5 to >2.
White	Insufficient published research on the intervention's effect on the outcome.	• No RCTs or 1 low-quality RCT (any result). • One moderate-to-high quality RCT where 95% CI of the RR includes 1. • Narrative reporting.

IPD, individual participant data meta-analysis; RCT, randomized controlled trial.

title and abstract screening, and the full texts were assessed against the inclusion criteria and discussed by Two researchers (YM and PJH).

Results

We found 9634 records across 8 searches. After electronic removal of duplicate records, we screened 6069 records for eligibility and reviewed 1639 full texts, of which 105 records met the inclusion criteria (Figure 1) [42]. Overall, 27 documents contributed to ES estimates for the reviewed interventions. Among the ES documents obtained, 8 were systematic reviews and meta-analyses, and 19 documents were RCTs.

Prevention and treatment of malaria in pregnancy

Eight ES documents (4 reviews and 4 RCTs) covered interventions focused on malaria prevention during pregnancy to reduce adverse birth outcomes. The documents reported results from a total of 19 RCTs, published between 1998 and 2019 (Table 3) [43–50].

Two trials in Kenya, published between 2002 and 2003 contributed to the ES of the *provision of insecticide-treated bed nets (ITNs) during pregnancy* compared with no nets or untreated nets on adverse birth outcomes. The target population was pregnant women living in malaria-endemic areas. The number of studies (participants) reporting specific outcome data was 2 ($n = 3506$) for LBW and 1 ($n = 2991$) for PTB. Compared to the control group, the RR of LBW among women

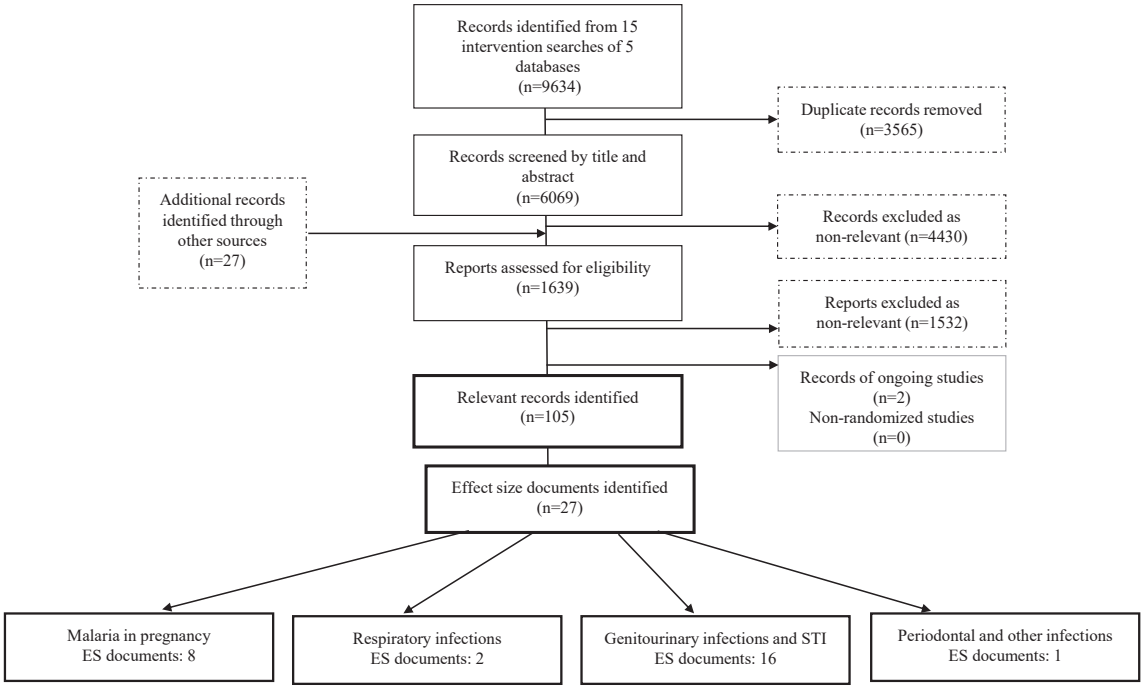

FIGURE 1. Summary flow diagram. Search and the selection process of antenatal interventions targeting maternal infections to prevent LBW. "Other sources" refers to free text searches in Google Scholar and reference lists from the articles that met the inclusion criteria. Adapted from PRISMA 2020 [42]. Some records may appear more than once due to being relevant to >1 category. ES, effect size; LBW, low birth weight; STI, sexually transmitted infections.

TABLE 3
Source documents for effect size estimates–prevention of malaria in pregnancy

Intervention	First author	Year	Study design	Country	Population	Description of intervention	Description of control
Provision of insecticide-treated bed nets (ITNs)	Gamble [43]	2007	Systematic review and meta-analysis	Kenya (2)	Pregnant women living in malaria-endemic areas	ITNs	No nets or untreated nets
Two-dose intermittent preventive treatment of malaria in pregnancy (IPTp) regimen to more frequent IPTp dosing	Kayentao [44]	2013	Systematic review and meta-analysis	Malawi (2), Kenya (1), Zambia (1), Burkina faso (1), Mali (1), Tanzania (1)	Pregnant women living in malaria-endemic areas	≥3 Doses of sulphadoxine–pyrimethamine (IPTp-SP)	Standard 2-dose IPTp-SP regimen
Change from sulphadoxine–pyrimethamine (SP) to dihydroartemisinin–piperaquine (DP)	Olaleye [45]	2019	Systematic review and meta-analysis	Kenya (1), Uganda (1)	Pregnant women who are HIV-negative	3 doses of dihydroartemisinin–piperaquine (IPTp-DP)	IPTp-SP
Replacement of IPTp with intermittent screening and treatment (ISTp)	Desai [46]	2018	Systematic review and meta-analysis	Kenya, Malawi, and Ghana, multicenter study–(Ghana, Mali, Burkina Faso, Gambia)	Pregnant women	Intermittent screening and treatment with rapid diagnostic tests and artemisinin-based combination therapy (ISTp-ACT)	IPTp-SP
	COSMIC consortium [47]	2019	Multicenter cluster-randomized controlled trial	The Gambia, Burkina Faso, and Benin	Pregnant women	Community scheduled malaria screening and treatment plus standard IPTp-SP	IPTp-SP
	Ahmed [48]	2019	Randomized controlled trial	Indonesia	Pregnant women	Intermittent screening ≥3 times during pregnancy and treatment of RDT-positive women with dihydroartemisinin–piperaquine (ISTp-DP)	Intermittent preventive treatment with dihydroartemisinin–piperaquine (IPTp-DP)
	Esu [49]	2018	Randomized controlled trial	Nigeria	Pregnant women	Artemether–lumefantrine (ISTp-AL)	IPTp-SP
Adding antibiotics to IPTp compared with standard IPTp	Luntamo [50]	2013	Randomized controlled trial	Malawi	Pregnant women	Monthly SP and 2 doses of active azithromycin (AZI-SP)	Monthly SP and a placebo for azithromycin

RDT, rapid diagnostic tests.

Table 4
Effect size estimates per intervention type: prevention and treatment of malaria in pregnancy

Intervention	Does the indicated intervention reduce the prevalence of the following adverse birth outcomes?			
	Low Birth Weight (LBW)	Preterm birth (PTB)	Small for Gestational Age (SGA)	Stillbirth (SB)
Provision of insecticide-treated bed nets in pregnancy	Possibly	No	Insufficient data	Insufficient data
	RR: 0.80 [0.64, 1.00] (N=3506)*	0.74 [0.42 to 1.31] (N=2991)*	N/A	N/A
	MODERATE	MODERATE	N/A	N/A
Changing a two-dose IPTp regimen to more frequent IPTp dosing	Yes	Insufficient data	Insufficient data	Insufficient data
	RR: 0.80 [0.69, 0.94] (N=6281)*	N/A	N/A	N/A
	MODERATE	N/A	N/A	N/A
Changing the IPTp regimen from SP to DP	No	Insufficient data	Insufficient data	Insufficient data
	OR: 1.20 [0.73, 1.97] (N=1231)*	N/A	N/A	N/A
	LOW	N/A	N/A	N/A
Replacement of IPTp with ISTp	No	No	No	No
	RR: 1.10 [0.99, 1.23] (N=8659)*	RR: 1.1 [0.88, 1.39] (N=5314)*	RR 1.39 [1.06, 1.81] (N=1210)	OR: 1.05 [0.64, 1.72] (N=4077)*
	MODERATE	MODERATE	MODERATE	MODERATE
Addition of an antibacterial antibiotic to the IPTp regimen	Insufficient data	Insufficient data	Insufficient data	Insufficient data
	RR: 0.86 [0.55, 1.36] (N=800)*	N/A	N/A	N/A
	MODERATE	N/A	N/A	N/A

**The proportion of studies coming from Sub-Saharan Africa or South Asia is 50% or higher.*
N/A - not applicable, OR - odds ratio, RR – relative risk [95% confidence interval]
IPTp – intermittent preventive treatment for malaria in pregnancy, ISPp – intermittent screening and treatment in pregnancy, SP- sulphadoxine pyrimethamine, DP - dihydroartemisinin–piperaquine

using ITNs was 0.80 (95% CI: 0.64, 1.00; 90% CI: 0.66, 0.96). There was no difference in risk of PTB with the use of ITN [RR: 0.74 (95% CI: 0.42, 1.31)] compared with no or untreated ITNs. The evidence was considered to be moderate quality. A detailed summary of the impact of the use of ITN on adverse birth outcomes is shown in Supplementary Data 1.

Seven trials published between 1998 and 2011 contributed to the ES *of changing a two-dose Intermittent Preventive Treatment (IPTp) regimen to more frequent IPTp dosing* in reducing adverse birth outcomes. The trials were conducted in Malawi, Zambia, Burkina Faso, Kenya, Mali, and Tanzania. The target population was pregnant women living in malaria-endemic areas. The number of studies (participants) reporting specific outcome data was 7 ($n = 6281$) for LBW. Three or more doses of SP were associated with a lower prevalence of LBW [RR: 0.80 (95% CI: 0.69, 0.94)] compared with the standard 2-dose regimen. The quality of evidence was considered to be moderate. A detailed summary of the efficacy of more frequent administration of IPTp in reducing adverse birth outcomes is shown in Supplementary Data 2.

Two trials in Kenya and Uganda, published between 2015 and 2016, contributed to the ES of *changing the IPTp regimen from sulphadoxine–pyrimethamine (SP) to dihydroartemisinin–piperaquine (DP).* The target population was pregnant women who were HIV-negative at 16–32 weeks of gestation living in malaria-endemic areas. The number of studies (participants) reporting specific outcome data was 2 ($n = 1231$) for LBW. There was no positive effect on the prevalence of LBW when identical dosing of IPTp-DP was compared with IPTp-SP [OR: 1.20 (95% CI: 0.73, 1.97)]. The quality of the evidence was considered low. A detailed summary of the effect of changing from SP to DP in reducing adverse birth outcomes is shown in Supplementary Data 3.

Seven trials published between 2010 and 2019 contributed to the ESs of the efficacy of *replacement of IPTp with intermittent screening and treatment (ISTp)*. The trials were conducted in Malawi, Kenya, Ghana, Mali, Burkina Faso, The Gambia, Burkina Faso, and Benin, Nigeria, and Indonesia. The target population was pregnant women of any gravidity living in malaria-endemic areas. The number of studies (participants) reporting specific outcome data was 4 ($n = 8659$) for LBW, 2 ($n = 5314$) for PTB, 1 ($n = 1207$) SGA, and 1 ($n = 4077$) for SB. Risk of LBW [RR: 1.1 (95% CI: 0.99, 1.23)] was not reduced in women who received ISTp compared with IPTp. Similarly, the ISTp strategy was not associated with a lower prevalence of PTB [RR: 1.1 (95% CI: 0.88, 1.40)], SGA [RR: 1.39 (95% CI: 1.06, 1.81)], or SB [OR: 1.05 (95% CI: 0.64, 1.72)]. The quality of the evidence was considered to be moderate. A detailed summary of the effect of changing from IPTp to ISTp is shown in Supplementary Data 4.

One RCT published in 2013 reported on the *addition of an antibacterial antibiotic to the IPTp regimen* on adverse birth outcomes. The trial was conducted in Malawi and the target population included women with uncomplicated second trimester pregnancies (gestational age: 14–26 wk) living in a malaria-endemic area. In the trial that

TABLE 5
Source documents for effect size (ES) estimates—respiratory infections

Intervention	First author	Year	Study design	Country	Population	Description of intervention	Description of control
Maternal viral influenza vaccination	Omer [51]	2020	Pooled analysis	Nepal, Mali, South Africa	Pregnant women, gestational age between 17 and 36 wk	Trivalent-inactivated influenza vaccine	Saline placebo or quadrivalent meningococcal conjugate vaccine
Maternal *Haemophilus influenzae* type b vaccination	Salam [24]	2015	Cochrane review	United States	Pregnant women	Capsular polysaccharide vaccine of *Haemophilus influenzae*	Saline injection

Table 6
Effect size estimates per intervention type: interventions targeting respiratory infections

Intervention	Does the indicated intervention reduce the prevalence of the following adverse birth outcomes?			
	Low Birth Weight (LBW)	Preterm birth (PTB)	Small for Gestational Age (SGA)	Stillbirth (SB)
Influenza virus vaccination administered during pregnancy	No	No	No	No
	RR: 0.96 [0.87, 1.06] (N=8897)*	RR: 0.97 [0.87, 1.08] (N=9681)*	RR: 0.99 [0.93, 1.06] (N=7388)*	RR: 1.02 [0.74, 1.42] (N=9950)*
	HIGH	HIGH	HIGH	HIGH
Hib (Haemophilus influenzae type b) vaccination administered during pregnancy	Insufficient data	Insufficient data	Insufficient data	Insufficient data
	N/A	RR: 1.28 [0.12, 13.86] (N=213)	N/A	N/A
	N/A	LOW	N/A	N/A
Screening for tuberculosis in pregnancy in endemic areas	Insufficient data	Insufficient data	Insufficient data	Insufficient data
	N/A	N/A	N/A	N/A
	N/A	N/A	N/A	N/A

**The proportion of studies coming from Sub-Saharan Africa or South Asia is 50% or higher.*

N/A - Not applicable, RR – relative risk [95% confidence interval]

TABLE 7
Source documents for effect size estimates—periodontal diseases and other infections

Intervention	First author	Year	Study design	Country	Population	Description of intervention	Description of control
Periodontal treatment	Iheozor-Ejiofor [32]	2017	Cochrane review	United States (2), United Kingdom, Hungary, Chile (2), Brazil, Colombia, Iran, India, Australia	Pregnant women considered to have periodontal disease after dental examination.	Periodontal treatment	No treatment in 11 RCTs and alternative treatment in 4 RCTs

RCT, randomized controlled trial.

reported outcome data for 800 participants for LBW, the addition of 2 doses of azithromycin to IPTp-SP showed no effect on the prevalence of LBW [RR: 0.86 (95% CI: 0.55, 1.36)] compared with IPTp-SP alone. The quality of the evidence was considered to be moderate. A detailed summary of adding an antibiotic to IPTp compared with standard IPTp is shown in Supplementary Data 5.

In summary, based on published literature, there was evidence that the provision of ITN possibly reduces the prevalence of LBW but not PTB. Additionally, there was evidence that LBW prevalence can be reduced by changing a 2-dose IPTp regimen to more frequent IPTp dosing. In contrast, changing the IPTp regimen from SP to DP or replacement of IPTp with ISTp, was unlikely to reduce the prevalence of LBW or PTB (IST only). For all other interventions and outcomes, there was insufficient data to draw conclusions on intervention efficacy (Table 4).

Respiratory infections

Two ES documents (1 review and 1 pooled analysis) focused on interventions targeting respiratory infections in pregnant women to prevent adverse birth outcomes. The documents reported results from 4 RCTs, published between 1992 and 2018. The trials took place in Sub-Saharan Africa and Southern Asia apart from 1 study in the United States (Table 5) [51,52].

Three trials published between 2014 and 2018 evaluated the effect of *influenza virus vaccination administered during pregnancy* on birth outcomes. The trials were conducted in Mali, Nepal, and South Africa.

Table 8
Effect size estimates per intervention type: periodontal disease and other infections during pregnancy

Intervention	Does the indicated intervention reduce the prevalence of the following adverse birth outcomes?			
	Low Birth Weight (LBW)	Preterm birth (PTB)	Small for Gestational Age (SGA)	Stillbirth (SB)
Treatment of documented periodontal disease during pregnancy	Possibly	No	No	Insufficient data
	RR: 0.67 [0.48, 0.95] (N=3470)	RR: 0.87 [0.70, 1.10] (N=5671)	RR: 0.97 [0.81, 1.16] (N=3610)	N/A
	LOW	LOW	LOW	N/A
Treatment of documented deep caries or periapical periodontal disease during pregnancy	Insufficient data	Insufficient data	Insufficient data	Insufficient data
	N/A	N/A	N/A	N/A
	N/A	N/A	N/A	N/A
Tetanus Toxoid vaccination during pregnancy	Insufficient data	Insufficient data	Insufficient data	Insufficient data
	N/A	N/A	N/A	N/A
	N/A	N/A	N/A	N/A

N/A – not applicable, RR – relative risk [95% confidence interval]

The target populations included pregnant women at a gestational age between 17 and 36 wk. The number of studies (participants) reporting specific outcome data was 3 (n = 8897) for LBW, 3 (n = 9681) for PTB, 3 (n = 7388) for SGA, and 3 (n = 9950) for SB. There was no association between maternal viral influenza vaccination and the prevalence of LBW [RR: 0.96 (95% CI: 0.87, 1.06)], PTB [RR: 0.97 (95% CI: 0.87, 1.08)], SGA [RR: 0.99 (95% CI: 0.93, 1.06)], or SB [RR: 1.02 (95% CI: 0.74, 1.42)]. The quality of evidence for the effect of the intervention on all outcomes was considered high. A detailed summary of maternal viral influenza vaccination is shown in Supplementary Data 6.

One quasi-randomized trial conducted in 1992 assessed the effect of *Haemophilus influenzae type b (Hib) vaccination administered during pregnancy* on birth outcomes. The trial was conducted in the United States and the target population included healthy pregnant women; the number of participants was 213. There was no clear difference in the prevalence of PTB [RR: 1.28 (95% CI: 0.12, 13.86)] between the vaccination and placebo group. The quality of the RCT was low. A detailed summary of maternal Hib vaccination is shown in Supplementary Data 7.

We did not find any eligible studies reporting on *screening for TB in pregnancy in endemic areas* to improve pregnancy outcomes that met our inclusion criteria (Supplementary Data 8).

Based on published literature, there was evidence that maternal viral influenza vaccination does not reduce the prevalence of LBW, PTB, SGA, or SB. There was insufficient data to draw conclusions on the effect of maternal Hib vaccination and screening for TB on the reviewed birth outcomes (Table 6).

Periodontal diseases and other infections during pregnancy

One ES document (review) published in 2017 reported on the impact of periodontal disease treatment and other infections on birth outcomes. The document reported data from 11 RCTs published between 2002 and 2011. The majority of the trials took place in high-income countries (HICs) with the exception of 2 trials that were conducted in LMICs (Table 7) [32].

Eleven RCTs reported on the *screening and treatment of periodontal disease* compared with no treatment. Periodontal treatment in these trials included scaling, root planing and polishing, or surgery, either singly or in combination with counseling on oral hygiene, antiseptic oral agents, and topical or systemic antimicrobial therapies. The target population was pregnant women considered to have periodontal disease after dental examination. The trials were conducted in the United Kingdom, Colombia, Chile, Australia, the United States, Hungary, Iran, India, and Brazil. The number of studies (participants) reporting specific outcome data was 7 (n = 3470) for LBW, 11 (n = 5671) for PTB, and 3 (n = 3610) for SGA. The prevalence of LBW was lower in the periodontal treatment group than in the comparison group [RR: 0.67 (95% CI: 0.48, 0.95)]. However, there was no difference in the prevalence of PTB [RR: 0.87 (95% CI: 0.70, 1.10)] or SGA [RR: 0.97 (95% CI: 0.81, 1.16)]. The quality of evidence was considered low. A detailed summary of screening and treatment of periodontal disease is shown in Supplementary Data 9.

We identified no eligible studies focusing on the effects of *treatment of documented deep caries or periapical periodontal disease or maternal tetanus vaccination* on our specified adverse birth outcomes (Supplementary Data 10 and 11).

In summary, there was evidence that periodontal treatment may reduce the prevalence of LBW compared with no treatment but did not significantly reduce risk of PTB and SGA. There was insufficient data on the effect of treatment of documented deep caries or periapical periodontal disease as well as maternal tetanus vaccination (Table 8).

Screening and treatment of urinary tract infections and sexually transmitted infections in pregnancy

Sixteen ES documents provided ESs on the effect of screening and treatment of urinary tract infections and sexually transmitted infections during pregnancy to reduce adverse birth outcomes. The documents reported 23 trials published between 1960 and 2019. The majority of the trials took place in HICs with the exception of 5 trials that were conducted in LMICs (Table 9) [27,53–67].

Eight trials published between 1960 and 2015 evaluated the effect of *screening and treatment of ASB in pregnancy* on birth outcomes. The trials were conducted in the United States, the United Kingdom, Australia, Denmark, and Netherlands. The target populations included pregnant women with ASB found during antenatal screening. The trials compared

TABLE 9
Source documents for effect size estimates-genitourinary tract and sexually transmitted infections

Intervention	First author	Year	Study design	Country	Population	Description of intervention	Description of control
Antibiotic treatment of asymptomatic bacteriuria (ASB)	Smaill and Vazquez [27]	2019	Cochrane review	United States (2), United Kingdom (2), Australia (2), Denmark, Netherlands	Pregnant women with ASB detected during antenatal screening.	Any antibiotic regimen	Placebo/no treatment
Treatment of pregnant women with documented bacterial vaginosis with metronidazole or clindamycin	Subtil [53]	2018	Randomized controlled trial	France	Pregnant women with bacterial vaginosis or intermediate flora	Single-course or triple-course 300 mg clindamycin capsules twice daily for 4 d	Placebo
	Bellad [54]	2018	Randomized controlled trial	India	Pregnant women with bacterial vaginosis or intermediate flora	Oral clindamycin 300 mg twice daily for 5 d	Placebo
	Bellad [55]	2015	Randomized controlled trial	India	Pregnant women with bacterial vaginosis or intermediate flora	300 mg oral clindamycin twice daily for 5 d	Placebo
	Moniri and Behrashi [56]	2009	Randomized controlled trial	Iran	Pregnant women with bacterial vaginosis or intermediate flora	Metronidazole 500 mg orally twice daily for 7 d	No treatment
	Shennan [57]	2006	Randomized controlled trial	United Kingdom	Pregnant women with bacterial vaginosis or intermediate flora	Metronidazole 400 mg 3 times daily for 7 d	Placebo
	Larsson [58]	2006	Randomized controlled trial	Sweden	Pregnant women with bacterial vaginosis or intermediate flora	7 d of clindamycin vaginal cream	No treatment
	Kiss [59]	2004	Randomized controlled trial	Austria	Pregnant women with bacterial vaginosis or intermediate flora	2% vaginal clindamycin cream for 6 d, given 7–10 d after diagnosis. (12–19 wk). Retreated if still present at follow-up	No treatment
	Ugwumadu [60]	2003	Randomized controlled trial	United Kingdom	Pregnant women with bacterial vaginosis or intermediate flora	Oral clindamycin 300 mg twice daily for 5 d	Placebo
	Lamont [61]	2003	Randomized controlled trial	United Kingdom	Pregnant women with bacterial vaginosis or intermediate flora	5 g of 2% Clindamycin intravaginal cream (+ 100 mg) for 3 nights, In addition 7 extra days if the vaginal swab still positive (BV/ intermediate flora) at visit 2	Placebo
	Guaschino [62]	2003	Randomized controlled trial	Italy	Pregnant women with bacterial vaginosis or intermediate flora	Intravaginal clindamycin 2% cream once daily for 7 d	No treatment
	Klebanoff [63]	2001	Randomized controlled trial	United States	Pregnant women with bacterial vaginosis or intermediate flora	250 mg Generic oral metronidazole each	Placebo
	Kekki [64]	2001	Randomized controlled trial	Finland	Pregnant women with bacterial vaginosis or intermediate flora	2% Vaginal clindamycin cream (single-course) for 7 d	Placebo
	Carey [65]	2000	Randomized controlled trial	United States	Pregnant women with bacterial vaginosis or intermediate flora	250 mg Metronidazole	Placebo
	McDonald [66]	1997		Australia			Placebo

(*continued on next page*)

TABLE 9 (*continued*)

Intervention	First author	Year	Study design	Country	Population	Description of intervention	Description of control
			Randomized controlled trial		Pregnant women with bacterial vaginosis or intermediate flora	Metronidazole (400 mg twice daily for 2 d at 24 weeks of gestation, if repeat swabs remained positive at 28 weeks of gestation, a further course of treatment was given).	
	Joesoef [67]	1995	Randomized controlled trial	Indonesia	Pregnant women with bacterial vaginosis or intermediate flora	Clindamycin cream 2% –5 g intravaginally at bedtime for 7 d	Placebo
Administration of metronidazole or clindamycin to pregnant women with current bacterial vaginosis and a previous preterm birth	McDonald [66]	1997	Randomized controlled trial	Australia	Pregnant women with bacterial vaginosis or intermediate flora and previous preterm birth	Metronidazole (400 mg twice daily for 2 d at 24 weeks of gestation, if repeat swabs remained positive at 28 weeks of gestation, a further course of treatment was given).	Placebo
	Carey [65]	2000		United States	Pregnant women with bacterial vaginosis or intermediate flora and previous preterm birth	250 mg Metronidazole	Placebo
	Shennan [57]	2006		United Kingdom	Pregnant women with bacterial vaginosis or intermediate flora and previous preterm birth	Metronidazole 400 mg 3 times daily for 7 d	Placebo

antibiotic treatment with placebo or no treatment. The number of studies (participants) reporting specific outcome data was 6 (n = 1437) for LBW and 3 (n = 327) for PTB. The prevalence of LBW and PTB was lower in the treated group than in the comparison group [RR for LBW: 0.64 (95% CI: 0.45, 0.93); RR for PTB: 0.34 (95% CI: 0.13, 0.88)]. The quality of the evidence was considered low. A detailed summary of the screening and treatment of ASB is shown in Supplementary Data 12.

Fifteen RCTs published between 1995 and 2018 assessed the use of *clindamycin or metronidazole in pregnant women with current BV.* The trials were conducted in France, India, Iran, the United Kingdom, Sweden, Austria, the United States, Italy, Finland, Australia, and Indonesia. The target populations included pregnant women with current BV diagnosis. BV was diagnosed using either microscopy (Nugent score or Amsel's criteria) or anaerobic culture. The trials used a single antibiotic before the onset of labor or membrane rupture and were heterogenous in the timing in pregnancy and mode of delivery (oral compared with vaginal) of the antibiotics. The number of studies (participants) reporting specific outcome data was 11 (n = 9091) for LBW and 15 (n = 10900) for PTB. There was no difference in the prevalence of LBW [RR: 1.06 (95% CI: 0.96, 1.16; I^2 = 47%)] or PTB [RR: 0.92 (95% CI: 0.73, 1.16)] between the intervention and control groups. The quality of the evidence was considered to be moderate. A detailed summary of treatment with clindamycin or metronidazole in pregnant women with BV is shown in Supplementary Data 13.

Three out of the 15 trials reported on *clindamycin or metronidazole treatment of pregnant women with current BV and previous PTB.* The target populations included pregnant women with BV and previous PTB. The number of studies (participants) reporting specific outcome data was 1 (n = 13) for LBW and 2 (n = 244) for PTB. Compared with the control group, the RR of LBW among high-risk pregnant women receiving antibiotic treatment was 1.25 (95% CI: 0.35, 4.49) and for PTB, the RR was 0.73 (95% CI: 0, 3.38). A detailed summary of treatment with clindamycin or metronidazole in pregnant women with current BV and previous PTB is shown in Supplementary Data 14.

We found no eligible studies reporting on the comparison of *screening and treatment of STI other than HIV and syphilis* with standard care to improve pregnancy outcomes (Supplementary Data 15).

In summary, the evidence suggested that antibiotic treatment of ASB possibly reduces the prevalence of LBW and PTB, but there was insufficient data on the effect of the intervention on SB and SGA. Treatment with clindamycin or metronidazole in pregnant women with BV did not appear to reduce the prevalence of LBW and PTB, and there was insufficient data on the effect on other birth outcomes. The data were inconclusive on the efficacy of treatment with clindamycin or metronidazole for women with current BV and a high risk of PTB due to having had a previous PTB (Table 10).

Search updates to identify recent evidence

We found a total of 708 reports covering the period from March 2020 to September 2022. Of those, 5 publications met our original inclusion criteria (flow chart, **Supplementary Data 16**). One of the publications covered the *replacement of IPTp with ISTp*, one addressed *changing the IPTp regimen from SP to DP*, and 3 publications dealt with the *treatment of periodontal disease*

during pregnancy. No new records were identified for the other 12 reviewed interventions.

A recent systematic review with individual participant data (IPD) meta-analysis reported on the efficacy of IST compared with IPTp-SP during pregnancy [68]. Among participants receiving IST with artemisinin-combination therapy, the RR was 1.08 (95% CI: 0.97, 1.20) for LBW, 1.00 (0.93, 1.07) for PTB, 1.00 (0.93, 1.08) for SGA, and 1.13 (0.88, 1.45) for SB. The evidence from this study pointed to no improvement in birth outcomes with the use of IST. The findings were consistent with our analysis of the ES documents identified in the original search and did not change the interpretation of the data.

The new publication addressing changing the IPTp regimen from SP to DP described a trial of 956 pregnant women in Tanzania [69]. The authors reported a lower prevalence of LBW and PTB in the DP group [RR: 0.49 (95% CI: 0.30, 0.80) for LBW, and RR: 0.42 (05% CI: 0.13, 1.32) for PTB]. The finding of lower LBW prevalence among women receiving IPTp with DP differs from the ES document identified in our original search covering 2 similar trials in Uganda and Kenya. The difference may be explained by the fact that the number of women with patent parasitemia at enrolment was lower than expected, possibly suggesting a relatively low malaria transmission in the study sample [70]. Because our interest was primarily in the high-transmission populations, the new publication did not change our interpretation of the data.

Out of the 3 recent systematic reviews and meta-analyses on the effect of periodontal disease treatment during pregnancy, the first compared the use of mouthwash compared with no mouthwash as part of periodontal disease treatment during pregnancy [71]. The second focused solely on the treatment of gingivitis [72], and the third systematic review and meta-analysis (SRMA) used a pooled analysis of RCT that compared alternative treatments together with RCT that compared treatment compared with no treatment [73]. There was no new SRMA of RCT reporting the ES of periodontal treatment compared with no treatment during pregnancy. Therefore, we did not change the interpretation of the evidence for this question.

Discussion

The aim of this review was to synthesize published literature on the effect of interventions targeting maternal infections on adverse birth outcomes. Using data synthesized from 5 scientific databases, there was evidence that 3 or more doses of IPTp-SP likely reduced risk of LBW. ITNs, antibiotic treatment of ASB, and periodontal treatment were summarized to possibly reduce the prevalence of birth outcomes. IPTp-DP compared with IPTp-SP and ISTp compared with IPTp, maternal viral influenza vaccination, and treatment of BV with metronidazole or clindamycin were summarized to unlikely reduce the prevalence of adverse birth outcomes. There was minimal or no evidence from RCTs on the effect of screening for TB during pregnancy, screening of STIs other than HIV and syphilis, treatment of documented deep caries or periapical periodontal disease, maternal tetanus vaccination, and Hib vaccination on adverse birth outcomes.

The validity of the results could potentially be influenced by the fact that this review focused only on meta-analyses of RCTs on single interventions, the outcomes of interest were in some cases reported as secondary outcomes, and the original searches were conducted in 2020. Focusing solely on the meta-analyses of RCTs has its deficits. Different study populations may experience treatment effects differently due to contextual factors, such as higher baseline prevalence of the risk factor (infections) and other mediating factors, therefore limiting the generalizability of pooled estimates from meta-analyses [74]. However, the advantage of our approach was that it highlighted where there is evidence of potential efficacy (yellow and green interventions) and where the evidence was lacking (white and gray interventions). The flipside of focusing on single intervention is that we may have missed interventions administered together as a package. Secondary outcomes were not always reported in the abstracts of the relevant articles, which made it difficult for the screening process to find them. To mitigate this, the search was complimented by hand searching of the reference list of included articles and a set of other quality control measures as previously reported [16].

The fact that our original literature search was conducted already in 2020 means that we might have missed some relevant recent publications. However, an updated search conducted in late 2022 yielded only very few new publications, none of which changed our interpretation of the availability or signals in the current evidence. Therefore, we consider our findings valid and representative of the published literature. Of the reviewed interventions, >2 doses of IPTp are likely to improve birth outcomes and provision of ITNs, antibiotic treatment of ASB, and periodontal treatment may improve birth outcomes. The other reviewed interventions are either unlikely to improve birth outcomes, or there is little evidence regarding their efficacy.

IPTp-SP and ITNs are currently recommended during ANC in malaria-endemic areas, with more focus geared toward increasing coverage and uptake of these interventions [75]. Although the history of the treatment of malaria during pregnancy stretches back many years, the evidence for IPTp is relatively recent as it followed from the discovery that protection against malaria infection was more efficacious than the treatment of patent malaria infection during pregnancy in reducing maternal anemia and adverse birth outcomes. Due to its broad-spectrum antimicrobial effect on both malarial parasites and clinically important gram-positive bacteria, SP may offer an additional benefit in treating undetected infections in pregnant women, therefore, improving birth outcomes compared with DP and ISTp [76]. However, it is also possible that growing resistance to SP may favor the use of DP in areas of high SP resistance. Furthermore, rapid diagnostic tests used in ISTp fail to detect subpatent and placental infections associated with anemia, LBW, and intrauterine growth restriction. The screen and treat approach may become more viable when more sensitive rapid diagnostic tests become available [46]. Currently, the coverage of IPTp (3+ doses) is below 50% in most malaria-endemic countries [77], which is below the coverage target of 80% by 2010 and 100% by 2015 set by the Roll Back Malaria Partnership [78]. Therefore, scaling up and increasing access to this intervention should be prioritized.

Screening and treatment of ASB is currently recommended by the WHO [11]. However, the justification for this recommendation lies in the strength of the evidence that treatment reduces the incidence of urinary tract infections and pyelonephritis, not adverse birth outcomes. The effect on LBW and PTB were driven by small studies, each using a different antibiotic, dosage, and timing within pregnancy. Furthermore, the RCTs were conducted many years ago using treatment regimens that would not be used today. For example, one of the larger studies from 1969 dominating the effect on PTB used 4 antibiotics from different classes for 3 mo [79]. Given the current concern about the growing threat of antibiotic resistance, it might be prudent to avoid using a single regimen for all ASBs. Instead, diagnosis should be combined with sensitivity testing to select the appropriate antibiotic, dose, and duration of treatment [80].

The pooled estimates on the treatment of BV with metronidazole or clindamycin using recent data from the PREMEVA trial [53] provide

Table 10
Effect size estimates per intervention type: screening and treatment of urinary tract infections and sexually transmitted infections in pregnancy

Intervention	Does the indicated intervention reduce the prevalence of the following adverse birth outcomes?			
	Low Birth Weight (LBW)	Preterm birth (PTB)	Small for Gestational Age (SGA)	Stillbirth (SB)
Screening and treatment of asymptomatic bacteriuria in pregnancy	Possibly	Possibly	Insufficient data	Insufficient data
	RR: 0.64 [0.45, 0.93] (N=1437)	RR: 0.34 [0.13, 0.88] (N=327)	N/A	N/A
	LOW	LOW	N/A	N/A
Clindamycin or metronidazole treatment of pregnant women with current BV	No	No	Insufficient data	Insufficient data
	RR: 1.06 [0.96, 1.16] (N=9091)	RR: 0.92 [0.73, 1.16] (N=10900)	N/A	N/A
	MODERATE	MODERATE	N/A	N/A
Clindamycin or metronidazole treatment of pregnant women with current BV and previous PTB	Insufficient data	Inconclusive	Insufficient data	Insufficient data
	RR: 1.25 [0.35, 4.49] (N=13)	RR: 0.73 [0, 3.38] (N=244)	N/A	N/A
	N/A	LOW	N/A	N/A
Screening and treatment of STI other than HIV and syphilis	Insufficient data	Insufficient data	Insufficient data	Insufficient data
	N/A	N/A	N/A	N/A
	N/A	N/A	N/A	N/A

N/A - not applicable, BV – bacterial vaginosis, HIV – human immunodeficiency virus, STI – sexually transmitted infections

an update of the previous Cochrane review [28], which also found no beneficial effect on birth outcomes. The inconclusive findings among high-risk women with previous PTB should be interpreted with caution as studies were small and from HICs. As with ASB, well-designed trials are needed to confirm whether screening and treatment of BV with appropriate antibiotics reduces adverse birth outcomes in LMICs and among high-risk women.

Although some studies report an association of maternal periodontal diseases and LBW and PTB [35], the possible positive effect of periodontal treatment during pregnancy was limited to LBW. In most of these trials, periodontal treatment started during the second trimester, and by this time it may be too late to address inflammatory responses to periodontal pathogens. This could explain the limited effect on birth outcomes, and it has therefore been suggested that periodontal therapy interventions offered during the preconception period might produce a better effect [31,81]. It would also be important to have more data from LMIC, as most of the available evidence comes from HIC and its applicability to LMIC context is uncertain.

Focusing on maternal infections during pregnancy as preventable causes of adverse birth outcomes is a promising strategy for achieving the goal of LBW reduction and improving maternal and child health. Scaling up of an effective intervention such as IPTp-SP to cover more pregnant women during ANC has been estimated to prevent ≤215,000 LBW deliveries [82]. There are also additional benefits in providing interventions targeting maternal infections, even if there was a marginal effect or insufficient data on birth outcomes. Some such interventions have already been incorporated into existing ANC recommendations with the goal of reducing maternal disease and neonatal infections. For instance, antenatal influenza and tetanus vaccination are recommended in areas of high transmission to prevent severe illness during pregnancy and to protect newborns through passive transfer of immunity across the placenta [83–86]. In view of the substantial burden of infections during pregnancy, addressing these infections during the antenatal period will likely be a cost-effective strategy for producing positive effects in the long term [87,88].

There may also be benefits to combining infection control with other interventions in multiple component health care packages [89,90]. Given that there are multiple contributors to small birth size, such combined interventions would theoretically have a better possibility to improve birth outcomes than single pronged approaches [91]. For example, in the WINGS trial in India [89], there was a substantial reduction in LBW prevalence among infants born to women who received an antenatal intervention that targeted household sanitation and water as well as maternal nutrition and mental health. Testing bundled interventions in other locations and combinations seems highly justified, given the positive findings from the WINGS trial, and the increasing appreciation of the multifactorial etiology of adverse pregnancy outcomes. This review and the modular review method more generally are ideally suited to support the design of intervention bundles by indicating which interventions are likely or unlikely to have effects and where the potential effects are unknown. Furthermore, it will be important to design RCT to test bundled interventions in such a way that the contribution of individual components of the bundle can be demonstrated.

Our decision to restrict the study types to RCTs may limit what can be concluded from the findings of our review. Conducting trials for interventions such as screening and treatment of TB during pregnancy may not be ethical or feasible. However, the absence of RCT evidence does not prove that the intervention is not effective and other types of evidence such as cohort and retrospective studies, can also provide evidence for the potential efficacy of an intervention. For some

interventions, such as antibiotic treatment of BV, the trials were primarily conducted in HICs, which may affect the generalizability of the findings.

Our review found that there is insufficient data on the intervention efficacy of several key interventions and outcomes of interest, despite a strong rationale and impetus to address maternal infections to reduce adverse outcomes. This presents an opportunity for future research. For the interventions that reduced risk of adverse birth outcomes and have established intervention efficacy, implementation research to aid in effective delivery, contextualization, and scale up is required.

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Author contribution

PA, UA, YM, PH, PNG, and AK designed research, including project conception and development of an overall research plan. PA and UA provided study oversight. YM, PH, PNG, and AK conducted research. YM, PH, PNG, AK, JI, MS, and MH collected or analyzed data. JL performed statistical analysis. YM and PH drafted the manuscript. YM had a primary responsibility for the final content. All authors have read and approved the final manuscript.

The study funder had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

Conflict of interest

The authors report no conflicts of interest.

Data Availability

Data described in the manuscript will be made available upon request pending application to and approval by the authors.

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Appendix A. Supplementary data

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