Are maternal vaccines effective and safe for mothers and infants? A systematic review and meta-analysis of randomised controlled trials

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ABSTRACT

Introduction Maternal vaccination is a promising strategy to reduce the burden of vaccine-preventable diseases for mothers and infants. We aimed to provide an up-to-date overview of the efficacy and safety of all available maternal vaccines.

Methods We searched PubMed, Embase, CENTRAL and ClinicalTrials.gov on 1 February 2022, for phase III and IV randomised controlled trials (RCTs) that compared maternal vaccination against any pathogen with placebo or no vaccination. Primary outcomes were laboratory-confirmed or clinically confirmed disease in mothers and infants. Secondary safety outcomes included intrauterine growth restriction, stillbirth, maternal death, preterm birth, congenital malformations and infant death. Random effects meta-analysis were used to calculate pooled risk ratio’s (RR). Quality appraisal was performed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE).

Results Six RCTs on four maternal vaccines, influenza, tetanus, diphtheria and pertussis (Tdap), pneumococcal and respiratory syncytial virus (RSV) were eligible. The overall risk of bias and certainty of evidence varied from low to high. Maternal influenza vaccination significantly reduced the number of laboratory-confirmed influenza cases (RR 0.58, 95% CI 0.42 to 0.79, event rate 57 vs 98, 2 RCTs, n=6003, I²=0%), and clinically confirmed influenza cases in mothers (RR 0.88, 95% CI 0.78 to 0.99, event rate 418 vs 472, 2 RCTs, n=6003, I²=0%), and laboratory-confirmed influenza in infants (RR 0.66, 95% CI 0.52 to 0.85, event rate 98 vs 148, 2 RCTs, n=5883, I²=0%), although this was not significant for clinically confirmed influenza in infants (RR 0.99, 95% CI 0.94 to 1.05, event rate 1371 vs 1378, 2 RCTs, n=5883, I²=0%). No efficacy data were available on maternal Tdap vaccination. Maternal pneumococcal vaccination did not reduce laboratory-confirmed and clinically confirmed middle ear disease (RR 0.49, 95% CI 0.24 to 1.02, event rate 9 vs 18, 1 RCT, n=133 and RR 0.88 95% CI 0.69 to 1.21, event rate 42 vs 47, 1 RCT, n=133, respectively), and clinically confirmed lower-respiratory tract infection (LRTI) (RR 1.08, 95% CI 0.82 to 1.43, event rate 18 vs 34, 1 RCT, n=70) in infants. Maternal RSV vaccination did not reduce laboratory-confirmed RSV LRTI in infants (RR 0.75, 95% CI 0.56 to 1.01, event rate 103 vs 71, 1 RCT, n=4527).

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Maternal vaccination is a promising public health strategy to prevent infectious diseases in mothers and their infants, with the current Advisory Committee on Immunisation Practices guidelines advising influenza, tetanus, diphtheria, pertussis (Tdap) and COVID-19, while ongoing efforts target respiratory syncytial virus (RSV) and group B streptococcus, necessitating a comprehensive overview for research-based recommendations.

WHAT THIS STUDY ADDS

- This systematic review and meta-analysis assesses randomised controlled trial (RCT) data on all available maternal vaccinations, revealing their varying efficacy in preventing disease in both mothers and infants. Furthermore, it indicates no elevated risk for adverse pregnancy outcomes associated with maternal influenza, Tdap, pneumococcal and RSV vaccinations.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- The review’s findings provide supporting evidence for integrating research-based recommendations into national clinical and practice guidelines concerning maternal vaccinations, yet limitations arise from the scarcity and size of RCTs, hindering the detection of safety concerns. Future investigations should prioritise updating data via larger clinical trials and observational studies encompassing high-risk populations, diverse vaccination timings, consistent outcome measures and concomitant vaccines.

Conclusions The few RCTs with low event rates suggest that, depending on the type of maternal vaccine, the vaccine might effectively prevent disease and within its size does not show safety concerns in mothers and infants.

PROSPERO registration number CRD42021235115.
INTRODUCTION

Maternal vaccination is the administration of vaccines to pregnant women to confer immune protection. It is a promising public health strategy to prevent infectious diseases in both mothers and their infants. Mothers are more susceptible to infections due to physiological and immunological adaptations during pregnancy. Infants are vulnerable to infections in the first months of life due to their immature immune system. Subsequently, vaccine-induced maternal pathogen-specific IgG antibodies, which transfer across the placenta, contribute to improving maternal and infant health.

Previous systematic reviews support the efficacy and safety of maternal inactivated influenza vaccination and maternal tetanus, diphtheria and pertussis (Tdap) vaccination. Both maternal influenza and Tdap vaccination are, therefore, recommended for all pregnant women by the Centers for Disease Control and Prevention (CDC). On the other hand, the CDC does not recommend routine vaccination with live-attenuated influenza vaccine (LAIV), measles-mumps-rubella (MMR) vaccine, human papillomavirus (HPV) vaccine, pneumococcal conjugate vaccine (PCV13), pneumococcal polysaccharide vaccine (PPSV23), varicella vaccine and zoster vaccine. Some vaccines are recommended in specific circumstances only, such as meningococcal (ACWY and B), hepatitis A and B, polio, and tetanus and diphtheria (Td).

Interest in other maternal vaccinations has increased significantly over time. The COVID-19 pandemic resulted in the introduction and CDC recommendation of a third vaccine administered during pregnancy protecting pregnant women and their infants against COVID-19. The development of other maternal vaccines is ongoing. Maternal group B streptococcus (GBS) vaccine is in phase II trials, whereas maternal respiratory syncytial virus (RSV) vaccine is in phase III trials.

With these upcoming maternal vaccines, providing a clear and complete overview helps implement research-based recommendations in national clinical and practice guidelines. To our knowledge, no systematic review and meta-analysis has yet addressed the efficacy and safety of all available maternal vaccinations. Therefore, this systematic review and meta-analysis aims to assess the efficacy and safety of vaccines administered to pregnant women, compared with placebo or no intervention, in both mothers and infants.

METHODS

This systematic review and meta-analysis followed a prospectively registered protocol in PROSPERO (CRD42021235115). Findings are reported according to the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) 2020 statement.

Data sources and search strategy

We searched PubMed, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL) and ClinicalTrials.gov from inception to 1 February 2022. The search strategy was developed using the Cochrane search development tool based on the Peer Review of Electronic Strategies (PRESS) criteria. The full search strategy is provided in online supplemental material. We did not apply any language or date restrictions. At this stage, no restrictions were applied to the search strategy regarding the study design, in order to comprehensively search all available data. In addition, we searched the reference lists of retrieved studies and used conference abstracts to identify unpublished data.

Study selection

For feasibility, we restricted the selection criteria to randomised controlled trials (RCTs) in phase III or IV comparing a maternal vaccine administered to pregnant women vs placebo or no vaccination. RCTs that compared two maternal vaccines with each other were not included in this meta-analysis. We did not exclude studies based on the race, trimester, setting and comorbidities of the included pregnant women or the type and dose of the maternal vaccines given. Eligible RCTs reported at least one of our outcomes of interest. Primary outcomes were laboratory-confirmed or clinically confirmed diseases in pregnant women and infants. Clinically confirmed disease was defined as disease-like illness without laboratory confirmation. Laboratory-confirmed disease was defined as the disease confirmed with PCR test. Secondary outcomes were intrauterine growth restriction (IUGR) or small for gestational age (SGA), stillbirth (intrauterine death prior to or during labour), maternal death (all causes), preterm birth (<37 weeks of gestation), congenital abnormalities and infant death (all causes). Infants’ safety outcomes were assessed during the first 12 months of life.

Data extraction

Two review authors (OdB and EP) independently screened titles and abstracts. They selected relevant studies using the open-source machine learning framework ASReview. This tool was designed to accelerate the screening of titles and abstracts. The tool employs active learning to train a machine learning model capable of predicting relevance from texts using a limited number of labelled examples. The most relevant articles, as determined by the model, are presented first. In simulation studies, they discovered that by using ASReview, 95% of the eligible studies is to be found after screening between 8% and 33%. Therefore, the two review authors (OdB and EP) screened 33% manually, and the remaining articles were considered irrelevant by the automation tool. Full-text screening of potentially relevant articles and data extraction of studies meeting the inclusion criteria was also done independently (OdB and EP). Any disagreements were resolved through consensus (OdB, EP
and FA). The Cochrane Pregnancy and Childbirth data extraction form was used for collecting and reporting information about relevant studies. When information was lacking or unclear, investigators were approached for clarification.

The risk of bias (RoB) was assessed using the Cochrane RoB 2 tool. The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) was used to assess the overall certainty of the evidence. Both were independently assessed by two review authors (OdB and EP). Disagreements were resolved through consensus (OdB, EP and FA).

**Statistical analysis**

The extracted summary data were entered in Review Manager (RevMan V.5.4). For all outcomes, we calculated the risk ratio (RR) with 95% CI. When outcomes of one trial were reported in two or more articles, data from the article containing the primary trial analysis was used. The effect estimates of individual studies were pooled using a random-effects model according to the Mantel-Haenszel method. We assessed statistical heterogeneity using the \( I^2 \) estimate and inspecting forest plots. We regarded heterogeneity as substantial if \( I^2 \) was greater than 50%. We used the GRADEpro GDT software to create the summary of findings tables (online supplemental tables S4 and S5).

Subgroup analyses on primary outcomes were planned for the timing of vaccination, gestational age at birth (<37 weeks and ≥37 weeks born infants), geographical setting (high-income countries and low-middle income countries) and race (American Indian or Alaska Native, Asian, black or African American, Native Hawaiian or other pacific islanders, white). When possible, a one-leave-out sensitivity analysis excluding the trials of lower methodological quality was conducted.

**Patient and public involvement**

Although patients were not directly involved in the design or execution of the meta-analysis, our goal was to provide clinically relevant findings that may be of interest to them.

**RESULTS**

The search identified 58 007 records. After removing duplicates, 38 616 records were screened on title and abstract. Of these, 12 473 were excluded manually and 25 486 by an automation tool. The full-text reports of the remaining 657 articles were assessed for eligibility. Exclusion of articles were mostly due to wrong study design, no availability of the full text and wrong outcomes. Finally, we assessed 21 articles thoroughly for data extraction. Twelve articles were excluded, six articles reported data from an RCT that was already included in another report of the same trial (wrong outcome) and six articles did not use placebo or no intervention as a control (wrong comparison). In total, nine articles met the inclusion criteria and were included in this systematic review and meta-analysis (figure 1). Online supplemental tables S1 and S2 list all excluded studies and their reasons for exclusion.

The nine included articles represent data from six RCTs on four diseases (n=11 674): influenza, pertussis, pneumococcal and RSV. All RCTs included pregnant women only whose ages ranged from 15 to 40 years. Timing of vaccination differed among included RCTs starting at 17 weeks’ gestation up to 36 weeks’ gestation. Some RCTs included pregnant women in one country, while others included pregnant women across multiple countries. As intervention, various types of vaccines were used, all of which were inactivated vaccines. The majority of vaccines did not contain any adjuvants, although some incorporated adjuvants including aluminium hydroxide or phosphate. The characteristics of the nine included studies are described in table 1.

When assessing the RoB, four articles were identified as low RoB, one article with some concerns and four articles as high RoB. A detailed assessment of the RoB is available in online supplemental table S3. Summary of findings tables with the GRADE classifications for all reported outcomes are included in online supplemental tables S4 and S5.

**Efficacy and safety of the maternal influenza vaccination**

Three articles with data on two RCTs for maternal influenza vaccination met the eligibility criteria to be included in the meta-analysis (table 2). One of the trials was conducted in South Africa, whereas the other trial was conducted in South Nepal. Both trials included healthy pregnant women and compared a trivalent inactivated influenza vaccine to placebo. Of note, the trial in South Africa also reported on HIV-positive women, which were analysed separately. Administration of the influenza vaccine occurred between 17 and 34 weeks’ gestation in South Africa and between 20 and 34 weeks’ gestation in Nepal. The women were followed for 180 days and 168 days, respectively. Both trials were assessed as having low RoB (online supplemental table S3). The certainty of the evidence for reported outcomes varied from moderate to high (online supplemental tables S4 and S5).

In mothers, maternal influenza vaccination likely reduced the number of laboratory-confirmed influenza cases (RR 0.58, 95% CI 0.42 to 0.79, event rate 57 vs 98, 2 RCTs, n=6003 mothers, \( I^2=0\% \), moderate certainty), and slightly reduced the number of clinically confirmed influenza cases (RR 0.88, 95% CI 0.78 to 0.99, event rate 418 vs 472, 2 RCTs, n=6003 mothers, \( I^2=0\% \), high certainty) (figure 2 and online supplemental table S4). In infants, maternal influenza vaccination reduced laboratory-confirmed influenza cases (RR 0.66, 95% CI 0.52 to 0.85, event rate 98 vs 148, 2 RCTs, n=5883 infants, \( I^2=0\% \), high certainty), although not statistically significant reduction in clinically confirmed influenza cases (RR 0.99, 95% CI 0.94 to 1.05, event rate 1371 vs 1378, 2 RCTs, n=5883 infants).
Regarding safety outcomes, maternal influenza vaccination did not increase the risk of SGA (RR 0.99, 95% CI 0.87 to 1.13, event rate 694 vs 701, 2 RCTs, n=4490 infants, I²=36%, moderate certainty), stillbirth (RR 1.19, 95% CI 0.79 to 1.81, event rate 48 vs 40, 2 RCTs, n=5574 mothers27/infants, 25 I²=0%, moderate certainty), maternal death (RR 1.41, 95% CI 0.22 to 8.92, event rate 6 vs 5, 2 RCTs, n=6003 mothers, I²=40%, moderate certainty), preterm birth (RR 0.97, 95% CI 0.84 to 1.11, event rate 346 vs 356, 2 RCTs, n=5859 infants, I²=0%, moderate certainty), congenital abnormalities (RR 1.11, 95% CI 0.59 to 2.09, event rate 20 vs 18, 1 RCT, n=3693 infants, moderate certainty) and infant death (RR 0.96, 95% CI 0.66 to 1.39, event rate 81 vs 80, 2 RCTs, n=5883 infants, I²=18%, moderate certainty) (figure 2 and online supplemental table S5). In both trials, SGA was defined as <10th percentile according to the INTERGROWTH standards.

**Efficacy and safety of maternal Tdap vaccination**

For pertussis, two RCTs met the eligibility criteria.28 29 One was conducted in the Netherlands and compared...
### Table 1 Characteristics of included studies

<table>
<thead>
<tr>
<th>Type</th>
<th>Population</th>
<th>Study type</th>
<th>Dates</th>
<th>Country</th>
<th>Intervention</th>
<th>Control</th>
<th>Timing of vaccination (weeks GA)</th>
<th>Reported outcome measures</th>
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<tr>
<td></td>
<td>Steinhoff et al, 2017</td>
<td>Healthy pregnant women. 15–40 years of age.</td>
<td>RCT phase 3</td>
<td>April 2011–September 2013</td>
<td>Nepal Trivalent inactivated influenza vaccine (n=1847). Type: inactivated vaccine Adjuvants: no</td>
<td>Placebo, sterile saline (n=1846).</td>
<td>17–34</td>
<td>Laboratory confirmed and clinically confirmed influenza in mothers and infants, SGA, stillbirth, maternal death, preterm birth, congenital abnormalities, infant death</td>
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<td>Pertussis</td>
<td>Barug et al, 2019</td>
<td>Healthy pregnant women. 18–40 years of age.</td>
<td>RCT phase 4</td>
<td>January 2014–March 2016</td>
<td>The Netherlands Tdap vaccine (n=58). Type: toxoid-containing vaccine Adjuvants: Aluminium hydroxide</td>
<td>No intervention during pregnancy, but Tdap vaccine within 48 hours after birth (n=60).</td>
<td>30–32</td>
<td>IUGR, stillbirth, maternal death, preterm birth, infant death</td>
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<td>Perrett et al, 2020</td>
<td>Healthy pregnant women. 18–45 years of age.</td>
<td>RCT phase 4</td>
<td>October 2015–October 2017</td>
<td>Australia, Canada, Czech Republic, Finland, Italy and Spain Tdap vaccine (n=344). Type: toxoid-containing vaccine Adjuvants: Aluminium hydroxide</td>
<td>Placebo, sterile saline during pregnancy and Tdap vaccine within 72 our after birth (n=346).</td>
<td>27–36</td>
<td>IUGR, stillbirth, maternal death, preterm birth, congenital abnormalities</td>
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**Pneumococcus**

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<td>RSV</td>
<td>Healthy pregnant women, 18–40 years of age.</td>
<td>RCT phase 3</td>
<td>December 2015–May 2018</td>
<td>Argentina, Australia, Chile, Bangladesh, Mexico, New Zealand, the Philippines, South Africa, Spain, the UK and the USA</td>
<td>RSV fusion (F) protein nanoparticle vaccine (n=3051) Type: particle based vaccine Adjuvants: Aluminium phosphate</td>
<td>Placebo, formulation buffer (n=1585).</td>
<td>28–36</td>
<td>Disease laboratory confirmed in infants, IUGR, stillbirth, preterm birth, congenital abnormalities, infant death</td>
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GA, gestational age; IUGR, intrauterine growth restriction; LRTI, lower respiratory tract infections; RCT, randomised controlled trial; RSV, respiratory syncytial virus; SGA, small for GA.
Figure 2  Forest plots comparing maternal influenza vaccination with control. M-H, Mantel-Haenszel.
maternal toxoid-containing Tdap vaccination between 30 and 32 weeks’ gestation with no vaccination during pregnancy. This trial was assessed to have high RoB (online supplemental table S3). The other RCT was conducted in multiple countries and compared maternal toxoid-containing Tdap vaccination between 27 and 36 weeks’ gestation with placebo. This trial was assessed to have some concerns about the RoB (online supplemental table S3). The certainty of the evidence for all reported outcomes was low (online supplemental tables S4 and S5).

Both trials did not meet our efficacy outcomes. Maternal Tdap vaccination did not increase the risk of IUGR (definition unclear) (RR 2.54, 95% CI 0.50 to 12.99, event rate 5 vs 2, 1 RCT, n=687 mothers, low certainty), preterm birth (RR 1.30, 95% CI 0.60 to 2.82, event rate 14 vs 11, 2 RCTs, n=805 infants/mothers, 12 = 0%, low certainty) and congenital abnormalities (RR 1.14, 95% CI 0.45 to 2.92, event rate 9 vs 8, 1 RCT, n=687 mothers, low certainty). In both trials, there were no stillbirths or maternal deaths reported. One trial reported no infant deaths (figure 3 and online supplemental table S5).

Efficacy and safety of maternal pneumococcal vaccination

Maternal pneumococcal vaccination was assessed in three articles based on one trial. The trial, conducted in Northern Territory, Australia, compared maternal 23-valent pneumococcal polysaccharide vaccine given between 30 and 36 weeks’ gestation with no vaccination during pregnancy. The trial was assessed to have high RoB due to not blinding participants and personnel (online supplemental table S3). The certainty of the evidence for all reported outcomes was low (online supplemental tables S4 and S5).

Maternal pneumococcal vaccination did not reduce the incidence of middle ear disease with laboratory-confirmed pneumococcal carriage in infants (RR 0.49, 95% CI 0.24 to 1.02, event rate 9 vs 18, 1 RCT, n=133 infants, low certainty). Similarly, maternal pneumococcal vaccination did not reduce the incidence of clinically confirmed middle ear disease (RR 0.88, 95% CI 0.69 to 1.12, event rate 42 vs 47, 1 RCT, n=133 infants, low certainty) and clinically confirmed lower respiratory tract infections (LRTI) (RR 1.08 95% CI 0.82 to 1.43, event rate 18 vs 34, 1 RCT, n=70 infants, low certainty) (figure 4 and online supplemental table S4). Maternal pneumococcal vaccination may result in little to no difference in the incidence of SGA (RR 0.85 95% CI 0.44 to 1.62, event rate 11 vs 26, 1 RCT, n=225 infants, low certainty), and preterm birth (RR 2.33 95% CI 0.81 to 6.70, event rate 7 vs 6, 1 RCT, n=225 mothers, low certainty) (figure 4 and online supplemental table S5). SGA was defined as birth weight lower than the tenth percentile for the gestational age at birth as per Australian national birth weight data. There were no reported stillbirths or maternal deaths.

Efficacy and safety of maternal RSV vaccination

Regarding RSV, one trial was included that compared maternal particle based RSV vaccination given between 28 and 36 weeks’ gestation with a placebo. The trial was conducted in multiple countries and was assessed to have low RoB (online supplemental table S3). The certainty of the evidence for all reported outcomes was moderate (online supplemental tables S4 and S5).

Maternal RSV vaccination probably did not reduce the incidence of laboratory-confirmed RSV LRTI in infants (RR 0.75, 95% CI 0.56 to 1.01, event rate 103 vs 71, 1 RCT, n=4527 infants, moderate certainty) (figure 5 and online supplemental table S4). The trial reported unpowered efficacy data by geographical setting and showed a greater reduction of laboratory-confirmed RSV LRTI in infants in low-income and middle-income countries (vaccine efficacy 42.2%, 95% CI 16.2% to 60.1%) compared with high income countries (vaccine efficacy –17.9%, 95% CI −95.7% to 29.0%). A subgroup analysis on geographical setting was not feasible due to the low number of included trials. Maternal RSV vaccination was not associated with increased risk of IUGR (RR 1.04, 95% CI 0.45 to 2.42, event rate 16 vs 8, 1 RCT, n=4569 mothers, moderate certainty), stillbirth (RR 0.91, 95% CI 0.38 to 2.16, event rate 14 vs 8, 1 RCT, n=4626 mothers, moderate certainty), preterm birth (RR 0.95, 95% CI 0.75 to 1.21, event rate 175 vs 96, 1 RCT, n=4540 infants, moderate certainty), congenital abnormalities (RR 0.94, 95% CI 0.85 to 1.04, event rate 790 vs 437, 1 RCT, n=4569 infants, moderate certainty) and infant death (RR 2.08, 95% CI 0.23 to 18.56, event rate 4 vs 1, 1 RCT, n=4569 infants, moderate certainty) (figure 5 and online supplemental table S5). IUGR was defined as a fetus whose estimated weight is below the 10th percentile for gestational age and whose abdominal circumference is below the 2.5 percentile.

DISCUSSION

This systematic review and meta-analysis provides a complete overview of RCTs assessing efficacy and safety of available maternal vaccinations. According to our findings, vaccines might effectively prevent disease in mothers and infants depending on the type of maternal vaccination. In addition, no evidence was found indicating any safety concerns for maternal influenza, Tdap, pneumococcal and RSV vaccination. We showed that all vaccines assessed as maternal vaccination in phase III and IV RCTs contain inactivated pathogens or their components. Inactivated vaccines are generally considered safe for use in pregnant women. Whereas, live attenuated vaccines, such as the MMR vaccine, are generally not recommended due to the theoretical risk of the virus causing fetal complications. Additionally, we showed that the timing of vaccination varied from 17 weeks of gestation up to 36 weeks of gestation. Optimal timing is a critical consideration to maximise both maternal and neonatal immune protection. While maternal vaccination during
### Figure 3

Forest plots comparing maternal Tdap vaccination with control. M-H, Mantel-Haenszel; Tdap, tetanus, diphtheria and pertussis.
### Figure 4

Forest plots comparing maternal pneumococcal vaccination with control. M-H, Mantel-Haenszel.
Figure 5  Forest plots comparing maternal RSV vaccination with control. M-H, Mantel-Haenszel; RSV, respiratory syncytial virus.
the second trimester is often recommended, the specific timing may vary based on vaccine type and disease prevalence. Previous studies assessing the effect of timing of vaccination report the highest cord blood antibody levels of infants born from mothers vaccinated during the second and third trimester and administered 5–12 weeks before delivery.35 36

To our knowledge, there has yet to be a previous systematic review and meta-analysis of all maternal vaccinations. Several systematic reviews and meta-analyses have been conducted previously to assess the effect of maternal influenza vaccination. Although some differences exist in the eligibility criteria for including, such as the inclusion of observational studies, their conclusions are consistent with our results, suggesting that maternal influenza vaccination reduces the number of laboratory-confirmed influenza cases in infants below 6 months of age and has no effect on clinically confirmed influenza disease in infants.28 29 38 Moreover, infants’ immune response, but the clinical significance of maternally acquired antibodies may interfere with the efficacy in infants.39 They concluded there was no evidence of a reduction in the incidence of pneumococcal middle ear infection in infants up to 1 year of age. Regarding safety outcomes, a review of multiple trials reported no safety concerns regarding preterm birth, congenital abnormalities, IUGR and infant death.40 But, no firm conclusions can be drawn since not all studies compared the vaccine with placebo or no vaccination and like our study, sample sizes were relatively small.

The first phase III trial on a maternal RSV vaccine, also included in our analysis, did not meet their prespecified efficacy outcome, but did show there were no safety concerns.30 RCTs assessing the efficacy and safety of maternal RSV vaccination are ongoing, and the results are expected soon.18 Moreover, a systematic review and meta-analysis of the efficacy and safety of a maternal RSV vaccine, including also phase I and II RCTs is ongoing.41

Overall, our findings support the current guidelines of the CDC to recommend influenza and Tdap vaccination for all pregnant women.13 However, our systematic review and meta-analysis has several limitations. First, this meta-analysis does not provide strong evidence on safety outcomes since we only included RCTs and the power to detect safety issues is limited. In addition, the certainty of the evidence of included studies ranged from moderate to very low, mostly due to the RoB and imprecision. Although we only included outcomes if the authors provided accurate clarifications, inconsistent time point measurements or unclear definitions may have led to inconsistencies across included studies. In addition, there were too limited data available to perform our predefined subgroup analyses, including RCTs and observational studies, on gestational age at birth, geographical setting, and race. Furthermore, the results of our review are predominantly transferable to healthy pregnant women. Data for specific subgroups need to be more conclusive. Lastly, at the time of our search, phase III and IV RCTs on maternal vaccination preventing other diseases, including COVID-19, GBS, Meningococcal and cytomegalovirus, were lacking and could not yet be included in our analysis.

A future update of this review would be much improved by including more clinical trials and observational studies to assess safety outcomes with greater sample sizes, consistent outcome definitions and time point measurements. Since pregnant women are frequently excluded from clinical trials, and evidence on the efficacy and safety of maternal vaccinations remains scarce, data from observational studies is needed. In addition, data are lacking for high-risk pregnant women, the effects of vaccine administration at different gestational ages, the efficacy stratified by country income levels and the effect of concomitant vaccines. The available evidence supporting the safety of current recommendations for the concomitant administration of maternal vaccinations is scarce. One pilot phase IV RCT was performed to assess the safety of simultaneous versus sequential administration of Tdap and inactivated influenza vaccination during 26–32 weeks’ gestation.12 The simultaneous vaccine arm received both Tdap and IIV on the same day (n=42). The sequential vaccine arm received the IIV first and Tdap 3 weeks later (n=38). Although this RCT was finished in 2018, no full outcomes report is available. Since already three maternal vaccines are recommended and there are more to come shortly, it

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is urgent to perform more research on the safety and efficacy of concomitant vaccinations.

**CONCLUSIONS**

Our systematic review and meta-analysis of few RCTs with low events rates suggests that, depending on the type of maternal vaccine, maternal vaccination is an effective strategy to reduce laboratory-confirmed disease. Within the size of the included RCTs, maternal influenza, Tdap, pneumococcal and RSV vaccination do not increase the risk of safety outcomes. Until more data are available, our results represent the best evidence from RCTs to inform decision-makers and healthcare providers on recommendations for available maternal vaccines.

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**REFERENCES**


**DATA AVAILABILITY STATEMENT**

Data are available on reasonable request. Review protocol and statistical analysis plan are available in PROSPERO (CRD42021235115). With publication, data extraction forms of included RCTs are available on request to the study authors.

**SUPPLEMENTAL MATERIAL**

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**AUTHOR CONTRIBUTIONS**


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**COMPETING INTERESTS**

JW participated in the advisory board of Janssen with fees paid to UMCU. MS leads a department that conducts studies on COVID-19 vaccines for the European Medicines Agency, Pfizer, AstraZeneca and Janssen. All according to the ENCePP code of conduct. KB is principal investigator of a phase 3 clinical trial on maternal RSV vaccination funded by Pfizer and of work package three of the Consign study funded by EMA. LJdB has regular interaction with pharmaceutical and other industrial partners. He has not received personal fees or other personal benefits. UMCU has received major funding (>€100 000 per industrial partner) for investigator initiated studies from AbbVie, MedImmune, Janssen, the Bill and Melinda Gates Foundation, Nutricia (Danone) and MeMed Diagnostics. UMCU has received major cash or in kind funding as part of the public private partnership IMI-funded RESCUE project by GSK, Novavax, Janssen, AstraZeneca, Pfizer and Sanofi. UMCU has received major funding by Julius Clinical for participating in the INFORM study sponsored by MedImmune. UMCU has received minor funding for participation in trials by Regeneron and Janssen from 2015 to 2017 (total annual estimate less than €20 000). UMCU received minor funding for consultation and invited lectures by AbbVie, MedImmune, Ablinity, Bavaria Nordic, MabiXience, Novavax, Pfizer, Janssen (total annual estimate less than €20 000). LJdB is the founding chairman of the ReSViNET Foundation. All other authors have nothing to disclose (ID, EP, FA and NvdM).

**PATIENT AND PUBLIC INVOLVEMENT**

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**PATIENT CONSENT FOR PUBLICATION**

Not applicable.

**PROVENANCE AND PEER REVIEW**

Not commissioned; externally peer reviewed.

**DATA AVAILABILITY STATEMENT**

Data are available on reasonable request. Review protocol and statistical analysis plan are available in PROSPERO (CRD42021235115). With publication, data extraction forms of included RCTs are available on request to the study authors.