



SYSTEMATIC REVIEW

Effectiveness and safety of COVID-19 vaccine in pregnant women: A systematic review with meta-analysis

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Abstract

Background: There are limited data regarding COVID-19 vaccination during pregnancy.

Objectives: To evaluate the effects of COVID-19 vaccination received during pregnancy on SARS-CoV-2 infection, COVID-19-related hospitalisation, COVID-19-related intensive care unit (ICU) admission and maternal–fetal complications.

Search strategy: MEDLINE, CINHAL, Embase, Scopus and CENTRAL databases, as well as [ClinicalTrials.gov](https://www.clinicaltrials.gov), reference lists, related articles and grey literature sources.

Selection criteria: Randomised controlled trials, non-randomised studies of interventions, pregnant women, COVID-19 vaccination during pregnancy.

Data collection and analysis: Study selection, risk-of-bias assessment, data extraction and assessment of the certainty of evidence using the GRADE method were performed independently by two authors. Meta-analyses were performed using Cochrane RevMan 5.4. PROSPERO registration number: CRD42022308849.

Main results: We included 14 observational studies (362 353 women). The administration of a COVID-19 vaccine during pregnancy resulted in a statistically significant reduction in SARS-CoV-2 infection (OR 0.46, 95% CI 0.28–0.76) and COVID-19-related hospitalisation (OR 0.41, 95% CI 0.33–0.51). The effect appeared to be greater in fully vaccinated women, for both infection (OR 0.31, 95% CI 0.16–0.59) and hospitalisation (OR 0.15, 95% CI 0.10–0.21). However, the certainty of evidence was very low. The difference in COVID-19-related ICU admission between vaccinated and unvaccinated individuals did not reach statistical significance (OR 0.58, 95% CI 0.13–2.58). Finally, there were no statistically significant differences in any of the maternal–fetal complications considered in the included studies.

Conclusions: COVID-19 vaccination administered during pregnancy seems to reduce SARS-CoV-2 infection and COVID-19-related hospitalisation, with no significant effects on maternal–fetal complications.

KEYWORDS

COVID-19 vaccine, effectiveness, meta-analysis, pregnancy, SARS-CoV-2, systematic review

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and there has been a rapid increase in COVID-19 cases and related deaths since it was identified in early December 2019.¹ SARS-CoV-2 infection during pregnancy is associated with severe illness, with an increased risk of intensive care unit

(ICU) admission, maternal death and adverse pregnancy outcomes.^{2–5} COVID-19 affects pregnancy in part because the immune system is directed towards fetal tolerance.⁶ In addition, SARS-CoV-2 is targeted to the respiratory and cardiovascular systems, which are physiologically stressed during pregnancy.⁷ Moreover, SARS-CoV-2 infection of the maternal placental surface may induce acute or chronic placental insufficiency, leading to pregnancy complications.^{7,8}

Studies have shown that COVID-19 vaccination during pregnancy was associated with lower odds of severe or critical COVID-19 during the pandemic,⁹⁻¹¹ and it has been reported that vaccinated individuals were less likely to experience adverse pregnancy outcomes.¹²⁻¹⁵ As a result, the Centers for Disease Control and Prevention (CDC), the American College of Obstetricians and Gynaecologists and the Society for Maternal–Fetal Medicine have each issued guidance supportive of offering COVID-19 vaccines during pregnancy.^{8,16,17,18,19}

COVID-19 vaccine hesitancy remains high, however, and concerns about safety and effectiveness are commonly cited barriers to vaccination among pregnant women.²⁰

As pregnant women were excluded from phase-III trials, the effects of the vaccine on mother and child were not based on results obtained in the monitored setting of a clinical trial, but instead were estimated based on delayed reports of pregnancy outcomes from healthcare settings.^{21,22} As a result, there are very limited data regarding the effectiveness of COVID-19 vaccines in pregnant women. Thus, the aim of this systematic review (SR) was to assess the effects of COVID-19 vaccination received during pregnancy on SARS-CoV-2 infection, COVID-19-related hospitalisation, COVID-19-related ICU admission and maternal–fetal complications.

2 | METHODS

We followed the Cochrane Handbook (v6.3) in conducting the study and the PRISMA Statement 2020 in reporting the results.^{23,24} We registered the protocol in PROSPERO (www.crd.york.ac.uk/prospero) with registration number CRD42022308849.

We used the following inclusion criteria to select studies:

- Study designs: randomised controlled trials (RCTs) and non-randomised studies of interventions (NRSI), such as non-randomised controlled trials, cohort studies and case–control studies.
- Participants: pregnant women in all three trimesters.
- Interventions: any type of COVID-19 vaccination administered during pregnancy.
- Comparators: absence of COVID-19 vaccination (no intervention, placebo vaccine).
- Outcomes: incidence of SARS-CoV-2 infection, COVID-19-related hospitalisation, COVID-19-related ICU admission and maternal–fetal complications.

With the collaboration of a professional librarian, we searched the electronic bibliographic databases: MEDLINE (PubMed), CINHAL (EBSCOhost), EMBASE, Scopus (Ovid) and Cochrane Central Register of Controlled Trials (CENTRAL). In addition, to identify other relevant studies, we searched ClinicalTrials.gov, the reference lists of other SRs on the topic and the reference lists of the included articles, and grey literature sources such as

databases of conference proceedings, theses and Google Scholar (scholar.google.com). The search strategies used for each database, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses literature search extension (PRISMA-S), are available in Appendix S1.²⁵ We limited the search to articles published in English, Italian, French and Spanish from 2019 to 4 February 2022, with no setting restrictions. We used Rayyan (www.rayyan.com) to eliminate duplicate records.

The selection process consisted of two phases: an initial screening by title and abstract and a second selection step, in which the full texts were read. Both steps were carried out independently by two authors (MT and CT), and disagreements were resolved through discussion with a third reviewer (SS). We report the number of studies retrieved and the number of included and excluded articles at every step in the Results section using the PRISMA 2020 flow diagram (Figure 1).²⁴

Data extraction was performed independently by two reviewers (MT and CT) using a data extraction sheet in Microsoft Excel (Microsoft, Redmond, WA, USA). Any discrepancies were resolved through discussion. In the case of uncertain or missing data, we contacted the study authors by email, with a maximum of two emails sent to each author if no response was received. To complete the information in Table 1 and Tables S1 and S2, we requested additional information from the authors of all included studies; however, authors from only six of the included studies replied to the email.^{13,15,26,27,28,29} In cases in which information is missing because of the lack of response or provision of additional data, we have filled in the table with the inscription ‘ns’ (not specified).

We collected data on reports (first author, publication year, study design), participants (sample size, sample characteristics), intervention (vaccine type received, vaccination strategy) and outcomes (incidence of SARS-CoV-2 infection, COVID-19-related hospitalisation, COVID-19-related ICU admission and maternal–fetal complications).

Two authors (MT and IP) independently assessed the risk of bias (RoB) of the included studies using the Risk of Bias in Non-randomised Studies of Interventions (ROBINS-I) tool,³⁰ and resolved disagreements by discussion with a third author (SS). We used robvis (visualisation tool) to produce the RoB summary and RoB graph.³¹

We reported the results as follows:

- Primary outcomes: SARS-CoV-2 infection, COVID-19-related hospitalisation and COVID-19-related ICU admission.
- Secondary outcomes: maternal–fetal complications.

We conducted a meta-analysis of data for both primary and secondary outcomes reported by at least two included studies, using odds ratio (ORs) as a measure of effect size. We judged the effectiveness based on statistical significance (i.e. the 95% CI of the effect between groups did not include the null value).

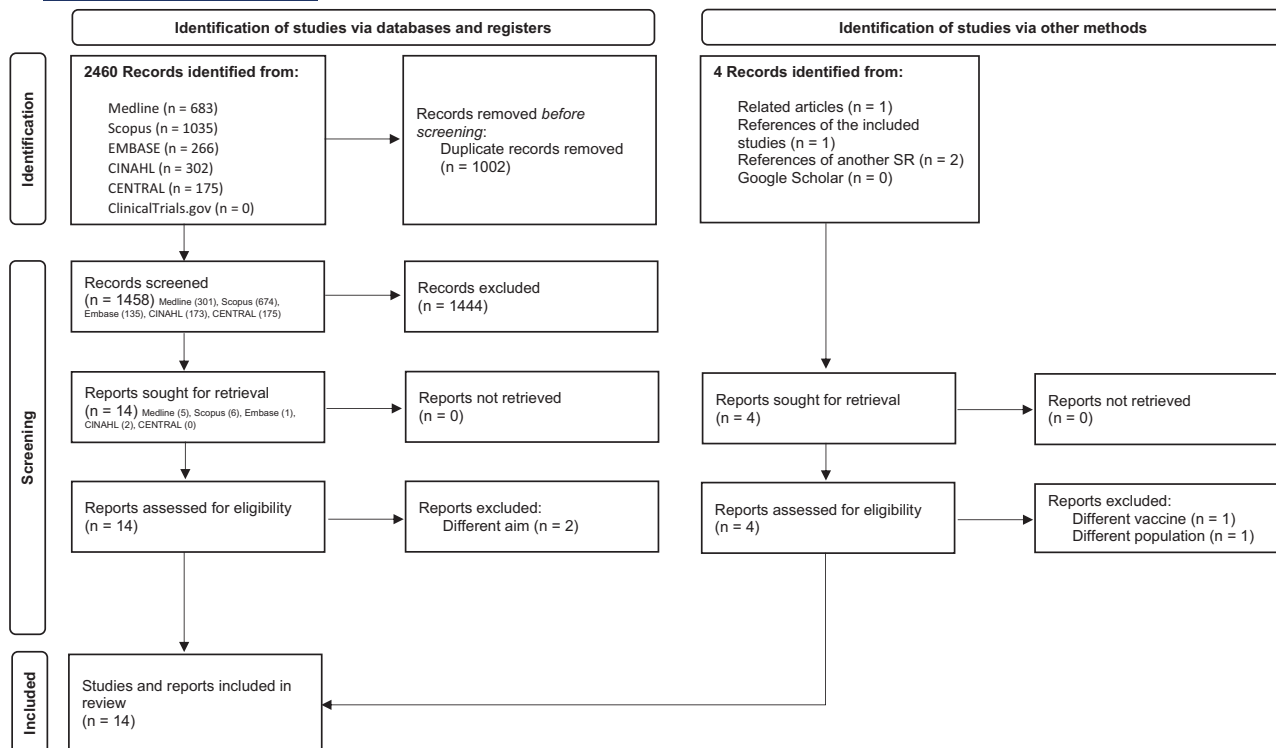


FIGURE 1 PRISMA 2020 flow diagram of the selection process

We used the DerSimonian–Laird random-effects model as a conservative approach to account for different sources of heterogeneity among studies. Statistical heterogeneity of the studies was evaluated using the I^2 test. We conducted a sensitivity analysis for primary outcomes in which we considered only studies and results from fully vaccinated women (i.e. at least 14 days after receiving the necessary vaccine doses, to define the vaccination as complete, which was either one or two doses depending on the vaccine type). We planned another sensitivity analysis to compare the effects of different COVID-19 vaccination strategies (different types, doses or timing), but we did not retrieve enough data to perform this analysis.

We examined publication bias using funnel plots. The Egger test for funnel plot asymmetry was not performed because no meta-analysis included at least ten studies.²³

We performed statistical analyses using Cochrane RevMan 5.4 (www.cochrane.org). We assessed the certainty of the body of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.³² Two authors (MT and SS) independently assessed the quality of evidence as high, moderate, low or very low by considering five domains that can reduce the quality of evidence (study design and RoB, inconsistency, indirectness, imprecision, publication bias) and three that can increase the quality of evidence (large magnitude of an effect, dose–response gradient, effect of plausible residual confounding).³² Following the Cochrane Handbook (v6.3),³³ we used GRADEpro GDT (www.gradepr.org) to elaborate a summary of findings table for the outcomes investigated.

No patients were involved in this research.

3 | RESULTS

3.1 | Selection process

We found 2460 records during the database search, and after the removal of duplicates, we screened 1458 records and evaluated 14 full-text reports for inclusion in the review. In addition, we identified four reports from other sources: one in the related articles in MEDLINE (PubMed), another in the references of the included studies and two in the references of another SR. Ultimately, we excluded a total of four studies,^{34–37} and included 14 reports describing 14 studies. The flow diagram of the selection process can be found in Figure 1, the reasons for exclusion are listed in Table S3 and the citations of the included studies are listed in Table S4.

3.2 | Characteristics of the individual studies

No RCTs were found. All the included studies were observational: four prospective cohort studies,^{15,26,38,39} eight retrospective cohort studies,^{10,11,13,14,27,40,41,42} and two case–control studies.^{28,29} The entire population consisted of 362 353 women, of whom 70 740 received at least one dose of a COVID-19 vaccine during pregnancy and 291 613 were not vaccinated against COVID-19 during pregnancy. The characteristics of the included studies are reported in Table 1.

TABLE 1 Characteristics of the included studies

Author, year	Study design	Sample size	Vaccinated, x (%)	Not vaccinated, x (%)	Vaccine type, x/n (%)	Vaccination period (trimester I, II, III), x/n (%)	Parity (N = nulliparous; P = parous), x/n (%)	Age (years)
Blakeway, 2022	Retrospective cohort study	1328	140 (10.5)	1188 (89.5)	Pfizer = 109/140 (77.8) Moderna = 18/140 (12.9) AstraZeneca = 13/140 (9.3)	I = 0/140 (0.0) II = 20/140 (14.3) III = 120/140 (85.7)	V: N = 78/140 (55.7) P = 62/140 (44.3) NV: N = 595/1188 (50.1) P = 593/1188 (49.9)	V = 35.0 (31.7–37.0) NV = 33.0 (30.0–36.0) median (IQR)
Bleicher, 2021	Prospective cohort study	326	202 (62)	124 (38)	Pfizer = 202/202 (100)	ns	ns	V = 31.7 ± 3.9 NV = 30.2 ± 5.09 mean ± SD
Butt, 2021	Prospective cohort study	814	407 (50)	407 (50)	Pfizer = ns Moderna = ns	I = 323/407 (79.4) II = 84/407 (20.6)	ns	V = 32 (29–36) NV = 32 (28–36) median (IQR)
Dagan, 2022	Prospective cohort study	21 722	10 861 (50)	10 861 (50)	Pfizer = 10 861/10 861 (100)	I = 2814/10 861 (26) II = 5242/10 861 (48) III = 2805/10 861 (26)	ns	V = 30 (26–33) NV = 30 (26–33) median (range)
Goldshtein, 2021	Retrospective cohort study	15 060	7530 (50)	7530 (50)	Pfizer = 7530/7530 (100)	I = 1581/7530 (21) II = 3464/7530 (46) III = 2485/7530 (33)	V: N = 3447/7530 (45.8) P = 4083/7530 (54.2) NV: N = 3447/7530 (45.8) P = 4083/7530 (54.2)	V = 31.1 ± 5.01 NV = 30.4 ± 5.53 mean ± SD
Kharbanda, 2021	Case-control study	105 446	15 079 (14.3)	90 367 (85.7)	Pfizer = 8218/15 079 (54.5) Moderna = 6333/15 079 (42.0) Janssen = 528/15 079 (3.5)	ns	ns	ns
Lipkind, 2022	Retrospective cohort study	46 079	10 064 (21.8)	36 015 (78.2)	Pfizer = 5478/10 064 (54.4) Moderna = 4162/10 064 (41.4) Janssen = 424/10 064 (4.2)	I = 172/10 064 (1.7) II = 3668/10 064 (36.5) III = 6224/10 064 (61.8)	ns	V = 32.3 ± 4.5 NV = 29.8 ± 5.3 mean ± SD
Magnus, 2021	Case-control study	18 477	1003 (5.4)	17 474 (94.5)	Pfizer = 790/1003 (78.7) Moderna = 137/1003 (13.7) AstraZeneca = 76/1003 (7.6)	ns	V: N = 643/1003 (64.1) P = 360/1003 (35.9) NV: N = 10 701/17 474 (61.2) P = 6773/17 474 (38.8)	ns
Morgan, 2022	Retrospective cohort study	10 092	1332 (13.2)	8760 (86.8)	Pfizer = 883/1332 (66.3) Moderna = 382/1332 (28.7) Janssen = 67/1332 (5.0)	ns	ns	V = 32.1 ± 5.9 NV = 27.8 ± 4.9 mean ± SD
Rottenstreich, 2021	Retrospective cohort study	1775	712 (40.1)	1063 (59.9)	Pfizer = 712/712 (100)	III = 712/712 (100)	ns	V = 30.6 ± 5.8 NV = 29.5 ± 6 mean ± SD

(Continues)

TABLE 1 (Continued)

Author, year	Study design	Sample size	Vaccinated, x (%)	Not vaccinated, x (%)	Vaccine type, x/n (%)	Vaccination period (trimester I, II, III), x/n (%)	Parity (N = nulliparous; P = parous), x/n (%)	Age (years)
Shimabukuro, 2021	Retrospective cohort study	3958	3958 (100)	0 (0.0)	Pfizer = 2136/3958 (54.0) Moderna = 1822/3958 (46.0)	Periconception = 92/3958 (2.3) I = 1132/3958 (28.6) II = 1714/3958 (43.3) III = 1019/3958 (25.7)	ns	ns
Stock, 2022	Prospective cohort study	130875	18399 (14.0) 25917 vaccinations	112476 (86.0)	Pfizer = 20572/25917 (79.4) Moderna = 3224/25917 (12.4) AstraZeneca = 2121/25917 (8.2)	I = 9905/25917 (38.2) II = 9317/25917 (35.9) III = 6695/25917 (25.8)	ns	ns
Theiler, 2021	Retrospective cohort study	2002	140 (7.0)	1862 (93)	Pfizer = 127 (90.7) Moderna = 12 (8.6) Janssen = 1 (0.7)	ns	V: N = 56 (40.0) P = 84 (60) NV: N = 546 (29.3) P = 1316 (70.7)	V = 31.8 ± 3.7 NV = 30.5 ± 5.2 mean ± SD
Wainstock, 2021	Retrospective cohort study	4399	Total = 913 (20.8) 1 dose = 155 (17.0) 2 doses = 758 (83.0)	3486 (79.2)	Pfizer-BioNTech = 913 (100)	ns	ns	V = 30.6 ± 5.3 NV = 28.2 ± 5.7 mean ± SD

Abbreviations: IQR, interquartile range; ns, not specified; NV, not vaccinated; SD, standard deviation; V, vaccinated.

3.3 | Effect of vaccination on SARS-CoV-2 infection, COVID-19-related hospitalisation and COVID-19-related ICU admission

Meta-analysis of eight studies showed a significant reduction in the probability of SARS-CoV-2 infection in vaccinated women (OR 0.46, 95% CI 0.28–0.76, $p = 0.002$), with a high heterogeneity ($I^2 = 94\%$) (Figure 2A).^{10,11,13,15,26,38,39,40} The sensitivity analysis considering only fully vaccinated women showed a stronger effect (OR 0.31, 95% CI 0.16–0.59, $p = 0.0004$), but the heterogeneity remained substantial ($I^2 = 75\%$) (Appendix S2).^{10,11,15,26}

Meta-analysis of four studies identified a significant reduction of COVID-19-related hospitalisation in vaccinated women (OR 0.41, 95% CI 0.33–0.51, $p < 0.00001$), with no heterogeneity ($I^2 = 0\%$) (Figure 2B).^{13,15,26,39} The sensitivity analysis considering only fully vaccinated women showed a stronger effect (OR 0.15, 95% CI 0.10–0.21, $p < 0.00001$), with no heterogeneity ($I^2 = 0\%$) (Appendix S2).^{15,26}

Meta-analysis of seven studies did not identify a significant reduction in COVID-19-related ICU admissions in vaccinated women (OR 0.58, 95% CI 0.13–2.58, $p = 0.47$), with a high heterogeneity ($I^2 = 71\%$) (Figure 2C).^{10,11,15,26,39,40,41} The effect size was not substantially modified in the sensitivity analysis considering only fully vaccinated women (OR 0.53, 95% CI 0.05–5.95, $p = 0.61$) (Appendix S2).

We report all primary outcomes data in Table S1.

3.4 | Effect of vaccination on maternal-fetal complications

Eight studies evaluated maternal complications occurring during pregnancy in vaccinated versus unvaccinated women (Table S2).^{10,11,13,38,39,40,41,42} We performed a meta-analysis for the following outcomes: composite pregnancy complications (OR 0.99, 95% CI 0.81–1.21, $p = 0.93$), hypertensive disorders and pre-eclampsia (OR 1.11, 95% CI 0.86–1.42, $p = 0.42$), placental abruption (OR 0.60, 95% CI 0.29–1.21, $p = 0.15$), thromboembolism (OR 2.44, 95% CI 0.12–51.05, $p = 0.57$), postpartum haemorrhage (OR 0.89, 95% CI 0.62–1.29, $p = 0.54$), puerperal fever (OR 0.91, 95% CI 0.55–1.50, $p = 0.71$) and maternal death (OR 2.19, 95% CI 0.09–53.82, $p = 0.63$). No significant differences between vaccinated and unvaccinated women were observed for these outcomes (Appendix S3).

Nine studies evaluated fetal complications occurring during pregnancy in vaccinated versus unvaccinated women (Table S2).^{10,11,13,14,15,38,40,41,42} We performed a meta-analysis for the following outcomes: pregnancy loss (OR 1.04, 95% CI 0.96–1.13, $p = 0.36$), fetal abnormalities (OR 0.91, 95% CI 0.40–2.07, $p = 0.82$), small for gestational age (OR 1.01, 95% CI 0.87–1.17, $p = 0.88$), intrauterine growth restriction (OR 0.97, 95% CI 0.62–1.52, $p = 0.90$), preterm birth (OR 0.82, 95% CI 0.64–1.06, $p = 0.12$), stillbirth (OR 0.73, 95% CI 0.28–1.87, $p = 0.51$), meconium-stained amniotic

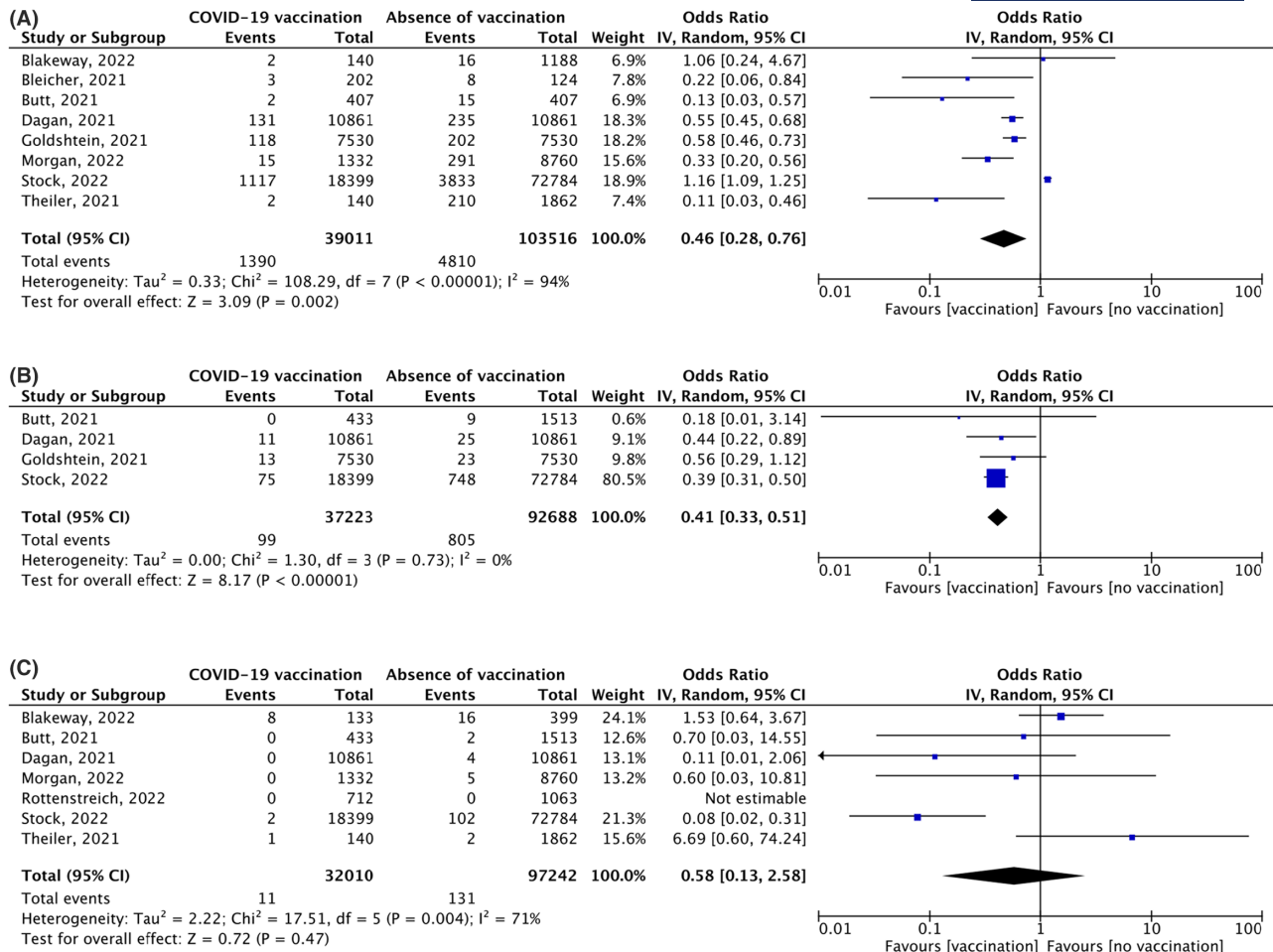


FIGURE 2 Forest plots of meta-analysis for primary outcomes (A) Outcome: incidence of SARS-CoV-2 infection. Comparison: vaccinated vs non-vaccinated pregnant women. (B) Outcome: COVID-19-related hospitalisation. Comparison: vaccinated vs non-vaccinated pregnant women. (C) Outcome: COVID-19-related ICU admission. Comparison: vaccinated vs non-vaccinated pregnant women.

fluid (OR 0.78, 95% CI 0.58–1.05, $p = 0.10$), neonatal ICU admission (OR 0.91, 95% CI 0.58–1.44, $p = 0.69$) and hypoxic ischaemic encephalopathy (OR 4.42, 95% CI 0.18–108.91, $p = 0.36$). No significant differences were observed for these outcomes between vaccinated and unvaccinated women (Appendix S3).

3.5 | Risk of bias within studies

The overall RoB was serious for 12,^{10,11,14,15,26,27,28,29,38,40,41,42} and moderate for two,^{13,39} of the included studies. This judgement was primarily influenced by the confounding bias domain, in which most of the studies had a serious RoB.^{10,11,14,15,26,27,28,29,38,40,41,42} In the domains of the selection of participants and the selection of reported results, all studies had a moderate RoB.^{10,11,13,14,15,26,27,28,29,38,39,40,41,42} Finally, in the biases resulting from the classification of the intervention,^{10,11,13,14,15,26,27,28,29,39,40,42} deviations from intended interventions,^{10,11,13,14,15,26,27,28,29,38,39,40,41,42} missing data,^{10,11,13,14,15,26,27,28,29,39,40,41,42} and the measurement

of outcome domains,^{10,11,13,14,15,26,27,28,29,38,39,40,41,42} most of the studies obtained a low RoB. The attrition rate of the included studies can be found in Table S5, the RoB assessment is presented in Figure S1 and the justifications for each judgement are listed in Table S6.

3.6 | Risk of publication bias

The funnel plots showed gaps and asymmetries for both primary and secondary outcomes, which could suggest the presence of publication bias (Appendix S4). However, we must consider that the asymmetry could result from several factors, such as non-reporting biases, poor methodological quality, leading to spuriously inflated effects in smaller studies, true heterogeneity, artefacts and chance.²³ Furthermore, none of the outcomes were addressed in at least ten studies, so one must be cautious in making a visual interpretation, and performing a statistical test for asymmetry (i.e. Egger test) is not appropriate.²³ In any case, the probable presence of publication bias was considered relevant in the GRADE approach.

3.7 | Certainty in the body of evidence

All considered outcomes started the GRADE process with a low certainty of evidence because the data were obtained from observational studies.³² All of the outcomes were downgraded to having a very low certainty of evidence because of the high RoB in most of the included studies and the probable presence of publication bias. In addition, some outcomes also exhibited unexplained high ($I^2 > 60\%$) or very high ($I^2 > 90\%$) heterogeneity and wide (with a range greater than 0.5 OR points) or very wide (with a range greater than 1.0 OR points) confidence intervals. For these reasons, the evidence is very uncertain for all outcomes considered. For more information, see the summary of findings tables with footnotes explaining judgements for primary (Figure 3) and secondary outcomes (Appendix S5).

Summary of findings:

COVID-19 vaccination compared to absence of vaccination for primary outcomes

Patient or population: pregnant women

Intervention: COVID-19 vaccination

Comparison: absence of vaccination

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with absence of vaccination	Risk with COVID-19 vaccination				
Incidence of SARS-CoV-2 infection	46 per 1.000	22 per 1.000 (13 to 36)	OR 0.46 (0.28 to 0.76)	142527 (8 observational studies)	⊕○○○ Very low ^{a,b,c}	The evidence is very uncertain about the effect of COVID-19 vaccination on the incidence of SARS-CoV-2 infection.
COVID-19 related hospitalisation	9 per 1.000	4 per 1.000 (3 to 4)	OR 0.41 (0.33 to 0.51)	129911 (4 observational studies)	⊕○○○ Very low ^{a,c}	The evidence is very uncertain about the effect of COVID-19 vaccination on COVID-19 related hospitalisation.
COVID-19 related admission in ICU	1 per 1.000	1 per 1.000 (0 to 3)	OR 0.58 (0.13 to 2.58)	129252 (7 observational studies)	⊕○○○ Very low ^{a,c,d,e}	The evidence is very uncertain about the effect of COVID-19 vaccination on COVID-19 related admission in ICU.
Incidence of SARS-CoV-2 infection in fully vaccinated	52 per 1.000	17 per 1.000 (9 to 31)	OR 0.31 (0.16 to 0.59)	104091 (4 observational studies)	⊕○○○ Very low ^{a,c,d}	The evidence is very uncertain about the effect of COVID-19 vaccination on incidence of SARS-CoV-2 infection in fully vaccinated.
COVID-19 related hospitalisation in fully vaccinated	10 per 1.000	2 per 1.000 (1 to 2)	OR 0.15 (0.10 to 0.21)	93129 (2 observational studies)	⊕○○○ Very low ^{a,c}	The evidence is very uncertain about the effect of COVID-19 vaccination on COVID-19 related hospitalisation in fully vaccinated.
COVID-19 related admission in ICU in fully vaccinated	1 per 1.000	1 per 1.000 (0 to 8)	OR 0.53 (0.05 to 5.95)	105223 (4 observational studies)	⊕○○○ Very low ^{a,c,d,e}	The evidence is very uncertain about the effect of COVID-19 vaccination on COVID-19 related admission in ICU in fully vaccinated.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; OR: odds ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

4 | DISCUSSION

4.1 | Main findings

Our SR demonstrated that the administration of a COVID-19 vaccine during pregnancy resulted in a statistically significant reduction in SARS-CoV-2 infection (OR 0.46, 95% CI 0.28–0.76) and COVID-19-related hospitalisation (OR 0.41, 95% CI 0.33–0.51), but the certainty of evidence was very low. The effect appeared to be greater for both infection (OR 0.31, 95% CI 0.16–0.59) and hospitalisation (OR 0.15, 95% CI 0.10–0.21) when considering only fully vaccinated women, although the level of certainty was still very low. Conversely, the difference in ICU admissions related to COVID-19 did not reach statistical significance (OR 0.58, 95% CI 0.13–2.58), probably because of the small

FIGURE 3 GRADE summary of findings table for primary outcomes. ^aDowngrade by one level due to a high risk of bias in most of the included studies for this outcome (see the ROB assessment results with ROBINS I). ^bDowngrade by two levels due to unexplained high heterogeneity, $I^2 > 90\%$ (see the forest plots and the results section). ^cDowngrade by one level due to probable publication bias (see the funnel plots and the results section). ^dDowngrade by one level due to unexplained heterogeneity, $I^2 > 60\%$ (see the forest plots and the results section). ^eDowngrade by two levels due to very wide confidence intervals. Confidence interval range greater than 1.0 OR points.

number of total cases among both vaccinated and unvaccinated women.

Finally, there was no significant difference between vaccinated and unvaccinated women in any of the maternal–fetal complications considered in the included studies.

4.2 | Strengths and limitations

Our SR is subject to several limitations. Of the few studies that addressed the questions of our SR, all were observational and most presented a serious RoB. Moreover, five of the 14 included studies did not recruit women with a history of SARS-CoV-2 infection,^{13,26,39,41,42} whereas the other studies did not provide information about SARS-CoV-2 infection history.^{10,11,14,15,27,28,29,38,40} This could indicate selection bias. Moreover, the included studies did not report data stratified by trimester of pregnancy; as a result, we were unable to study the outcomes in each trimester. Additionally, we must consider that time-varying exposure outcomes (i.e. pregnancy loss, preterm birth, stillbirth, placental abruption and maternal death) can occur at any time during pregnancy, and if they occur early, participants have a lower likelihood of getting the vaccine. This may affect the results by creating a bias suggesting a protective effect of the vaccine on such outcomes.⁴³ In our case, it may have particularly influenced the outcome of the meta-analysis for preterm birth (OR 0.82, 95% CI 0.64–1.06) (Appendix S3). Finally, we have restricted the eligibility based on the language of publication, and thus otherwise eligible studies could have been excluded.

On the other hand, our SR also had several strengths, including the completion of a sensitive search in multiple databases, high methodological quality, according to the standards, and the use of the GRADE approach.³²

4.3 | Interpretation

The results of our SR should be interpreted with caution because of the very low level of certainty of the evidence. Nevertheless, COVID-19 vaccination administered during pregnancy seems to reduce the incidence of SARS-CoV-2 infection and COVID-19-related hospitalisation, with no significant effects on maternal–fetal complications. These findings should be considered by both clinicians and pregnant women and could help to overcome vaccine hesitancy. Reducing the number of infections or hospitalisations is an important goal that would limit the risk of pregnancy and perinatal complications associated with symptomatic or severe COVID-19,^{3,4,5,44,45} prevent hospital-related adverse events,^{46–48} and reduce the economic burden on healthcare facilities.

A recent SR and meta-analysis published by Prasad et al. addressed a similar question, but there are a few differences between their review and ours.⁴⁹ Some of the studies in their review included women vaccinated before pregnancy or non-pregnant individuals. In addition, they did not consider COVID-19-related hospitalisation and many maternal–fetal

complications (i.e. composite pregnancy complications, puerperal fever, small for gestational age, intrauterine growth restriction, meconium-stained amniotic fluid and hypoxic ischaemic encephalopathy). Nonetheless, their results are similar to our results; however, they found a significant reduction in stillbirth in the vaccinated cohort (OR 0.85, 95% CI 0.73–0.99, $p < 0.01$, $I^2 = 93.9\%$) and we did not. This discrepancy may result from the fact that they included data from two study registers, which increased the sample size.

Another SR and meta-analysis studied the effect of vaccination on SARS-CoV-2 infection and COVID-19-related hospitalisation during pregnancy.⁵⁰ It included only six observational studies published up to September 2021. Its results are consistent with our findings.

Additional SRs found that COVID-19 vaccination does not appear to be associated with maternal–fetal complications; rather, it was associated only with common adverse reactions, such as transient headache, pain at the injection site and fatigue.^{50–54}

Our study contributed to the knowledge on the topic by including new studies in the SR and providing additional data related to the certainty of evidence using the GRADE method.³²

5 | CONCLUSION

COVID-19 vaccination administered during pregnancy seems to reduce the incidence of SARS-CoV-2 infection and COVID-19-related hospitalisation, with no significant effects on maternal–fetal complications. However, the certainty of evidence is very low. For future research, we recommend high-quality RCTs to increase the level of the certainty of evidence, performing studies or generating data comparing different vaccination strategies with each other (e.g. different types, doses or timing) and further data stratification according to the trimester of pregnancy to enable subgroup analysis and meta-regression.

AUTHOR CONTRIBUTIONS

MT, PG, and RC proposed the review project and identified the framework. MT, IP, CT, SS, GS, PG and RC defined the protocol, developed the search strategy, extracted the data and assessed the RoB. SS provided methodological support and performed statistical analyses. SS and MT applied the GRADE method. All authors approved the final version of the article and agreed to be accountable for all aspects of it.

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CONFLICT OF INTERESTS

None declared. Completed disclosure of interests form available to view online as supporting information.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

ETHICS APPROVAL

None.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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