SYSTEMATIC REVIEW

Safety and Effectiveness of COVID-19 Vaccines During Pregnancy: A Living Systematic Review and Meta-analysis

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Abstract

Background Pregnant persons are susceptible to significant complications following COVID-19, even death. However, worldwide COVID-19 vaccination coverage during pregnancy remains suboptimal.

Objective This study assessed the safety and effectiveness of COVID-19 vaccines administered to pregnant persons and shared this evidence via an interactive online website.

Methods We followed Cochrane methods to conduct this living systematic review. We included studies assessing the effects of COVID-19 vaccines in pregnant persons. We conducted searches every other week for studies until October 2023, without restrictions on language or publication status, in ten databases, guidelines, preprint servers, and COVID-19 websites. The reference lists of eligible studies were hand searched to identify additional relevant studies. Pairs of review authors independently selected eligible studies using the web-based software COVIDENCE. Data extraction and risk of bias assessment were performed independently by pairs of authors. Disagreements were resolved by consensus. We performed random-effects meta-analyses of adjusted relative effects for relevant confounders of comparative studies and proportional meta-analyses to summarize frequencies from one-sample studies using R statistical software. We present the GRADE certainty of evidence from comparative studies. Findings are available on an interactive living systematic review webpage, including an updated evidence map and real-time meta-analyses customizable by subgroups and filters.

Results We included 177 studies involving 638,791 participants from 41 countries. Among the 11 types of COVID-19 vaccines identified, the most frequently used platforms were mRNA (154 studies), viral vector (51), and inactivated virus vaccines (17). Low to very low-certainty evidence suggests that vaccination may result in minimal to no important differences compared to no vaccination in all assessed maternal and infant safety outcomes from 26 fewer to 17 more events per 1000 pregnant persons, and 13 fewer to 9 more events per 1000 neonates, respectively. We found statistically significant reductions in emergency cesarean deliveries (9%) with mRNA vaccines, and in stillbirth (75–83%) with mRNA/viral vector vaccines. Low to very low-certainty evidence suggests that vaccination during pregnancy with mRNA vaccines may reduce severe cases or hospitalizations in pregnant persons with COVID-19 (72%; 95% confidence interval [CI] 42–86), symptomatic COVID-19 (78%; 95% CI 21–94), and virologically confirmed SARS-CoV-2 infection (82%; 95% CI 39–95). Reductions were lower with other vaccine types and during Omicron variant dominance than Alpha and Delta dominance. Infants also presented with fewer severe cases or hospitalizations due to COVID-19 and laboratory-confirmed SARS-CoV-2 infection (64%; 95% CI 37–80 and 66%; 95% CI 37–81, respectively).

Conclusions We found a large body of evidence supporting the safety and effectiveness of COVID-19 vaccines during pregnancy. While the certainty of evidence is not high, it stands as the most reliable option available, given the current absence of pregnant individuals in clinical trials. Results are shared in near real time in an accessible and interactive format for scientists, decision makers, clinicians, and the general public. This living systematic review highlights the relevance of continuous vaccine safety and effectiveness monitoring, particularly in at-risk populations for COVID-19 impact such as pregnant persons, during the introduction of new vaccines.

Clinical Trial Registration PROSPERO: CRD42021281290.

Agustín Ciapponi, Mabel Berrueta are both first authors.

Key Points

Pregnant persons are susceptible to significant complications following COVID-19, even at the present stage of the pandemic, but vaccination coverage during pregnancy remains suboptimal.

Our living systematic review found a large body of evidence supporting the safety and effectiveness of COVID-19 vaccines during pregnancy.

The lower effectiveness during Omicron variant dominance, which decreases over time, and the less robust evidence for non-mRNA vaccines emphasized the need for continuous vaccine safety and effectiveness monitoring among pregnant persons.

1 Introduction

The COVID-19 pandemic caused a significant global health crisis leading to over 770 million cases and seven million deaths worldwide [1]. The development and distribution of COVID-19 vaccines have been critical steps in controlling the spread of the virus and mitigating its impact on health worldwide [2, 3]. Many COVID-19 vaccines were authorized for use [4, 5]. Although clinical trials demonstrated promising results regarding the efficacy and safety of these vaccines [6], real-world effectiveness and safety data on these vaccines continue to emerge.

Early in the pandemic, pregnant persons with COVID-19 were found to be at a greater risk of experiencing severe illness than non-pregnant adults [7–9]. Various factors, including maternal age, high body mass index, non-white race/ethnicity, pre-existing health conditions, and gestational diabetes mellitus, increased the risk of severe COVID-19 during pregnancy further, including a higher risk of admission to intensive care units or needing invasive ventilation than non-pregnant women of reproductive age [10, 11]. Pregnant persons also exhibited an elevated likelihood of experiencing adverse pregnancy and birth outcomes associated with SARS-CoV-2 infection [12]. In particular, pregnant persons with COVID-19 are prone to delivering preterm babies, who may require admission to neonatal intensive care units (NICUs). The rates of SARS-CoV-2 infection in pregnant women varied significantly by region, with the highest rates observed in Latin America and the Caribbean (19%) and in lower- to middle-income countries (13%). Lower-income to middle-income countries

(LMICs) also reported significantly higher rates of maternal mortality (0.68%) and stillbirths (1.09%) than high-income countries (HICs). [13]

Unfortunately, completed randomized controlled trials (RCTs) of COVID-19 vaccines did not include pregnant persons in their eligible population [14]. Consequently, the efficacy and safety of multiple vaccine products during pregnancy were not fully assessed at the time of their recommendation for widespread use in response to the public health emergency. Many regulatory bodies advised the use of COVID-19 vaccines for pregnant persons on the premise that the benefits of vaccination would outweigh the potential risks [15]. It was therefore crucial to provide a timely comprehensive evaluation of the available evidence on the safety and benefits of COVID-19 vaccines in this population. Considering the growing body of evidence, we conducted a living systematic review (LSR) and meta-analysis designed to periodically assess the effectiveness, safety, and immunogenicity of COVID-19 vaccines to inform clinical practice, public health policy, and future research efforts.

2 Methods

We followed the Cochrane and World Health Organization (WHO) methods [16–18] and the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement/extension for reporting this LSR [19, 20]. The protocol was registered in the PROSPERO database (CRD42021281290) and published elsewhere [21], but we summarize the main methodology here.

2.1 Inclusion Criteria

We included RCTs, quasi-experimental studies, and observational studies assessing COVID-19 vaccination during pregnancy, irrespective of publication status (pre-print or standard publication), publication year, and language. Case reports for unexpected adverse events were also included. Study participants were pregnant persons, irrespective of prior exposure to SARS-CoV-2, age, comorbidities, immune status, or baseline risk with or without exposure to virologically confirmed SARS-CoV-2 infection.

We included all COVID-19 vaccines authorized by the WHO or national regulatory authorities, regardless of dosage or administration schedule. Any comparison group was considered, including usual care, no intervention, another COVID-19 vaccine, or other active comparators. We also included non-comparative

studies; therefore, a control group was not mandatory. We considered any safety outcomes, i.e., pregnancy-related maternal or obstetric outcomes, adverse events following immunization (AEFIs), infant outcomes, efficacy or effectiveness outcomes, and immunogenicity results available in published studies.

2.2 Search Strategy

We conducted searches every other week from January 2020 to October 2023 of published and unpublished studies without restrictions on language or publication status (see the full search in the Electronic Supplementary Material [ESM]). The searches were conducted in the Cochrane Library databases, MEDLINE, EMBASE, Latin American and Caribbean Health Sciences Literature (LILACS), Science Citation Index Expanded (SCI-EXPANDED), China Network Knowledge Information (CNKI), Chinese Biomedical Literature Database (CBM), Chinese Science Journal Database (VIP), WHO Database of publications on SARS-CoV-2, EPPI-Centre map of the current evidence on COVID-19, guidelines published by national and international professional societies (e.g., American College of Obstetricians and Gynecologists, Royal College of Obstetricians and Gynecologists, International Federation of Gynecology and Obstetrics), pre-print servers (ArXiv, BiorXiv, medRxiv, search.bioPreprint), and COVID-19 research websites, including the WHO Global research on coronavirus disease (COVID-19) website, COVID-19 Vaccine Tracker, the L-OVE Platform, and the COVID-19 Living Evidence. Additional relevant studies were identified by hand searching the reference lists of the identified systematic reviews.

2.3 Selection of Studies and Data Collection

Pairs of review authors independently screened each title and abstract and retrieved all potentially relevant full-text studies. Pairs of review authors independently selected the full texts, documenting the reasons for the exclusion of ineligible studies. We resolved disagreements through discussion with the review team. This process was performed using the web-based software COVIDENCE [22]. Study data were abstracted independently by pairs of review authors and stored using REDCap electronic data capture tools [23] hosted and designed by the Institute for Clinical Effectiveness and Health Policy. If needed, we contacted the study authors for additional data. Data extraction items included study identification elements, methods, participants' characteristics, countries involved,

group allocation, intervention, outcomes, risk of bias, and summary of results.

2.4 Risk of *Bias* Assessment

For observational cohort, case-control, cross-sectional, and case-series studies, we used the National Institutes of Health Quality Assessment Tools [24]. After answering the different signaling questions, the reviewers (see the signaling questions in Tables S2, S3, S4, and S5 of the ESM) classified the study quality as good, fair, or poor.

2.5 Data Synthesis

We performed meta-analyses for each comparison according to the Cochrane Handbook of Systematic Reviews of Interventions and used a random-effects meta-analysis for the primary analysis [25]. Only studies with adjusted effect measures (e.g., adjustment for at least two confounders as age, smoking status, parity, body mass index) or using matched controls were included for comparative meta-analyses. We also performed proportional meta-analyses to summarize frequencies from one-sample studies and conducted targeted searches for background rates of each maternal-infant event. These background rates encompass global, HIC, and LMIC rates and serve as reference points for contextualizing the findings within the frame of maternal-infant health knowledge. R statistical software was used for this project [26] to analyze the data. The main packages selected for data analyses were Meta [27], Metafor [28], and Tidyverse [29]. For the selection process of the study data for each meta-analysis, we avoided double-counting populations or comparators through an algorithm, which selected the data from each study with the greatest amount of available information (significant quantity of trimesters, vaccines, types of variants) that complied with the selected analysis. When one study had more than one effect estimate for the same outcome, we included in the analysis only the data with the most follow-up and the largest sample size. The researchers performed a validation process to ensure the validity of the endpoint selection algorithm monthly.

We extracted or calculated hazard ratios (HRs), risk ratios (RRs), or odds ratios (ORs) with a 95% confidence interval (CI) for dichotomous outcomes and the mean difference or standardized mean difference for continuous outcomes. We also calculated proportions with a 95% CI for non-comparative studies using arcsine transformation [30].

We estimated the vaccine efficacy/effectiveness (VE) by determining the percentage reduction in disease risk among vaccinated persons compared with unvaccinated persons based on adjusted relative effects [31]. We analyzed maternal safety outcomes, including pregnancy-related outcomes and AEFIs, and infant safety outcomes mainly

based on standardized case definitions developed by the Global Alignment of Immunization Safety Assessment in Pregnancy (GAIA) and the Brighton Collaboration [32].

For maternal and infant VE, we included the prevention of laboratory-confirmed SARS-CoV-2 infection and symptomatic COVID-19 by nucleic acid amplification tests and their complications, including hospital and intensive care unit admissions and deaths, among pregnant persons vaccinated during pregnancy and their offspring. Results regarding immunogenicity outcomes will be presented in a separate publication.

We performed the following pre-specified subgroup analyses when analyzing the primary outcomes: pregnancy trimester (first/early pregnancy 0–12 weeks; second trimester 13–27 weeks or third trimester/late pregnancy 28 weeks to full term), vaccine platform (mRNA, viral vector, inactivated virus), dominant variant of SARS-CoV-2 among the study population (Alpha, Beta, Delta, Omicron), and vaccination schedule (primary series and booster).

In the "Summary of Findings" tables, we summarized the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) certainty of evidence from comparative studies [33]. The estimates were downgraded for serious and very serious imprecision if 95% CIs were < 0.90 or > 1.10, and < 0.5 or > 1.50, respectively (or VE reaching 0% for effectiveness), and for serious and very serious inconsistency if not all 95% CIs are at the same side of the minimal important difference and I^2 values were > 60% and > 75%, respectively.

2.6 Data Visualization

We developed an online interactive dashboard for data visualization using Microsoft Power BI [34], available at https://www.safeinpregnancy.org/living-systematic-review/. The most relevant variables can be selected among maternal and neonatal safety and effectiveness outcomes. They are presented in figures, tables, and maps. The living meta-analysis section is available for users as an interactive tool developed as a Shiny application through RStudio [35]. The application allows the users to display meta-analyses of interest by outcome selecting by filters such as trimester, vaccine platform, vaccine doses, population, and comparator, among others. The research team designed an algorithm for the endpoint selection of each study included in the living meta-analysis.

3 Results

We included in this review 177 studies (see the study flow diagram in Fig. 1) that provided data on the safety, effectiveness, and/or immunogenicity of COVID-19 vaccines in pregnant persons and their infants, published until October 2023 (56% in 2022). The studies included a total of 638,791 vaccinated pregnant persons from 41 countries who were exposed to mRNA (154 studies), viral vector (51), and inactivated virus vaccines (17). Only ten studies (6%) were from LMICs and 23 studies (13%) were from upper-middle-income countries, the rest were from HICs. Among the included studies, 42% reported pregnancy outcomes, 35% maternal AEFI, 37% infant safety outcomes, 16% VE, and 39% immunogenicity results.

For this analysis, we included 137 studies reporting safety or effectiveness outcomes (immunogenicity outcomes will be reported elsewhere). Most were conducted in the USA (43 [31%]), Israel (25 [18%]), Brazil (7 [5%]), and seven (5%) were multi-country. These studies used one or more study designs: cohort studies (95 [69%]), cross-sectional (12 [9%]), case-control (10 [7%]), case series (10 [7%]), case report (9 [7 %]), and controlled clinical trial (1 [1%]). The only included RCT reported only AEFIs. It is noteworthy that 21 of the studies reported data from surveillance systems (15%). Out of 137 publications, 33 reported adjusted measures and were included in the meta-analysis.

Among the ten COVID-19 vaccine products identified, the most frequently assessed were the BNT162b2 (Pfizer/BioNTech) mRNA vaccine in 108 studies (79%), the mRNA-1273 (Moderna) vaccine in 71 studies (52%), and the Janssen/Johnson & Johnson (Ad26,COV2,S) in 24 studies (18%) (Table S1 of the ESM). All descriptive information is available online in real time at https://www.safeinpregnancy.org/living-systematic-review/ (last updated January 2024). It can be filtered by publication date, country/region, study design, population, and vaccine type and product from the sidebar, the map, or the figures. A snapshot of 10/30/2023 is presented in the evidence map in Fig. 2.

3.1 Risk of *Bias* of Included Studies

The comprehensive quality assessment according to each study design revealed a substantial proportion of studies meeting the criteria for good or fair quality. Among the cross-sectional and cohort studies, 93% (99/107) were rated as good or fair quality, while 70% (7/10) of case-series studies reached the same categories. All the case-control studies were deemed to be of good or fair quality (10/10) and the only controlled clinical trial included met the criteria for fair quality. The risk of bias for the included studies by study design is presented in Tables S2, S3, S4, and S5, of the ESM.

3.2 Effects of COVID-19 Vaccines During Pregnancy

We present the "Summary of Findings" tables with the most important outcomes by subgroup meta-analyses/estimates.

Fig. 1 Study flow diagram
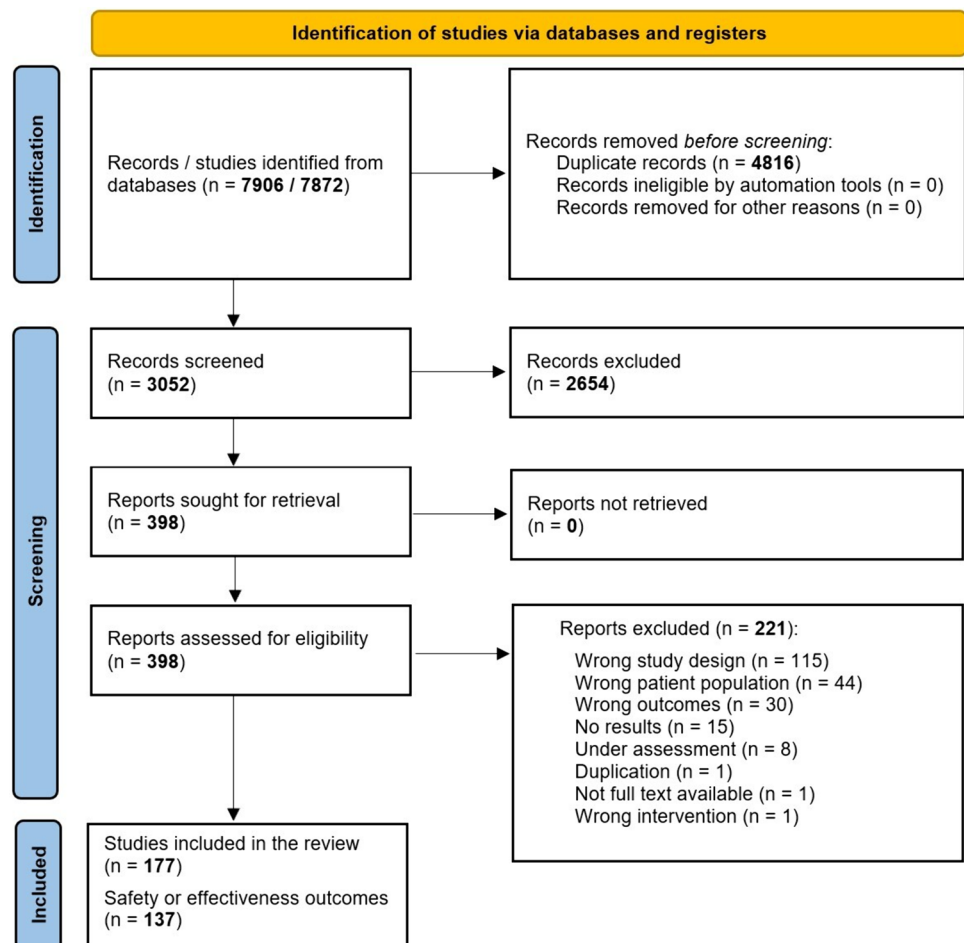
Maternal pregnancy-related safety outcomes and infant safety outcomes are presented by trimester and by vaccines, and efficacy by vaccine type and SARS-CoV-2 variant dominance. All remaining results, organized by outcome groups, are also presented in our LSR platform at https://www.safeinpregnancy.org/summary-tables/.

The results of each comparative (see https://www.safeinpregnancy.org/meta-analysis/) and non-comparative (see https://www.safeinpregnancy.org/proportional-meta-analyses/) meta-analysis are shown on the online and interactive LSR platform through forest plot/meta-analyses and summary tables organized by outcome.

3.2.1 Maternal Pregnancy-Related Safety Outcomes

The pooled absolute and relative effects of adjusted comparative studies on maternal pregnancy-related safety outcomes and their certainty of evidence are presented in Table 1 and the pooled proportions of outcomes and background rates, including the supporting references, are in Table S6 of the ESM.

For this particular set of outcomes, the level of evidence ranged from low to very low certainty. Evidence suggests a

lower risk of stillbirth among those who received at least one dose of the COVID-19 mRNA vaccine compared with those who did not when the exposure was in the first or second trimester (1,2T) or in the third trimester (3T) [RR 0.17; 95% CI 0.07–0.43 and RR 0.25; 95% CI 0.08–0.80, respectively], but there was no statistically significant difference between arms when the exposure was in the 2T (RR 1.12; 95% CI 0.52–2.40) and at any trimester. Pooled estimation of three studies [36–38] of vaccination at any trimester with mRNA/viral vector showed a RR of 0.49 (95% CI 0.20–1.19; I^2 87%) (Fig. 3). We found similar findings when we analyzed this outcome by vaccine platform (Fig. S1 of the ESM).

Three observational studies reported adjusted effect measures for miscarriage/abortion [39–41]. Pooled studies of two of them [39, 41] did not show a higher risk of miscarriage/abortion among vaccinated pregnant women with mRNA in 1T or 1/2T (OR 0.91; 95% CI 0.70–1.20; I^2 77%) with at least one dose during pregnancy (Fig. S2 of the ESM). The third study assessing viral vector vaccines found similar results (RR 0.84 95% CI 0.48–1.47) [not shown in the plot because it uses a different effect measure] [40]. Only one study reported adjusted effect measures for a gestational diabetes outcome [42] and did not show a
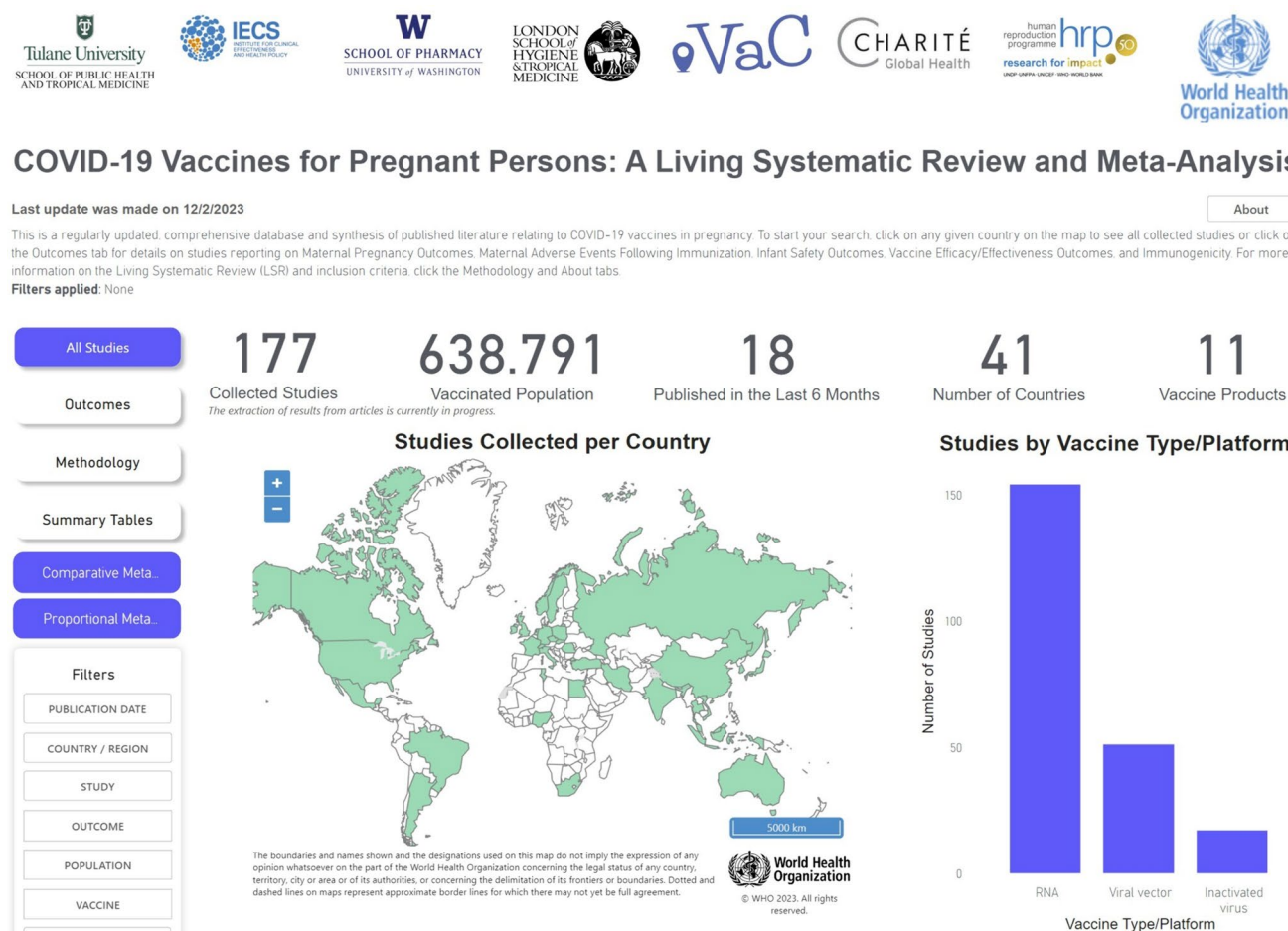
Fig. 2 Evidence map

higher risk after vaccination at 2T and 3T (RR 1.21; 95% CI 0.93–1.58 and RR 0.99; 95% CI 0.77–1.27, respectively) between vaccinated pregnant people with the mRNA vaccine and unvaccinated groups.

The pooled estimation of three studies reporting adjusted effect measures [42–44] did not show a higher risk of hypertensive disorders of pregnancy between vaccinated pregnant women with the mRNA vaccine administered in 2,3T and unvaccinated pregnant women (RR 1.07; 95% CI 0.81–1.40; $p = 0.49$; I^2 0%) [Fig. S3 of the ESM]. Six studies reported adjusted effect measures for emergency cesarean delivery [37, 42–46]. The single study meeting the trimester filter showed a lower incidence of this outcome in the vaccinated group at 2,3T with the mRNA vaccine (RR 0.97; 95% CI 0.94–1.00).

A postpartum hemorrhage-adjusted outcome was reported by six studies [36, 42, 43, 45–47]. Pooled estimates of five of them ([36, 37, 42, 43, 46] showed a trend toward a higher incidence of postpartum hemorrhage in those receiving mRNA vaccines during 2,3T (regardless of the completeness of the scheme) versus unvaccinated pregnant persons (RR 1.44; 95% CI 0.85–2.45; I^2 89%). The subgroup analysis by vaccination schedule (partial, completed, and booster) showed different incidences of this outcome (RR 1.09; 95% CI 0.56–2.12 [45]; RR 0.95; 95% CI 0.86–1.05 [36, 37, 43, 46] and RR 3.88; 95% CI 2.41–6.25 [46], respectively) (Figs. S4 and S5 of the ESM).

The background rates of maternal pregnancy-related safety outcomes were within the CIs of the proportional meta-analysis estimations, which means that proportions were not unexpected in vaccinated individuals. The subgroup analysis by trimester of exposure and vaccine type showed similar results to each other or presented a significant imprecision.

As an example, we illustrated the pooled proportions of stillbirth by trimester in Fig. 4 and by vaccine type in Fig. S6 of the ESM. The rest of the outcomes are shown in https://www.safeinpregnancy.org/proportional-meta-analyses/.

Table 1 Maternal pregnancy-related outcomes associated with COVID-19 vaccination compared to no vaccination during pregnancy, by trimester of exposure and vaccine type. Population: pregnant persons; setting: any; intervention: COVID-19 vaccination; comparison: no vaccination

Outcomes[#]	Anticipated absolute risks[*] (95% CI)		Adjusted relative effect[^] (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	With no vaccination	With vaccination			
Stillbirth					
First or second trimester (mRNA, viral vector vaccine)	5 per 1000	**4 fewer per 1000** (4 to 3 fewer)	**RR 0.17** (0.07–0.43)	7107 (1)	+ + − − Low
Second trimester (mRNA, viral vector vaccine)	10 per 1000	**1 more per 1000** (5 fewer to 14 more)	**RR 1.12** (0.52–2.40)	4277 (1)	+ − − − Very low[a]
Third trimester (mRNA, viral vector vaccine)	10 per 1000	**7 fewer per 1000** (9 to 2 fewer)	**RR 0.25** (0.08–0.80)	4642 (1)	+ + − − Low
Any trimester (mRNA, viral vector vaccine)	1 per 1000	**1 fewer per 1000** (1 fewer to 0 fewer)	**RR 0.49** (0.20–1.19)	254,972 (3)	+ − − − Very low[bc]
Miscarriage/abortion					
First trimester (mRNA vaccine)	125 per 1000	**26 fewer per 1000** (47 fewer to 0 fewer)	**OR 0.77** (0.59–1.00)	2228 (1)	+ + − − Low
First trimester (viral vector vaccine)	5 per 1000	**1 fewer per 1000** (2 fewer to 2 more)	**RR 0.84** (0.48–1.47)	17,550 (2)	+ − − − Very low[bc]
First or second trimester (mRNA vaccine)	1 per 1000	**0 fewer per 1000** (0 fewer to 0 fewer)	**OR 0.91** (0.70–1.20)	266,332 (2)	+ − − − Very low[b]
Gestational diabetes					
Second trimester (mRNA vaccines)	83 per 1000	**17 more per 1000** (6 fewer to 48 more)	**RR 1.21** (0.93–1.58)	4277 (1)	+ − − − Very low[a]
Third trimester (mRNA vaccines)	83 per 1000	**1 fewer per 1000** (19 fewer to 22 more)	**RR 0.99** (0.77–1.27)	4642 (1)	+− − − Very low[b]
Hypertensive disorders of pregnancy					
Second trimester (mRNA vaccines)	13 per 1,000	**4 fewer per 1000** (9 fewer to 7 more)	**RR 0.71** (0.33–1.53)	4277 (1)	+ − − − Very low[a]
Third trimester (mRNA vaccines)	13 per 1000	**2 fewer per 1000** (7 fewer to 7 more)	**RR 0.83** (0.45–1.54)	4642 (1)	+ − − − Very low[a]
Second or third trimester (mRNA vaccines)	30 per 1000	**2 more per 1000** (6 fewer to 12 more)	**RR 1.07** (0.81–1.40)	13,717 (3)	+ − − − Very low[b]
Emergency cesarean					
Second or third trimester (mRNA vaccines)	118 per 1000	**11 fewer per 1000** (16 to 5 fewer)	**RR 0.97** (0.94–1.00)	52,775 (1)	+ + − − Low
Postpartum hemorrhage					
Second trimester (mRNA, viral vector vaccine)	31 per 1000	**3 more per 1000** (9 fewer to 23 more)	**RR 1.11** (0.71–1.74)	4277 (1)	+ − − − Very low[b]
Third trimester (mRNA, viral vector vaccine)	31 per 1000	**7 more per 1000** (5 fewer to 25 more)	**RR 1.22** (0.83–1.79)	4642 (1)	+ − − − Very low[a]
Second or third trimester (mRNA vaccines, viral vector vaccine)	31 per 1000	**14 more per 1000** (5 fewer to 46 more)	**RR 1.44** (0.85–2.45)	66,986 (5)	+ − − − Very low[a,c]

The relative effect could be RRs, ORs or HRs. Bold values prevents confusions about the effect measure. The absolute effect with vaccination correlates with the relative effect measure and it is the main result for readers

CI confidence interval, *NICU* neonatal intensive care unit, *RR* risk ratio

[#]Follow-up not reported

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

[^]We reported here the effect measure with more information, and we reported the RR if other relative effects provided similar information

GRADE (Grading of Recommendations Assessment, Development and Evaluation) 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
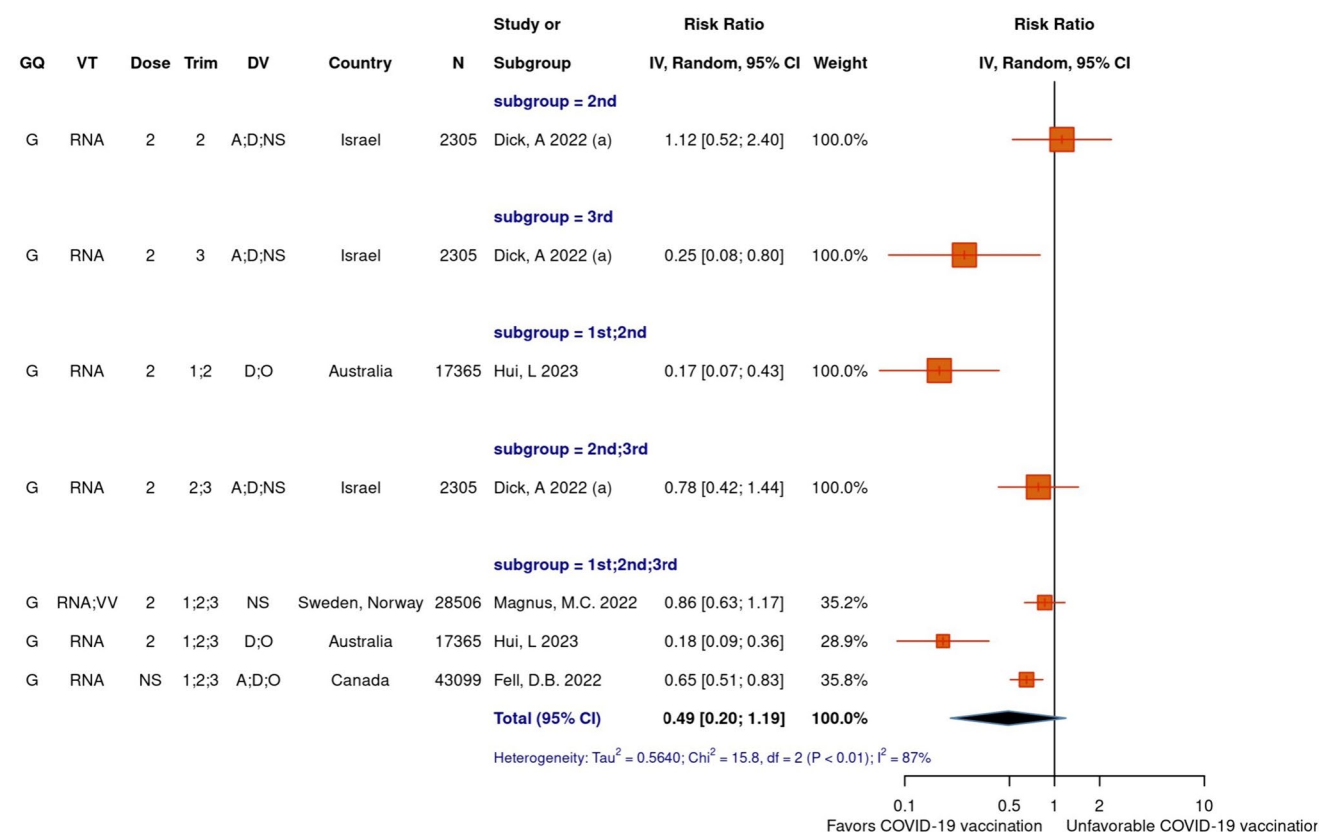
[a]Upper limit of the 95% CI > 1.5

Table 1 (continued)

Fig. 3 Adjusted risk of stillbirth associated with COVID-19 vaccination during pregnancy versus unvaccinated pregnant population, by trimester of exposure. *A* Alpha, *CI* confidence interval, *D* Delta, *DV* dominant variant, *G* good, *GQ* global quality, *NS* not specified, *O* Omicron, *VT* vaccine type, *VV* viral vector

3.2.2 Maternal AEFIs

The pooled proportions of AEFIs among vaccinated pregnant persons are presented by vaccine platform in Table S7 of the ESM. The pooled anaphylaxis proportion by vaccine type was 2 per 100,000 vaccinated persons (95% CI 0–92) with mRNA vaccines, and no events were reported with viral vector vaccines [48]. For serious adverse events, proportions were 0.25% (95% CI 0.13–0.41) and 0.41% (95% CI 0.10–2.24), and for lymphadenopathy, 4.41% (95% CI2.48–6.83) and 6.36 % (95% CI 4.70–8.24) with mRNA and viral vector vaccines respectively. The pooled proportion of myocarditis was 0.00% (95% CI 0.00–1.19) and the proportion of seizures was 0.05% (95% CI 0.00–0.26), both with mRNA vaccines. The pooled proportion of fever was 6.88% (95% CI 4.15–10.21) with mRNA vaccines and 30.96% (95% CI 7.47–26.15) with viral vector vaccines. The observed pooled proportion of headache was 19.83%

(95% CI 14.20–26.14) with mRNA vaccines, 12.40% (95% CI 0.00–44.20) with viral vector vaccines, and 10.05% (95% CI 4.03–18.00) with inactivated virus vaccines. Fatigue proportions were 40.91% (95% CI 33.16–48.89) with mRNA, 27.76% (95% CI 0.00–94.00) with viral vector vaccines, and 11.46% (95% CI 2.02–25.42) with inactivated virus vaccines, respectively. The rest of the analyzed AEFI outcomes (chills, diarrhea, injection-site reactions, joint pain, myalgia, rash, and vomiting) are shown in Table S7 of the ESM, and in our interactive LSR online platform (https://www.safeinpregnancy.org/proportional-meta-analyses/≡).

The pooled proportions by vaccine schedule (partial, complete, and booster) were generally similar with few exceptions. The proportion of headache, fatigue, fever, and lymphadenopathy was more than double with the second dose compared withthe first dose (shown in https://www.safeinpregnancy.org/proportional-meta-analyses/)
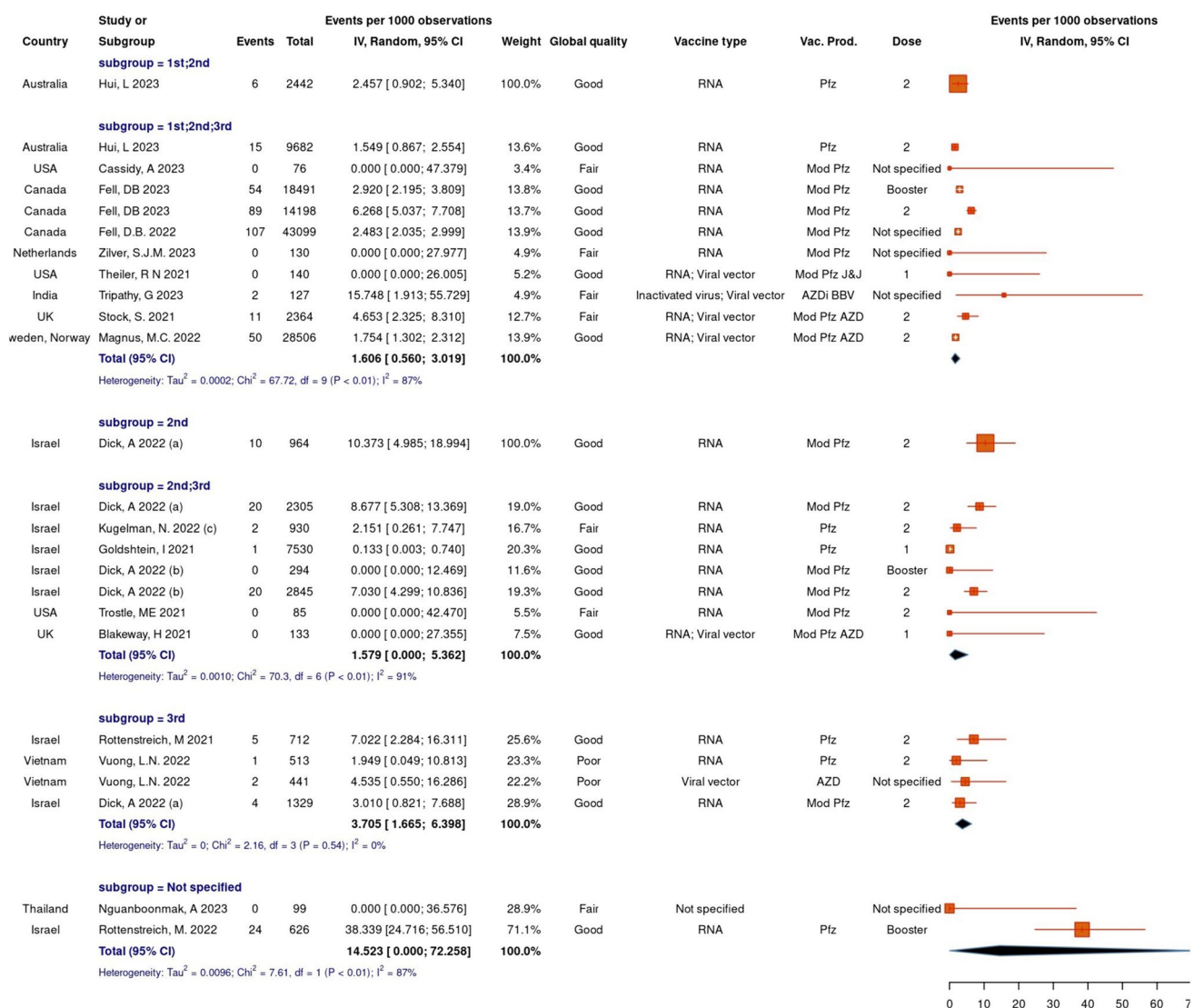
Country	Study or Subgroup	Events	Total	Events per 1000 observations IV, Random, 95% CI	Weight	Global quality	Vaccine type	Vac. Prod.	Dose	Events per 1000 observations IV, Random, 95% CI
	subgroup = 1st;2nd									
Australia	Hui, L 2023	6	2442	2.457 [0.902; 5.340]	100.0%	Good	RNA	Pfz	2	
	subgroup = 1st;2nd;3rd									
Australia	Hui, L 2023	15	9682	1.549 [0.867; 2.554]	13.6%	Good	RNA	Pfz	2	
USA	Cassidy, A 2023	0	76	0.000 [0.000; 47.379]	3.4%	Fair	RNA	Mod Pfz	Not specified	
Canada	Fell, DB 2023	54	18491	2.920 [2.195; 3.809]	13.8%	Good	RNA	Mod Pfz	Booster	
Canada	Fell, DB 2023	89	14198	6.268 [5.037; 7.708]	13.7%	Good	RNA	Mod Pfz	2	
Canada	Fell, D.B. 2022	107	43099	2.483 [2.035; 2.999]	13.9%	Good	RNA	Mod Pfz	Not specified	
Netherlands	Zilver, S.J.M. 2023	0	130	0.000 [0.000; 27.977]	4.9%	Fair	RNA	Mod Pfz	Not specified	
USA	Theiler, R N 2021	0	140	0.000 [0.000; 26.005]	5.2%	Good	RNA; Viral vector	Mod Pfz J&J	1	
India	Tripathy, G 2023	2	127	15.748 [1.913; 55.729]	4.9%	Fair	Inactivated virus; Viral vector	AZDi BBV	Not specified	
UK	Stock, S. 2021	11	2364	4.653 [2.325; 8.310]	12.7%	Fair	RNA; Viral vector	Mod Pfz AZD	2	
Sweden, Norway	Magnus, M.C. 2022	50	28506	1.754 [1.302; 2.312]	13.9%	Good	RNA; Viral vector	Mod Pfz AZD	2	
	Total (95% CI)			1.606 [0.560; 3.019]	100.0%					
	Heterogeneity: Tau^2 = 0.0002; Chi^2 = 67.72, df = 9 (P < 0.01); I^2 = 87%									
	subgroup = 2nd									
Israel	Dick, A 2022 (a)	10	964	10.373 [4.985; 18.994]	100.0%	Good	RNA	Mod Pfz	2	
	subgroup = 2nd;3rd									
Israel	Dick, A 2022 (a)	20	2305	8.677 [5.308; 13.369]	19.0%	Good	RNA	Mod Pfz	2	
Israel	Kugelman, N. 2022 (c)	2	930	2.151 [0.261; 7.747]	16.7%	Fair	RNA	Pfz	2	
Israel	Goldshtein, I 2021	1	7530	0.133 [0.003; 0.740]	20.3%	Good	RNA	Pfz	1	
Israel	Dick, A 2022 (b)	0	294	0.000 [0.000; 12.469]	11.6%	Good	RNA	Mod Pfz	Booster	
Israel	Dick, A 2022 (b)	20	2845	7.030 [4.299; 10.836]	19.3%	Good	RNA	Mod Pfz	2	
USA	Trostle, ME 2021	0	85	0.000 [0.000; 42.470]	5.5%	Fair	RNA	Mod Pfz	2	
UK	Blakeway, H 2021	0	133	0.000 [0.000; 27.355]	7.5%	Good	RNA; Viral vector	Mod Pfz AZD	1	
	Total (95% CI)			1.579 [0.000; 5.362]	100.0%					
	Heterogeneity: Tau^2 = 0.0010; Chi^2 = 70.3, df = 6 (P < 0.01); I^2 = 91%									
	subgroup = 3rd									
Israel	Rottenstreich, M 2021	5	712	7.022 [2.284; 16.311]	25.6%	Good	RNA	Pfz	2	
Vietnam	Vuong, L.N. 2022	1	513	1.949 [0.049; 10.813]	23.3%	Poor	RNA	Pfz	2	
Vietnam	Vuong, L.N. 2022	2	441	4.535 [0.550; 16.286]	22.2%	Poor	Viral vector	AZD	Not specified	
Israel	Dick, A 2022 (a)	4	1329	3.010 [0.821; 7.688]	28.9%	Good	RNA	Mod Pfz	2	
	Total (95% CI)			3.705 [1.665; 6.398]	100.0%					
	Heterogeneity: Tau^2 = 0; Chi^2 = 2.16, df = 3 (P = 0.54); I^2 = 0%									
	subgroup = Not specified									
Thailand	Nguanboonmak, A 2023	0	99	0.000 [0.000; 36.576]	28.9%	Fair	Not specified		Not specified	
Israel	Rottenstreich, M. 2022	24	626	38.339 [24.716; 56.510]	71.1%	Good	RNA	Pfz	Booster	
	Total (95% CI)			14.523 [0.000; 72.258]	100.0%					
	Heterogeneity: Tau^2 = 0.0096; Chi^2 = 7.61, df = 1 (P < 0.01); I^2 = 87%									

Fig. 4 Pooled proportion of stillbirth in vaccinated pregnant population per 1000 patients by trimester of exposure. *CI* confidence interval

Only two cohort studies reported comparative effect measures for AEFIs between pregnant and non-pregnant persons [49, 50]. Kachikis et al. [49] observed that in comparison to non-pregnant non-lactating persons ($N = 4726$), pregnant persons ($N = 2009$) experienced more local reactions to a COVID-19 booster or third dose (adjusted OR 1.2; 95% CI 1.0–1.4 but fewer systemic reactions (adjusted OR 0.7; 95% CI 0.6–0.8). The majority of pregnant individuals (97.6%) reported no obstetric concerns following vaccination.

Shapiro et al. [50] reported that pregnant persons ($N = 1650$ first dose and 1014 second dose) experienced side effects less frequently than non-pregnant persons ($N = 6600$ first dose and 4052 second dose). Pregnancy was a weak predictor for reporting any side effect in general and in particular fatigue, myalgia, headache, chills, and fever.

Estimation of each study and meta-analyses of both studies are reported in Table S8 of the ESM.

3.2.3 Infant Safety Outcomes Following COVID-19 Vaccination During Pregnancy

The pooled absolute and relative effects of adjusted comparative studies on infant safety outcomes following COVID-19 vaccination during pregnancy and their certainty of evidence are presented in Table 2. Pooled proportions and background rates, including the supporting references, are shown in Table S9 of the ESM. For this particular set of outcomes, the level of evidence ranged from low to very low certainty.

Three studies reported adjusted effect measures for any congenital malformations [36, 45, 51]. Regardless of the

Table 2 Infant safety outcomes associated with COVID-19 vaccination during pregnancy compared to no vaccination in pregnancy, by trimester of exposure and vaccine type

Outcomes[#]	Anticipated absolute risks[*] (95% CI)		Adjusted relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	With no vaccination	With vaccination			
NICU hospitalization					
First trimester (mRNA vaccines)	56 per 1000	**8 fewer per 1000** (from 18 fewer to 5 more)	**RR 0.86** (0.67–1.10)	5602 (1)	+ + − − Low
Second trimester (mRNA, viral vector vaccines)	85 per 1000	**8 fewer per 1000** (from 26 fewer to 23 more)	**RR 0.905** (0.70–1.27)	142,027 (1)	+ + − − Low
Third trimester (mRNA, viral vector vaccines)	85 per 1000	**8 fewer per 1000** (from 15 fewer to 4 fewer)	**RR 0.91** (0.83–0.96)	143,367 (1)	+ + − − Low
Any trimester (mRNA vaccines)	65 per 1000	**3 fewer per 1000** (from 9 fewer to 3 more)	**RR 0.95** (0.86–1.04)	242,393 (5)	+ + − − Low
Any trimester (mRNA, viral vector vaccines)	85 per 1000	**4 fewer per 1000** (from 13 fewer to 5 more)	**RR 0.95** (0.85–1.06)	158,053 (2)	+ + − − Low
Apgar score < 7 at 5 minutes					
Second trimester (mRNA, viral vector vaccines)	16 per 1000	**1 more per 1000** (from 3 fewer to 6 more)	**RR 1.07** (0.83–1.39)	142,027 (1)	+ − − − Very low[a]
Third trimester (mRNA, viral vector vaccines)	16 per 1000	**3 fewer per 1000** (from 5 fewer to 0 fewer)	**RR 0.840** (0.711–0.992)	143,383 (1)	+ + − − Low
Any trimester (mRNA vaccines)	16 per 1000	**2 fewer per 1000** (from 3 fewer to 0 fewer)	**RR 0.888** (0.810–0.973)	223,783 (5)	+ + − − Low
Any trimester (mRNA, viral vector vaccines)	16 per 1000	**1 fewer per 1000** (from 3 fewer to 1 more)	**RR 0.940** (0.837–1.056)	157,521 (1)	+ + − − Low
Prematurity (gestational age at delivery < 37 weeks)					
First trimester (mRNA vaccines)	66 per 1000	**9 fewer per 1000** (from 18 fewer to 3 more)	**RR 0.87 (0.73–1.04)**	11,204 (2)	+ + − − Low
Second trimester (mRNA, viral vector vaccines)	44 per 1000	**7 more per 1000** (from 18 fewer to 3 more)	**RR 1.17 (0.77–1.78)**	146,304 (2)	+ − − − Very low[bc]
Third trimester (mRNA, viral vector vaccines)	44 per 1000	**13 fewer per 1000** (from 28 fewer to 17 more)	**RR 0.71 (0.36–1.38)**	148,025 (2)	+ − − − Very low[ab]
Any trimester (mRNA, viral vector vaccines)	20 per 1000	**2 fewer per 1000** (from 5 fewer to 1 more)	**RR 0.89 (0.73–1.07)**	284,489 (5)	+ + − − Low
Small for gestational age					
First trimester (mRNA vaccine)	63 per 1000	**9 more per 1000** (from 5 fewer to 26 more)	**RR 1.14** (0.92–1.41) **HR** 1.000 (95% CI 0.896–1.116)	5602 (1)	+ − − − Very low[a]
Second trimester (mRNA, viral vector vaccine)	84 per 1000	**8 fewer per 1000** (from 29 fewer to 23 more)	**RR 0.91** (0.65–1.27) **HR** 1.02 (95% CI 0.96–1.08)	146,304 (2)	+ − − − Very low[a b]
Third trimester (mRNA, viral vector vaccine)	84 per 1000	**6 fewer per 1000** (from 11 fewer to 0 fewer)	**RR 0.93** (0.87–1.00) **HR** 0.93 (95% CI 0.88–0.98)	148,025 (2)	+ + − − Low
Any trimester (mRNA vaccine)	77 per 1000	**2 fewer per 1000** (from 5 fewer to 0 fewer)	**RR 0.97** (0.93–1.01) **HR** 1.01 (95% CI 0.66–1.55) **OR** 0.94 (95% CI 0.89–0.99)	281,210 (7)	+ + − − Low
Any trimester (mRNA, viral vector vaccine)	84 per 1000	**2 fewer per 1000** (from 6 fewer to 3 more)	**RR 0.98** (0.92–1.04) **HR** 0.95 (95% CI 0.87–1.03) **OR** 1.00 (95% CI 0.55–1.82)	157,521 (1)	+ + − − Low
Any congenital malformations or birth defects					
First trimester (mRNA vaccine)	21 per 1000	**7 fewer per 1000** (from 12 fewer to 1 more)	**RR 0.69** (0.45–1.06)	5602 (1)	+ + − − Low

Table 2 (continued)

Outcomes[#]	Anticipated absolute risks[*] (95% CI)		Adjusted relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	With no vaccination	With vaccination			
First/second trimester (mRNA vaccine)	31 per 1000	**6 fewer per 1000** (from 13 fewer to 4 more)	**RR 0.80** (0.57–1.13)	5110 (1)	+ − − − Very low[a]
Second/third trimester (mRNA, viral vector vaccine)	25 per 1000	**3 fewer per 1000** (from 19 fewer to 58 more)	**RR 0.89** (0.24–3.31)	532 (1)	+ − − − Very low[c]
Any trimester (mRNA vaccine)	25 per 1000	**7 fewer per 1000** (from 11 fewer to 3 fewer)	**RR 0.71** (0.57–0.89)	18,281 (2)	+ + − − Low
Respiratory distress in the newborn					
Second/third trimester (mRNA vaccine)	18 per 1000	**2 fewer per 1000** (from 10 fewer to 14 more)	**RR 0.88** (0.44–1.78)	4399 (1)	+ − − − Very low[c]
Infant death					
Any trimester (mRNA vaccine)	2 per 1000	**0 fewer per 1000** (from 1 fewer to 1 more)	**RR 0.840** (0.42–1.68)	24,190 (1)	+ − − − Very low[c]

The relative effect could be RRs, ORs or HRs. Bold values prevents confusions about the effect measure. The absolute effect with vaccination correlates with the relative effect measure and it is the main result for readers

CI confidence interval, *HR* hazard ratio, *NICU* neonatal intensive care unit, *RR* risk ratio

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

[#]Follow-up not reported

^We reported here the effect measure with more information, and we reported the RR if other relative effects provided similar information

GRADE (Grading of Recommendations Assessment, Development and Evaluation) 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

Population: pregnant persons; setting: any; intervention: COVID-19 vaccination; comparison: no vaccination

[a]Upper limit of the 95% CI > 1.10

[b]I^2 > 70%, but every study shows the same direction

[c]Upper limit of the 95% CI > 1.5

trimester of exposure, the studies did not show an increased risk of congenital malformations in the vaccinated group (RR 0.69 for 1T, 0.80 for 2,3T, and 0.72 for 1,2,3T). Pooled studies by vaccine type (RR 0.71; 95% CI 0.47–1.06 and RR 0.89; 95% CI 0.56–0.93 for mRNA and viral vector, respectively). Analysis by vaccine schedule showed similar results (Figs. S7, S8, and S9 of the ESM).

Five pooled studies [36–38, 42, 46] that recorded the incidence of an Apgar score ≤5 minutes revealed no statistically significant difference between vaccinated during 2T-3T or any T and unvaccinated groups (RR 0.74; 95% CI 0.33–1.88 and RR 0.90; 95% CI 0.77–1.04, respectively); pooled results were homogenous (I^2 29% and 50%, respectively). Subgroup analyses by vaccine type or vaccine schedule do not show any differences (Figs. S10 and S11 of the ESM).

Nine studies reported adjusted effect measures for prematurity (gestational age at delivery < 37 weeks) [36–38, 42, 44, 46, 51, 52]. Pooled estimations did not show a higher incidence of preterm infants in vaccinated persons exposed at any trimester (RR 0.89; 95% CI 0.73–1.07). There were some differences by trimester but never reached statistical significance. When we analyzed pooled studies by vaccine schedule and type of vaccine (mRNA and viral vector), there was no increased risk of prematurity either (Figs. S12 and S13 of the ESM).

Ten studies reported adjusted effect measures for small for gestational age [36, 37, 42–46, 51, 52]. Pooled estimations did not show a higher incidence of small for gestational age cases in vaccinated persons exposed at any trimester (RR 0.98; 95% CI 0.94–1.01). There were some differences by trimester but these never reached statistical significance.

When we analyzed pooled studies by vaccine status and type of vaccine (mRNA and viral vector), there was no increased risk for preterm infants (Figs. S14 and S15 of the ESM).

Six studies reported adjusted effect measures for NICU hospitalization [36–38, 44, 45, 51]. Pooled estimations did not show a higher incidence of NICU hospitalizations and even showed a lower incidence among vaccinated pregnant persons at 3T and 2,3T (RR 0.92; 95% CI 0.87–0.97 and RR 0.92; 95% CI 0.87–0.97, respectively) [Fig. S16 of the ESM]. A subgroup analysis by vaccine platform and vaccine status did not show any relevant difference between groups.

Only one study reported adjusted effect measures for respiratory distress in the newborn (not due to COVID-19) [43] and one reported for infant death [51] among pregnant persons receiving mRNA vaccination at any trimester. There was no increased risk (RR 0.84; 95% CI 0.42–1.68).

The background rates of infant safety outcomes were within the CIs of the proportional meta-analysis performed (see Table S9 of the ESM). Data were analyzed by trimester of exposure and vaccine type. The pooled proportions showed no important differences by vaccine type, except for low birth weight, which presented half the proportion with viral vector vaccines than with mRNA vaccines (2.25%; 95% CI 1.25–3.50 vs 5.56%; 95% CI 4.23–7.06, respectively) [Fig. S17 of the ESM; see https://www.safeinpregnancy.org/proportional-meta-analyses/ for the rest of the outcomes].

3.2.4 Effectiveness Outcomes

The absolute and relative effects of adjusted comparative studies and their certainty of evidence by vaccine type and SARS-CoV-2 variant dominance are presented in Table 3. Seven studies reported adjusted effect measures of vaccination compared with no vaccination on the VE on severe or hospitalized COVID-19 [53–59]. The available evidence, characterized by low to very low certainty, indicates a potential reduction in severe or hospitalized COVID-19 cases among mothers with varying vaccine types. The comparison group for all VE analyses was 0 doses (unvaccinated pregnant individuals). Specifically, combining across variants, the VE was estimated at 72% (95% CI 42–86) with mRNA vaccines, 49% (95% CI 0–74) with viral vector vaccines, and 61% (95% CI 0–93) with inactivated vaccine regardless of vaccine schedule (see Fig. 5). Different follow-ups, which can be explored online activating days to outcome, did not change significantly the estimations. The VE during Omicron SARS-CoV-2 dominance was 58% (95% CI 15–79) for the primary series and 65% (95% CI 33–81) after a booster dose regardless of the timing of vaccination. Schrag et al. reported an estimated VE of 86% (95% CI 28–97) against hospitalization in the Omicron period from 7 to 119 days after the receipt of a booster dose. This suggests a high level of protection during this period. However, the booster dose did not provide a statistically significant protective effect beyond 120 days before virologically confirmed SARS-CoV-2 or hospitalization [59] (Figs. S18 and S19 of the ESM).

The pattern was similar for symptomatic COVID-19 by type of vaccine with VE of 78% (95% CI 21–94) for mRNA, 39% (95% CI 26–49) for inactivated virus, and 25% (95% CI 0–100) for viral vector regardless the SARS-CoV-2 variant dominance. The VE with mRNA or viral vector vaccines during Omicron SARS-CoV-2 dominance was 56% (95% CI 21–75) and was not possible to compare with a single type of vaccine.

The same happens regarding laboratory-confirmed SARS-CoV-2 infection by vaccine type, with VE 82% (95% CI 39–95) with mRNA vaccines, 27% (95% CI 0–47) with inactivated vaccines, and 20% (95% CI 0–36) with viral vector vaccines. However, the reduction was lower during Omicron dominance: VE 30% (95% CI 19–39).

Low-certainty evidence suggests that mothers' vaccination may reduce severe or hospitalized COVID-19 in their infants, based on three studies that reported adjusted effect measures for this outcome in infants up to 6 months of age [14, 60, 61]. Pooled studies showed a VE of 79% (95% CI 45–92) with the mRNA vaccine and complete scheme (two doses) in mothers evaluating during Delta dominance and 48% (95% CI 32–60) during Omicron dominance. One study [14] showed that a third vaccine dose during pregnancy bolstered the protection of infants raising the VE to 80% (63–88) during Omicron dominance and maintaining protection for 6 months. These meta-analyses by trimester of exposure are available at https://www.safeinpregnancy.org/meta-analysis/.

4 Discussion

To our knowledge, this is the first LSR that has regularly evaluated, updated, and publicly disseminated the latest findings on the safety and effectiveness of COVID-19 vaccines during pregnancy, including 177 studies involving 631,957 pregnant persons worldwide exposed to ten COVID-19 vaccine products. Out of the 137 publications included in meta-analyses, 33 provided adjusted measures and thus incorporated them into the comparative meta-analysis.

4.1 Main Findings

We found no associations between COVID-19 vaccination during pregnancy with at least one dose and adverse maternal-pregnancy-related and infant outcomes, regardless of the trimester of exposure and type of vaccine. Outcomes included miscarriage, gestational diabetes, hypertensive disorders, congenital anomalies, Apgar score at 5 minutes

Table 3 Effectiveness of COVID-19 vaccination compared to no vaccination during pregnancy by vaccine type and SARS-CoV-2 variant dominance

Outcomes (follow-up: range 13–365 days)#	Anticipated absolute risks* (95% CI)		Adjusted relative effect (VE %; 95% CI)	No. of participant (studies)	Certainty of the evidence (GRADE)
	With no vaccination	With vaccination			
Severe or hospitalized COVID-19 in mothers					
mRNA vaccines (Omicron/Alpha/other dominance)	31 per 1000	**22 fewer per 1000** (from 86 to 13 fewer)[a]	**VE 72** (42–86)	34,495 (4)	+ + − − Low
Inactivated vaccines (Omicron/Delta/other dominance)	58 per 1000	**35 fewer per 1000** (from 54 fewer to 80 more)[a]	**VE 61** (0–93)	17,805 (2)	+ − − − Very low[b,c]
Viral vector (Omicron dominance)	49 per 1000	**24 fewer per 1000** (from 36 to 0 fewer)[a]	**VE 49** (0 –74)	2286 (1)	+ − − − Very low[b,c]
mRNA/viral vector vaccines (Omicron dominance)	82 per 1000	**53 fewer per 1000** (from 66 to 27 fewer)[a]	**VR 65** (33–81)	13,651 (3)	+ + − − Low
Symptomatic COVID-19 in mothers					
mRNA vaccines	95 per 1000	**74 fewer per 1000** (from 89 to 20 fewer)[a]	**VE 78** (21–94)	35,610 (4)	+ + − − Low[d]
Inactivated vaccines	90 per 1000	**35 fewer per 1000** (from 44 to 23 fewer)[a]	**VE 39** (26–49)	2533 (2)	+ − − − Very low[e]
Viral vector vaccines	123 per 1000	**31 fewer per 1000** (from 54 to 0 fewer)[a]	**VE 25** (0–100)	1732 (1)	+ − − − Very low[b,c]
mRNA/viral vector vaccines (Omicron dominance)	232 per 1000	**130 fewer per 1000** (from 174 to 49 fewer)[a]	**VE 56** (21–75)	14,766 (3)	+ + − − Low[d]
Virologically confirmed SARS-CoV-2 infection in mothers					
mRNA vaccines	42 per 1000	**35 fewer per 1000** (from 40 to 17 fewer)[a]	**VE 82** (39–95)	39,328 (4)	+ + − − Low[d]
Inactivated vaccines	365 per 1000	**99 fewer per 1000** (from 172 to 0 fewer)[a]	**VE 27** (0–47)	2108 (1)	+ − − − Very low[c]
Viral vaccines	365 per 1000	**73 fewer per 1000** (from 131 to 0 fewer)[a]	**VE 20** (0–36)	2286 (1)	+ − − − Very low[b,c]
mRNA/viral vector vaccines (Omicron dominance)	365 per 1000	**109 fewer per 1000** (from 142 fewer to 69 fewer)[a]	**VE 30** (19–39)	2610 (1)	+ − − − Very low[b]
Severe or hospitalized COVID-19 in infants					
mRNA vaccines	302 per 1000	**194 fewer per 1000** (from 242 to 112 fewer)[a]	**VE 64** (37–80)	3716 (3)	+ + − − Low[d]
mRNA vaccines (Omicron dominance)	294 per 1000	**188 fewer per 1000** (from 259 fewer to 26 more)[a]	**VE 64** (0–88)	3330 2)	+ + − − Low[d]
Virologically confirmed SARS-CoV-2 infection in infants					
mRNA vaccines (Omicron dominance)	106 per 1000	**70 fewer per 1000** (from 85 to 39 fewer)[a]	**VE 66** (37–81)	10,939 (3)	+ + − − Low[d]

The relative effect could be RRs, ORs or HRs. Bold values prevents confusions about the effect measure. The absolute effect with vaccination correlates with the relative effect measure and it is the main result for readers

Population: pregnant persons; setting: any; intervention: COVID-19 vaccination; comparison: no vaccination

CI confidence interval, *VE* vaccine effectiveness

***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). Only mRNA vaccines were identified for infant outcomes and no study for symptomatic COVID-19 in infants

GRADE (Grading of Recommendations Assessment, Development and Evaluation)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
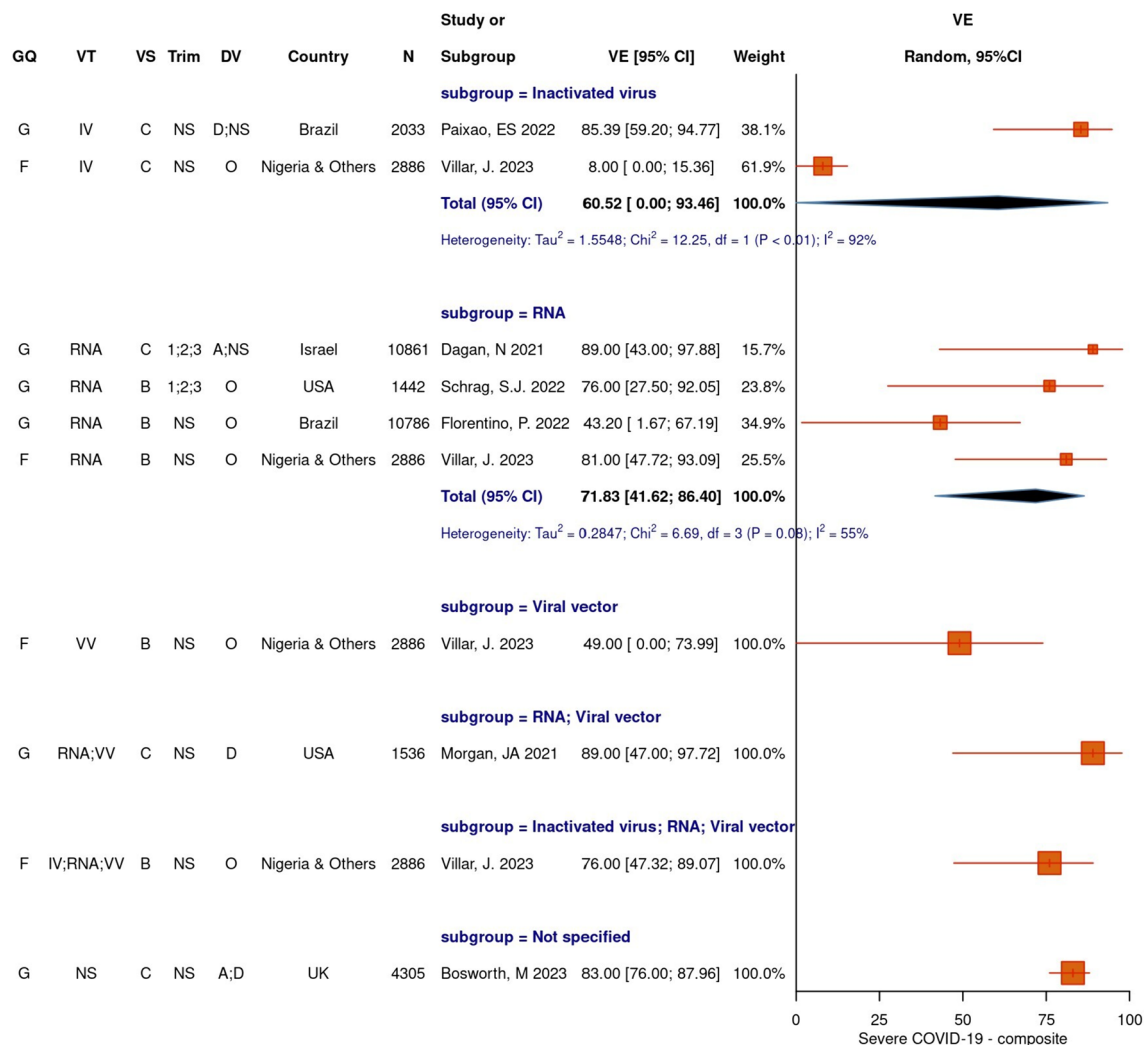
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect

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

[a]Calculated outside GRADEpro GDT to report vaccine efficacy percentage

[b]Fair quality, single study

[c]Lower limit of the 95% CI of VE reaches 0%

Table 3 (continued)

GQ	VT	VS	Trim	DV	Country	N	Study or Subgroup	VE [95% CI]	Weight	VE Random, 95%CI
							subgroup = Inactivated virus			
G	IV	C	NS	D;NS	Brazil	2033	Paixao, ES 2022	85.39 [59.20; 94.77]	38.1%	
F	IV	C	NS	O	Nigeria & Others	2886	Villar, J. 2023	8.00 [0.00; 15.36]	61.9%	
							Total (95% CI)	**60.52 [0.00; 93.46]**	**100.0%**	
							Heterogeneity: Tau² = 1.5548; Chi² = 12.25, df = 1 (P < 0.01); I² = 92%			
							subgroup = RNA			
G	RNA	C	1;2;3	A;NS	Israel	10861	Dagan, N 2021	89.00 [43.00; 97.88]	15.7%	
G	RNA	B	1;2;3	O	USA	1442	Schrag, S.J. 2022	76.00 [27.50; 92.05]	23.8%	
G	RNA	B	NS	O	Brazil	10786	Florentino, P. 2022	43.20 [1.67; 67.19]	34.9%	
F	RNA	B	NS	O	Nigeria & Others	2886	Villar, J. 2023	81.00 [47.72; 93.09]	25.5%	
							Total (95% CI)	**71.83 [41.62; 86.40]**	**100.0%**	
							Heterogeneity: Tau² = 0.2847; Chi² = 6.69, df = 3 (P = 0.08); I² = 55%			
							subgroup = Viral vector			
F	VV	B	NS	O	Nigeria & Others	2886	Villar, J. 2023	49.00 [0.00; 73.99]	100.0%	
							subgroup = RNA; Viral vector			
G	RNA;VV	C	NS	D	USA	1536	Morgan, JA 2021	89.00 [47.00; 97.72]	100.0%	
							subgroup = Inactivated virus; RNA; Viral vector			
F	IV;RNA;VV	B	NS	O	Nigeria & Others	2886	Villar, J. 2023	76.00 [47.32; 89.07]	100.0%	
							subgroup = Not specified			
G	NS	C	NS	A;D	UK	4305	Bosworth, M 2023	83.00 [76.00; 87.96]	100.0%	

Severe COVID-19 - composite

Fig. 5 Effectiveness of COVID-19 vaccination compared to no vaccination during pregnancy, by vaccine type: severe or hospitalized maternal COVID-19. Global quality (*GQ*): Fair (*F*), Good (*G*); Vaccine type (*VT*): Inactivated virus (*IV*), Ribonucleic acid (*RNA*), Viral vector (*VV*), Not specified (*NS*); Vaccination status (*VS*): Complete (*C*), Booster (*B*); Trimester (*Trim*): 1 (1st), 2 (2nd), 3 (3rd), Not specified (*NS*); Dominant variant (*DV*): Alpha (*A*), Delta (*D*), Omicron (*O*), Not specified (*NS*)

< 7, prematurity, small for gestational age, NICU admission or hospitalization, and respiratory distress. In fact, we observed statistically significant reductions in stillbirth with mRNA/viral vector vaccines administered in the early stages of pregnancy and in emergency cesarean deliveries with mRNA vaccines at any time. Postpartum hemorrhage was the only outcome where we found a non-statistically significant higher incidence in vaccinated versus non-vaccinated pregnant persons. However, only three studies were included in this meta-analysis. The pooled proportions of

maternal and infant safety outcomes were in line with what was anticipated, considering the background rates reported globally in HIC and LMIC settings. We only identified two studies directly comparing the effects of vaccination in pregnant versus non-pregnant persons on AEFIs [49, 50]. For most of the maternal AEFIs reported and analyzed, such as chills, eye irritation, facial swelling, rash, fatigue, fever, gastrointestinal, myalgias, systemic reactions, vomiting, nausea, and diarrhea, the frequency was lower in pregnant than in non-pregnant persons. The only exception was injection-site

reactions, with a 20% higher frequency among pregnant persons.

COVID-19 VE in pregnant persons against severe complications (severe symptoms, hospitalization, and intensive care unit admission), during the Omicron period, was 58% (95% CI 15–79) after the primary series, and the VE increased to 65% (33–81) with a booster dose. Effectiveness was higher if the booster dose was administered within the past 120 days. Variability of VE by type of vaccine ranged across variants, from 49% with viral vector vaccines to 72% with mRNA vaccines. Even after a booster dose, protection against symptomatic COVID-19 and laboratory-confirmed SARS-CoV-2 infection during Omicron dominance was just 56% (95% CI 21–75) and 30% (95% CI 19-39), respectively. Maternal COVID-19 vaccination protects against severe illness both among pregnant women and their infants up to 6 months of age who are too young to be vaccinated.

The certainty of the evidence in our LSR was determined to be low to very low for all outcomes using the GRADE process primarily owing to the derivation of data from observational studies [33]. Starting for this reason with low certainty evidence, each of the outcomes can be downgraded, resulting in a classification of very low certainty of evidence. This downgrading was attributed to reasons such as imprecision, heterogeneity, or risk of bias, and they were detailed for each outcome and comparison as footnotes in the summary of findings tables. Consequently, the evidence for many considered outcomes is characterized as very uncertain.

In the contemporary landscape, there is an increasing body of information concerning the safety and effectiveness of vaccines administered to pregnant women. These accumulating data indicate that the advantages of vaccination for pregnant women surpass the acknowledged or potential risks. The present LSR builds upon and extends the findings of two prior reviews from our group that foreshadowed the safety outcomes reported in this study [7, 62] and with other published systematic reviews that also supported the safety and effectiveness of COVID-19 vaccines during pregnancy [63–74]. We show some similarities and differences. We did not find a statistically significantly lower risk of prematurity as other systematic reviews did [63, 66, 71]. However, our analyses showed that COVID-19 vaccination during pregnancy significantly decreases the incidence of stillbirth and emergency cesarean section compared with the unvaccinated group, which was also demonstrated by other reviews [63, 65, 72]. The AEFIs observed in pregnant persons were the same as found in two systematic reviews assessing the effects of immunization in general populations [75, 76]. Local AEFIs such as pain, swelling, erythema, and redness, as well as systemic AEFIs such as fatigue, headache, and myalgia, were consistently the most frequently reported, irrespective of the population

under study. Potentially life-threatening adverse events related to vaccination were rarely reported. The proportion of headache, fatigue, fever, and lymphadenopathy was more than double with the second dose compared with the first dose. This finding was consistent with one review [75] but not with the other [76].

Some of the studies in previous systematic reviews included women vaccinated before pregnancy or non-pregnant individuals, but we focused on vaccinated versus unvaccinated pregnant persons. Previous systematic reviews occasionally amalgamated unadjusted measures with adjusted measures. In contrast, our approach concentrated on observational studies adjusted for pivotal confounders, conducting distinct analyses for crucial maternal and infant safety as well as VE endpoints. These differences in methodology could explain some of the differences in findings. However, irrespective of the methodological precision exhibited in these antecedent systematic reviews, they uniformly affirmed the safety of COVID-19 vaccines during pregnancy.

In light of the inherent biases present in observational data used for assessing VE, these evaluations typically necessitate specific design parameters and definitions including methodologies such as the test-negative design and the adjustment of VE estimates for key confounders in cohort studies. The reference group for all VE analyses conducted in our study comprises pregnant individuals who received zero vaccine doses. Our findings reveal positive albeit varying levels of effectiveness across all vaccine types, including mRNA and non-mRNA vaccines. Vaccine efficacy/effectiveness appears to decline more rapidly in the Omicron era; however, we observed an improvement in VE after booster doses. Additionally, decreased protection of the primary series after 150 or more days since the second dose against the hospitalization endpoint was more evident during the Omicron period than during the earlier Delta period, highlighting the importance of additional doses among pregnant persons, in line with current recommendations [4]. The current findings contribute to bolstering confidence among both the general populace and clinicians, affirming that COVID-19 vaccination serves as a protective measure against severe maternal SARS-CoV-2 infection.

Our study also provides insight into whether vaccination in pregnancy prevents COVID in the infant (through antibody transfer or indirect protection). The available evidence suggests that vaccination during pregnancy protects against COVID-19 hospitalization (severe disease) in infants during their first 6 months of life, although protection is lower in the Omicron period [14, 60, 61]. Similar studies support these findings and thus an addition potential benefit for vaccination during pregnancy [77, 78].

4.2 Strengths

Our LSR has relevant strengths. Our study contributed to the knowledge on the topic by including new studies and providing additional data related to the certainty of evidence using the GRADE method [33]. The utilization of adjusted measures by key confounders, such as age, gestational age, residential area, smoking status, parity, body mass index, or having a seasonal influenza vaccine, or using matched controls for comparing the safety and effectiveness of COVID-19 vaccines in pregnant individuals with those not vaccinated is a noteworthy facet of this study. This approach is critical to ensure that observed effects are not influenced by other variables, thereby enhancing the reliability and validity of our findings. Considering that the number of studies using this approach is limited, we also performed proportional meta-analyses to include many more studies and to provide an alternative perspective on the effects of COVID-19 vaccination during pregnancy. In this way, we estimated the frequency/incidence of maternal and infant safety outcomes after the pregnant persons were exposed to the vaccines, which is crucial to understanding maternal and infant health across trimesters. While the absence of a control group presents a challenge, background rates of maternal-infant events in global, HIC, and LMIC settings served as reference points for contextualizing the findings within the framework of existing maternal-infant health data.

This comprehensive and methodologically rigorous LSR presents separate results by trimester of vaccination, in addition to vaccine type, as the primary analysis of safety maternal and neonatal outcomes since the first trimester is generally considered the most vulnerable period for the fetus in the context of medication or infectious agents [79]. In the same way, in addition to vaccine type and number of doses, we analyzed VE stratified by dominant variant dominance with a focus on the Omicron SARS-CoV-2 variant, the most concerning at the moment of reporting our study. We conducted an exhaustive and regular search across multiple databases and found more studies than any other published systematic review. Another strength is the visualization of up-to-date information. We developed an interactive and public online platform that presented data with less than a month of delay from its publication. Furthermore, we presented effect estimates through customizable real-time meta-analyses of the effectiveness, maternal pregnancy-related outcomes, maternal AEFIs, and infant safety outcomes following COVID-19 vaccination during pregnancy, representing an innovation for policy making and research. No less important, this project had the support of a Strategic and Technical Advisory Group, including immunization experts and WHO representatives, that provided real-time guidance on collecting and analyzing data and reporting it in a way that was most useful in evidence synthesis and decision making.

4.3 Limitations

Our study has also limitations. We did not find RCTs evaluating the safety and efficacy of COVID-19 vaccination during pregnancy because RCTs considered pregnancy an exclusion criterion during the first years of the pandemic. To minimize the inherent risk of bias of observational studies, we only conducted comparative meta-analyses of adjusted estimations, but that limited the number of studies available for a meta-analysis. Nevertheless, several important confounding factors were not considered and may be missed across included studies. We could not pool many studies by outcomes because effect measures were reported by subgroups exposed to vaccinations and compared with the same control group, so the effect measures' adjusted nature precluded splitting the control group. Additionally, HRs could not be combined with other effect measures such as RRs or ORs, and further limited the number of studies to meta-analyze. Proportional meta-analyses included many more studies, but as they come from non-comparative studies or unadjusted estimates, they are exposed to a high risk of bias.

4.4 Implications for Practice and Research

The implications of this LSR for public health policy, clinical practice, and research are extensive. As the global vaccination campaign against COVID-19 continues, it is imperative to have evidence-based guidelines for pregnant individuals. Although the most urgent phase of the pandemic is over, pregnant women continue to be at risk of adverse outcomes, and they are still recommended to receive a dose of vaccine in every pregnancy, which is why data on the safety and effectiveness of pregnancy must continue to be explored, particularly for non-mRNA vaccines for which there are fewer data. The real-time nature of this LSR permitted timely updates, ensuring access to the most current and pertinent information for making informed decisions regarding vaccination during pregnancy.

5 Conclusions

This LSR established a robust foundation for evaluating the safety and effectiveness of COVID-19 vaccines during pregnancy. By presenting the evidence in an accessible and interactive format that included GRADE summary of findings tables, we also provided a valuable resource to the scientific community, the decision makers, the clinicians,

and the general public to protect pregnant persons and their neonates even at the current stage in the pandemic. Further research, including studies with larger sample sizes from different countries and sociodemographic diversity, is required to confirm the external validity of our findings. This work underscores the significance of ongoing research and continuous vaccine safety and effectiveness monitoring, in populations at particular risk for adverse outcomes such as pregnant persons.

Declarations

Conflicts of Interest/Competing Interests Agustín Ciapponi, Mabel Berrueta, Fernando J. Argento, Jamile Ballivian, Ariel Bardach, Martin E. Brizuela, Noelia Castellana, Daniel Comandé, Sami Gottlieb, Beate Kampmann, Agustina Mazzoni, Edward P.K. Parker, Juan M. Sambade, Katharina Stegelmann, Xu Xiong, Andy Stergachis, and Pierre Buekens have no conflicts of interest that are directly relevant to the content of this article.

Ethics Approval Systematic reviews do not require any original research and are not subject to ethics approval.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Availability of Data and Material Data and materials are available in the supplemental material and at https://www.safeinpregnancy.org/living-systematic-review/.

Code Availability Not applicable.

Authors' Contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by AC, MB, FA, JB, AB, NC, DC, MEB, JMS, KS, and AM. The first draft of the manuscript was written by AC and MB, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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