Safety of components and platforms of COVID-19 vaccines considered for use in pregnancy: A rapid review

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ABSTRACT

Background: Rapid assessment of COVID-19 vaccine safety during pregnancy is urgently needed.

Methods: We conducted a rapid systematic review, to evaluate the safety of COVID-19 vaccines selected by the COVID-19 Vaccines Global Access-Maternal Immunization Working Group in August 2020, including their components and their technological platforms used in other vaccines for pregnant persons. We searched literature databases, COVID-19 vaccine pregnancy registries, and explored reference lists from the inception date to February 2021 without language restriction. Pairs of reviewers independently selected studies through COVIDENCE, and performed the data extraction and the risk of bias assessment. Discrepancies were resolved by consensus. Registered on PROSPERO (CRD42021234185).

Results: We retrieved 6757 records and 12 COVID-19 pregnancy registries from the search strategy; 38 clinical and non-clinical studies (involving 2,398,855 pregnant persons and 56 pregnant animals) were included. Most studies (89%) were conducted in high-income countries and were cohort studies (57%).

Most studies (76%) compared vaccine exposures with no exposure during the three trimesters of pregnancy. The most frequent exposure was to AS03 adjuvant, in the context of A/H1N1 pandemic influenza vaccines, (n=24) and aluminum-based adjuvants (n=11). Only one study reported exposure to messenger RNA in lipid nanoparticles COVID-19 vaccines. Except for one preliminary report about A/H1N1 influenza vaccination (adjuvant AS03), corrected by the authors in a more thorough analysis, all studies concluded that there were no safety concerns.

Conclusion: This rapid review found no evidence of pregnancy-associated safety concerns of COVID-19 vaccines or of their components or platforms when used in other vaccines. However, the need for further data on several vaccine platforms and components is warranted, given their novelty. Our findings support current WHO guidelines recommending that pregnant persons may consider receiving COVID-19 vaccines, particularly if they are at high risk of exposure or have comorbidities that enhance the risk of severe disease.

Keywords: Pregnancy; COVID-19; Vaccine safety; Adjuvant; Systematic review

BACKGROUND

The COVID-19 Vaccines Global Access Facility (COVAX) is a multilateral initiative to ensure that all countries have fair and equitable access to Coronavirus Disease 2019 (COVID-19) vaccines. Co-led by the GAVI Alliance (formerly the Global Alliance for Vaccines and Immunisation), the Coalition for Epidemic Preparedness Innovations (CEPI), and the World Health Organization (WHO), COVAX is a voluntary arrangement that enables countries to pool their resources and risk by collectively investing in vaccine candidates while developing the political and logistical infrastructure needed for vaccine distribution in a transparent and coordinated manner[1-3]. Preauthorization clinical trials of COVID-19 vaccines excluded pregnant persons, and only limited human data on their safety during pregnancy was available at the time of emergency use authorization[4]. However, pregnant persons with COVID-19 are at increased risk of adverse pregnancy and birth outcomes and severe illness compared to non-pregnant persons [5-9]. Many countries are vaccinating or considering vaccinating pregnant persons, especially if they are at risk of being exposed, even with limited available data about the safety of this strategy. Consequently, it is imperative to identify early safety concerns of COVID-19 vaccines, their components, or their platforms, defined as any underlying technology -a mechanism, delivery method, or cell line- that can be used to develop multiple vaccines: whole virus, protein, viral vector, or nucleic acid. To assist pregnant persons to make more fully informed decisions, we aimed to identify safety concerns during pregnancy associated with these exposures over a subset of COVID-19 vaccines selected for review by COVID-19 Vaccines Global Access - Maternal Immunization Working Group (COVAX-MIWG) in August 2020, through a rapid review of the literature databases as the first phase of an ongoing full systematic review. Given the urgency of the issue for current public health practice across the globe, we performed a rapid review as an interim analysis of the vaccines that the COVAX-MIWG selected in August 2020.

OBJECTIVES

To evaluate the effects of COVID-19 vaccines that the COVAX-MIWG selected in August 2020, or their components used in other vaccines, on pregnancy safety outcomes.

METHODS

For this rapid review, we followed the Cochrane methods[10, 11] and the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[12] for reporting results. This review was registered in PROSPERO (CRD42021234185).

Inclusion criteria

We included studies that used comparative or non-comparative study designs. Case series were only included if they reported more than 50 exposed pregnant persons. We also included experimental studies of any sample size with exposed pregnant animals. We excluded systematic reviews (SRs) but explored their reference lists as an additional primary study source.

The exposures or interventions of interest are the COVID-19 candidate vaccines that the COVAX-MIWG selected for review in August 2020; or the vaccine platforms (protein/subunit, vectored, nucleic acid/mRNA-LNP); or the components (antigen, vehicle, construct, adjuvants, lipid nanoparticles or other components) used by the selected COVID-19 vaccines (**Table 1**). At least one of these exposures was explicitly described in the report.

We considered outcomes concerning exposure to the vaccines based on the reported gestational age at vaccination (based on validated methods including ultrasound or last menstrual period [LMP] for human studies). We used the 21 standardized case definitions developed by the Global Alignment of Immunization Safety Assessment in Pregnancy (GAIA) of prioritized obstetric and neonatal outcomes

based on the Brighton Collaboration process[13]. The ten GAIA obstetric outcomes include hypertensive disorders of pregnancy, maternal death, non-reassuring fetal status, pathways to preterm birth, postpartum hemorrhage, abortion/miscarriage, antenatal bleeding, gestational diabetes, dysfunctional labor, and fetal growth retardation. The 11 neonatal outcomes include congenital anomalies, neonatal death, neonatal infections, preterm birth, stillbirth, low birth weight, small for gestational age, neonatal encephalopathy, respiratory distress, failure to thrive, and microcephaly.

For this rapid review, we considered the integrative outcome "safety concerns" as any statistically significant adverse outcome reported in the comparative studies, or unexpected frequencies with respect to the published incidences in the peer-reviewed literature reported in uncontrolled studies. We described all the adverse events as they were reported by the authors of the original studies. For the full review, safety outcomes will be analyzed according to the US Food and Drug Administration (FDA) Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials[14]. An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product regardless of its causal relationship to the study treatment[15]. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product. These include local reactions at the injection site (pain, tenderness, erythema, edema, pruritus, other) and systemic reactions (fever $\geq$ 38°C or 100.4°F, headache, malaise, myalgia, fatigue, etc.). We will also consider other post-vaccination medical events (unsolicited in the studies, reported by organ system as per Medical Dictionary for Regulatory Activities - MedDRA)[16].

We will use the classification in a four grade for the severity of AEs.

We also will consider other classifications of AEs commonly reported in safety studies, including:

-Medically attended adverse events (MAEs): AEs leading to an otherwise unscheduled visit to or from medical personnel for any reason, including visits to an accident and emergency department.

-Serious adverse events (SAEs): AEs that resulted in death, were life-threatening, required hospitalization or prolongation of existing hospitalization, resulted in disability/incapacity or resulted in a congenital anomaly/birth defect in the child of a study participant.

-Adverse events of special interest (AESIs): AEs worthy of closer follow-up over six months post-vaccination. These include vaccine-associated enhanced diseases such as multisystem inflammatory syndrome in children or adults (MIS-C/A).

The operative definition of each specific AE was reported elsewhere (PROSPERO- CRD42021234185).

Search strategy

We searched published and unpublished studies, without restrictions on language or publication status, from inception date to February 2021 (See the full search strategies and search terms in **Appendix 1**) 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), WHO Database of publications on SARS CoV2, TOXLine, preprint servers (ArXiv, BiorXiv, medRxiv, search.bioPreprint), and COVID-19 research websites (PregCOV-19LSR, Maternal and Child Health, Nutrition: John Hopkins Centre for Humanitarian health, the LOVE database).

We also searched reference lists of relevant primary studies and systematic reviews retrieved by the search strategy and the adverse events/safety reported in active COVID-19 pregnancy registries. The Food and Drug Administration (FDA), the European Medicines Agency (EMA), and clinical trials websites will be searched for the full review. We will then contact original authors and experts in the field for clarification

or to obtain extra information. For the full review, we will re-run the search strategy, between March 2021 and the current date and time, to capture any new evidence in databases.

Selection of studies, data extraction, and assessment of the risk of bias in included studies

Pairs of authors independently screened each identified record by title and abstract and retrieved all the full texts of the potentially eligible studies. Pairs of review authors independently examined the full-text articles for compliance with the inclusion criteria and selected the eligible studies. We resolved any disagreements by discussion. We documented the selection process with a PRISMA flow chart[12], conducted through COVIDENCE[17], a software for systematic reviews.

Pairs of review authors independently extracted data from eligible studies using a data extraction form designed and pilot-tested by the authors. Any disagreements were resolved by discussion. Extracted data included study characteristics and outcome data. Where studies have multiple publications, we collated multiple reports of the same study under a single study ID with multiple references.

In **Appendix 2,** we describe the risk of bias assessment tools used for each study design. Briefly, we independently assessed the risk of bias of the included clinical trials using the Cochrane risk of bias assessment tool[18]. We used the Cochrane EPOC group tools[19] to assess controlled before-after studies (CBAs), nationwide uncontrolled before-after studies (UBAs), interrupted time series (ITSs), and controlled-ITSs (CITSs). We rated the risk of bias in each domain as “low”, “high”, or “unclear”. For observational cohort, case-control, cross-sectional, and case-series studies we used the NIH Quality Assessment Tool[20]. After answering the different signaling questions “Yes”, “No”, “Cannot determine”, “Not applicable”, or “Not reported”, the raters classified the study quality as “good”, “fair”, or “poor”. For consistency with the other designs, we use the classifications low, high, or unclear risk of bias, respectively.

Data synthesis

The primary analysis was the comparison of participants exposed and unexposed to the vaccines or their components. For this rapid review, we tabulated the study exposure characteristics and compared them against the unexposed. We analyzed the results of each study to determine any safety concerns as "Yes", "No", or "Unclear".

Data from non-comparative studies, including registries, were collected and analyzed in the context of background rates of neonatal and obstetric outcomes. For specific indicators, we take into consideration group-specific definitions such as low-to-middle-income countries (LMICs).

We described the effect estimates as reported by the authors of the included studies. For dichotomous data, we used the numbers of events in the control and intervention groups of each study to calculate Risk Ratios (RRs), Hazard Ratios (HRs), or Mantel-Haenszel Odds Ratios (ORs).

We planned to conduct meta-analysis and subgroup analyses by the trimester of exposure and sensitivity analysis restricted to studies with a low risk of bias. However, these were not pursued for this rapid review, given the lack of safety concerns identified. We plan to perform a meta-analysis and present GRADE 'Summary of findings' tables[10, 21] for the full review as was previously stated (PROSPERO-CRD42021234185).

RESULTS

We retrieved 6756 records and 12 COVID-19 pregnancy registries from the search strategy,;- 266 potentially eligible studies were assessed by full-text, and 227 were excluded, mainly because of wrong exposure or intervention (114) or insufficient information (67). We included 38 clinical and non-clinical

studies, involving 2,398,855 pregnant persons and 56 pregnant animals from 39 reports.[4, 22-59] (**Fig 1**). The list of excluded studies and the reasons for exclusion is presented in **Appendix 3**.

Description of studies

The characteristics of included studies are described in **Table 2**. The most frequent study design was cohort studies (n=22) followed by surveillance studies (n=8), controlled trials (n=5), and registry analyses (n=3). Twenty-nine of the included studies (76%) allowed comparisons between vaccinated and unvaccinated pregnant persons (n=26) or were conducted in animals (n=3). Nine out of the 38 studies (24%) were abstracts.

The most frequent study location was the USA (n=7), followed by Sweden and the United Kingdom (n=5 each), Australia, Canada, and Denmark (n=3 each), Cuba, France, and Netherlands (n=2 each), and Argentina, Belgium, Finland, Germany, Norway, and multi-country (n=1 each). Only 4 out of 37 studies (11%) involved LMICs[27, 36, 45, 50].

Only 3 out of 37 studies were conducted on animals (8%)[28, 33, 58]. Most of the studies reported exposures during the three trimesters (n=17), only the first trimester (n=5), and the second and third trimester (n=4). The time of exposure was not reported in six studies.

We only identified one COVID-19 vaccine study reporting exposure to mRNA-LNP from Pfizer & Moderna COVID-19 vaccines[4]. The most frequent exposures were to the AS03 adjuvant (536,240 pregnant participants from 23 studies) and aluminum-based adjuvants (1,861,462 pregnant participants from 11 studies) (**Table 3**). AS03 was the adjuvant of several A/H1N1 pandemic influenza vaccines (Pandemrix® and Arepanrix), while the influenza vaccine Equilis® used ISCOM-Matrix[32]. Aluminum phosphate was used in the testing of candidate Respiratory Syncytial Virus Fusion (RSV F) vaccines in

pregnant persons [28, 44, 48] (n=3). Aluminum phosphate was also used in Tdap vaccines[36, 46, 55] (n=3). Different aluminum salts were used in Hepatitis vaccines[23, 29, 30, 37, 47, 48]. One study reported the use of the ChAdOx1 vector for a Rift Valley fever vaccine[58].

The 12 COVID-19 and pregnancy registries identified (UKOS, PAN-COVID, BPSU, NPC-19, EPICENTRE, periCOVID, INTERCOVID, PregCOV-19LSR, PRIORITY, COVI-PREG), OTIS/MotherToBaby, CHOPAN, and V-safe registries) are presented in **Appendix 4**.

Risk of bias in included studies

The risk of bias for the included controlled trials is presented in **Table 4** and for the included observational studies in **Table 5**.

We assessed the 38 included reports. Among the five RCTs, two (40%) presented a high risk of bias in the randomization process, and one (20%) in the blinding of participants and personnel. Among the 33 observational study reports, 14 were classified as "good" (43%), 12 as "fair" (36%), and seven as "poor" (21%).

Outcomes of exposures

The results of included studies are described in **Table 2**. There were 13 pregnancy-related outcomes (26 reports), eight neonatal outcomes (19 reports), and nine maternal outcomes (13 reports). The most-reported pregnancy outcomes were preterm delivery (n=12), stillbirth (n=9), spontaneous abortion (n=9), fetal growth restriction/small gestational age (n=8), and fetal death (n=6). The most reported neonatal outcomes were congenital anomalies (n=9) and low birth weight (n=8), and the most reported maternal outcomes were local reactions (n=7), systemic reactions (n=5), and serious adverse events (n=6).

The adjusted relative effects comparing exposed vs. not exposed pregnant participants by vaccine components/platforms were summarized in **Table 3**. None of the available exposures, including AS03, aluminum phosphate, or aluminum salts only, was statistically associated with adverse outcomes. AS03 showed a statistically lower frequency of very preterm aRR 0.73 (95%CI 0.58 to 0.91)[25] and peripartum complications aOR 0.65 (95%CI 0.42 to 0.99)[54], and aluminum salts showed lower stillbirth aHR 0.49 (95%CI 0.29 to 0.84)[55]. The lack of more comparative information regarding "safety concerns" precludes further subgroup analysis by exposure.

Of the 37 included studies, 36 (97%) concluded that there was no evidence of safety concerns. Only one study[56], reported as abstract, mentioned unclear safety concerns regarding the 9,026 pregnancies ending in a delivery that had a record of the swine flu vaccine during or just before their pregnancy. The authors reported that they may not have captured early pregnancy losses, that some misclassification of outcome may have occurred, or residual confounding may have been present after adjusting for age and chronic comorbidity. However, the full-text manuscript reported one year later by these authors[57], including 9,445 persons vaccinated with the swine flu vaccine before or during pregnancy, found no difference in the hazard of fetal loss during weeks 25 to 43 and a lower hazard of fetal loss than unvaccinated pregnancies in gestational weeks 9 to 12 and 13 to 24.

The planned subgroup analyses by the trimester of exposure and sensitivity analysis, restricted to studies with low risk of bias, were not conducted, given the lack of reported safety concerns in every study.

Table 4 shows the characteristics of the 12 identified COVID-19 and pregnancy registries, with potential data on safety/adverse events. The USA and the UK were the most represented countries. Some large registries are multinational, such as EPICENTRE, COVI-PREG, or PAN-COVID, which gathers data from 42 countries. Most registries include information on obstetric/pregnancy outcomes like early pregnancy loss, fetal growth, stillbirths, and delivery outcomes. All of them include neonatal and infant

outcomes. Additionally, UKOSS and V-safe include specific vaccination information on the pregnant population. PeriCOVID was the only registry that collected blood samples. More detailed information on the relevant information from these registries will be described in the full systematic review, which is currently ongoing.

We also identified three ongoing studies in the COVID-19 vaccine tracker, developed by the Vaccine Centre at the London School of Hygiene and Tropical Medicine, which contains information from the WHO, the Milken Institute, and clinicaltrials.gov databases[60]. A phase-2 trial, assessing the Ad26.COV2.S vaccine (a monovalent vaccine composed of a recombinant, replication-incompetent adenovirus type 26 vector)[61], and a phase-2/3 trial, assessing the BNT162b2 vaccine (an RNA vaccine)[62], are being conducted in the United States, Australia, Brazil, Canada, Finland, South Africa, Spain, and in the United Kingdom. In addition, a phase-4 nonrandomized controlled study is being conducted in Belgium to verify if SARS-Cov-2 specific antibodies can be found in blood serum and milk of lactating mothers vaccinated with the CX-024414 vaccine (mRNA vaccine)[63].

DISCUSSION

Through this rapid review of studies of vaccine components and platforms also used by COVID-19 vaccines, we found no evidence of safety concerns regarding the COVID-19 vaccines that the COVAX MIWG selected for review in August 2020, their components, or platforms used in other vaccines during pregnancy.

None of the adjusted relative effects comparing exposed vs. not exposed pregnant participants of the available exposure results were statistically associated with adverse outcomes. Only AS03 showed a statistically lower frequency of very preterm[25] and peripartum complications[54], and aluminum salts showed lower stillbirth aHR 0.49 (95%CI 0.29 to 0.84)[55]. Uncontrolled studies, in general,

reported low frequencies of adverse outcomes. One study[56], reported as an abstract, suggested safety concerns regarding the swine flu vaccine (AS03 adjuvant) during or just before pregnancy, but the authors recognized potential bias for this finding. The authors published the full-text manuscript[56] one year later, and after a complete analysis, they concluded that there is no evidence of safety concerns.

Nine systematic reviews consistently supported the safety of influenza vaccines during pregnancy[64-72]. In general, cohort studies showed the benefits of vaccination during pregnancy, such as significantly decreased risks for preterm birth, small for gestational age, and fetal death. However, after adjusting for the season at the time of vaccination and countries' income level, only the reduction of fetal death remained significant[68]. There is no evidence of an association between influenza vaccination and serious adverse events in the comparative studies[69]. When assessing only major malformations, no increased risk was detected after immunization at any trimester. Neither adjuvanted nor unadjuvanted vaccines were associated with an increased risk for congenital anomalies[71].

Other systematic reviews also assessed the safety of different vaccines. One SR evaluated the safety of the hepatitis B vaccine, the pneumococcal polysaccharide vaccine, and the meningococcal polysaccharide vaccine during pregnancy and found no clear association with a teratogenic effect on the fetus, preterm labor, or spontaneous abortion[73]. Another SR evaluated the safety of vaccines frequently given to travelers on pregnant persons, such as yellow fever, MMR (mumps, measles, and rubella), influenza, Tdap (tetanus, diphtheria, and pertussis), meningococcus, or hepatitis A and B[74]. The authors concluded the safety of the influenza vaccine is supported by high-quality evidence. For the Tdap vaccine, no evidence of any unexpected harm was found in the meta-analysis of RCTs. Meningococcal vaccines are probably safe during pregnancy, as supported by RCTs comparing meningococcal vaccines to other vaccines. Data supported the safety of hepatitis A and hepatitis B

vaccines during pregnancy. In summary, primary and secondary evidence of studies of vaccine components and platforms also used by COVID-19 vaccines supports the safety of COVID-19 vaccines, their components, or their platforms used in other vaccines during pregnancy.

Three recent studies about mRNA-LNP vaccines in pregnant persons, published after this rapid review was finalized, reinforced these findings[75-77]. Shimabukuro et al. published preliminary results from the U.S. surveillance review of the safety of mRNA COVID-19 vaccines during pregnancy[77]. The local and systemic reactions reported were similar among persons who identified as pregnant and non-pregnant persons. Prabhu et al. studied the antibody response of 122 pregnant persons and their neonates at the time of birth who had received one or both doses of an mRNA-based COVID-19 vaccine[75]. COVID-19 vaccination during pregnancy induced a robust maternal immune response, with transplacental antibody transfer detectable as early as 16 days after the first dose. Rottenstreich et al. reported on 20 pregnant persons who received two doses of the SARS-CoV-2 BNT162b2 (Pfizer/BioNTech) mRNA vaccine and found a similar antibody response[76]. No safety concern was reported in any of these studies. Also, the proportions of adverse pregnancy and neonatal outcomes among completed pregnancies in the registry were similar to the published incidences in pregnant populations studies before the COVID-19 pandemic[78-84].

This rapid review has several strengths. First, we included reports without time, language, or publication type restriction in humans and animals, to provide a timely answer to a hot topic. Second, we adhered to rigorous recommended quality standards to conduct rapid reviews[11] including independent, data extraction and risk of bias assessment, and a sensitive and comprehensive search strategy on literature databases to reduce the risk of missing relevant studies. Third, we categorized the exposure to the vaccine components and platforms, which was a challenging issue that frequently demanded exploring additional sources. Finally, we summarized and critically appraised a considerable

amount of evidence to conclude if there are safety concerns of the components or platforms used by the vaccines that the COVAX MIWG selected for review in August 2020. The vaccine availability has changed over time[85], but we plan to update the search strategy covering the new vaccines for the ongoing full systematic review.

Our study is not exempt from limitations. Twenty-four percent of the included studies were reported as abstracts.

Only 11% of the total body of evidence comes from LMICs, limiting the generalizability to these settings. Additionally, only 76% of included studies allowed comparisons between vaccinated and unvaccinated pregnant persons, and only five of them were RCTs. Therefore, most of this evidence is observational. Nevertheless, the absence of safety concerns regardless of the study design and publication type suggest that this could not be a major limitation. Adverse events were reported by the classification used by authors of the original studies; however, we plan to analyze them in the ongoing full review accordingly to our protocol.

Moreover, the set of non-controlled studies do not show unexpected figures with respect to the incidences published in the peer-reviewed literature of neonatal or obstetric outcomes[77]. Regardless of the exposure, all reported rates of spontaneous abortion in exposed pregnant persons, described in Table 2, are below the reported highest global incidence of 31%, or 10%, when considering only losses occurring in clinically recognized pregnancies[78]. Tavares 2011, reported a rate of congenital anomalies of 1.9%, in line with the reported rate in the general population of approximately 2 to 4% of live births[79-83]. Regarding fetal death, rates reported by Läkemedelsverket 2010, (0.2%) in Sweden, are consistent with the reported rates of stillbirth for high-income countries: approximately 3 deaths per 1000 live births[84]. None of the included studies conducted in LMICs reported stillbirth rates,

which have been reported to be higher than in HIC: approximately 21 deaths per 1000 live births in low-income countries[84].

We are aware that the list of Tdap vaccines included in our review is incomplete due to the focus of our research question. This vaccine contains aluminum phosphate as an adjuvant, which is not used for the COVID-19 vaccines under study, like the alhydrogel adjuvant. Therefore, our search strategy did not include the term "Tdap". Nevertheless, any aluminum adjuvant retrieved by our search strategy was included and reported.

The nature of this rapid review did not allow us to search in FDA, the EMA websites, and clinical trials registers, or to contact authors and experts in the field to obtain additional data. For the same reason, we could not conduct the meta-analysis that is planned for the full review phase. Regarding COVID-19 and pregnancy registries, we identified 12 national or international databases with potentially helpful information on safety outcomes. These will be further inspected in the next phase of this work.

Based on existing data, it seems that there are no evident safety risks of COVID-19 vaccines, their components, or the technological platforms used for pregnant persons. It is reasonable to consider COVID-19 vaccination in pregnant persons because of their higher risk of adverse outcomes. The next full review phase will add more robust evidence over this critical public health issue.

Future experimental data will be needed to assess the pregnancy-related maternal and neonatal COVID-19 vaccine safety. Good quality safety registries, ideally with active surveillance, would also provide extremely useful evidence from real-world data.

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Generic License has already been assigned to the Author Accepted Manuscript version that might arise from this submission. The sponsors had no role in conducting the present study.

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Author contributions: All authors contributed to the conception and design of this study, and AC, FA, AB, MB, SZ, BK, EP, XX, AM, and PB prepared the first manuscript draft. All authors interpreted the data, revised the first draft critically, and signed off on the final version.

Figure 1. Study flow diagram

Supplementary Material

- Appendix 1. Search strategy
- Appendix 2. Risk of bias assessment tools by study design
- Appendix 3. List of excluded studies
- Appendix 4. COVID-19 and Pregnancy Registries
- Appendix 5. PRISMA checklist

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Appendix 1. Search strategy

Structure description in PubMed

(((**Pregnancy[Mesh]** OR Pregnan*[tiab] OR **Pregnancy Complications[Mesh]** OR **Abortion, Spontaneous[Mesh]** OR Abortion*[tiab] OR Miscarriage*[tiab] OR Gestational[tiab] OR **Parturition[Mesh]** OR Childbirth*[tiab] OR Parturition*[tiab] OR Partum[tiab] OR **Fetus[Mesh]** OR Fetal[tiab] OR Fetus[tiab] OR Maternofetal[tiab] OR Materno Fetal[tiab] OR Fetomaternal[tiab] OR DART[tiab]) **AND** (**Adjuvants, Immunologic[Mesh]** OR Immunoadjuvant*[tiab] OR Immunologic Adjuvant*[tiab] OR Immunological Adjuvant*[tiab] OR Matrix-M*[all] OR Alhydrogel[all] OR Aluminum*[all] OR AS03[all] OR MF59[all] OR CpG 1018[all] OR Recombinant Spike-Protein[all] OR Baculovirus Expressed[all] OR Baculo*[tiab] OR Stabilized Spike[all] OR S-Protein Stabilized[all] OR S-Protein*[all] OR Molecular Clamp[tiab] OR Full-Length[all] OR Replication Incompetent[all] OR Ad26*[all] OR Adenovirus 26[all] OR Ad5*[all] OR Adenovirus 5[all] OR ChAdOx1[all] OR Measles-vector[all] OR V591[all] OR AZD1222[all] OR BNT162b2[all] OR mRNA-1273[all] OR mRNA-LNP[all] OR Vector Expressing[all] OR Influenza Vaccines[Mesh] OR Influenza Vaccine*[tiab] OR Flu Vaccine*[tiab] OR **Saponins[Mesh]** OR Saponin*[tiab] OR **Nanoparticles[Mesh]** OR Nanoparticle*[tiab] OR LNP[tiab] OR Nanocrystal*[tiab] OR Tween 80[all] OR Span 85[all] OR CpG*[all] OR Water Emulsion[tiab] OR HEK293[tiab] OR Arepanrix[all] OR Pandemrix[all] OR FLUAD[all] OR Dynavax[all] OR Hepatitis B Vaccines[Mesh] OR Hepatitis-B Vaccin*[tiab] OR HEPLISAV-B[all] OR Polyethylene Glycol[all]) **AND** (**Vaccination[Mesh] OR Vaccines[Mesh]** OR Vaccin*[tiab]))) **OR** (**(Nanoparticles[Mesh]** OR Nanoparticle*[tiab] OR Nanocrystal*[tiab]) AND (Pregnancy[Mesh] OR Pregnan*[tiab] OR DART[tiab])) NOT (Human[Mesh] NOT Animals[Mesh])

Ovid MEDLINE

1	exp Pregnancy
2	Pregnan*.ti,ab.
3	exp Pregnancy Complications
4	exp Abortion, Spontaneous
5	Abortion*.ti,ab.
6	Miscarriage*.ti,ab.
7	Gestational.ti,ab.
8	exp Parturition/
9	Childbirth*.ti,ab.
10	Parturition*.ti,ab.
11	Partum.ti,ab.
12	exp Fetus/
13	Fetal.ti,ab.
14	Fetus.ti,ab.
15	Maternofetal.ti,ab.
16	(Materno adj1 Fetal).ti,ab.
17	Fetomaternal.ti,ab.
18	DART.ti,ab.
19	or/1-18
20	exp Adjuvants, Immunologic
21	Immunoadjuvant*.ti,ab.
22	(Immunologic* adj1 Adjuvant*).ti,ab.
23	Matrix-M*.mp.
24	Alhydrogel.mp.
25	Aluminum*.mp.
26	AS03.mp.
27	MF59.mp.
28	CpG1.mp.
29	(Recombinant adj1 Spike-Protein).mp.
30	Baculo*.mp.
31	(Stabilized adj1 Spike).mp.

32 S-Protein*.mp.
33 (Molecular adj1 Clamp).mp.
34 (Full adj1 Length).mp.
35 (Replication adj1 Incompetent).mp.
36 Ad26*.mp.
37 Adenovirus-26.mp.
38 Ad5*.mp.
39 Adenovirus-5.mp.
40 ChAdOx1.mp.
41 Measles-Vector.mp.
42 V591.mp.
43 AZD1222.mp.
44 BNT162b2.mp.
45 mRNA*.mp.
46 (Vector adj1 Expressing).mp.
47 exp Influenza Vaccines/
48 (Influenza adj1 Vaccine*).mp.
49 (Flu adj1 Vaccine*).mp.
50 exp Saponins/
51 Saponin*.mp.
52 exp Nanoparticles/
53 Nanoparticle*.mp.
54 LNP.mp.
55 Nanocrystal*.mp.
56 Arepanrix.mp.
57 Pandemrix.mp.
58 FLUAD.mp.
59 Dynavax.mp.
60 exp Hepatitis B Vaccines/
61 (Hepatitis-B adj1 Vaccin*).mp.
62 HEPLISAV-B.mp.
63 (Polyethylene adj1 Glycol).mp.
64 or/20-63
65 exp Vaccination/
66 exp Vaccines/
67 Vaccin*.ti,ab.
68 or/65-67
69 19 and 64 and 68
70 exp Nanoparticles/
71 Nanoparticle*.mp.
72 LNP.mp.
73 Nanocrystal*.mp.
74 or/70-73
75 exp Pregnancy/
76 Pregnan*.ti,ab.
77 DART.ti,ab.
78 or/75-77
79 exp Animals/
80 74 and 78 and 79
81 69 or 80

8.2

EMBase

#83. #70 OR #82
#82. #81 NOT #80

#81. #75 AND #79
#80. 'animal'/exp
#79. #76 OR #77 OR #78
#78. dart:ti,ab
#77. pregnan*:ti,ab
#76. 'pregnancy'/exp
#75. #71 OR #72 OR #73 OR #74
#74. nanocrystal*:ti,ab
#73. lnp:ti,ab
#72. nanoparticle*:ti,ab
#71. 'nanoparticle'/exp
#70. #19 AND #65 AND #69
#69. #66 OR #67 OR #68
#68. vaccin*:ti,ab
#67. 'vaccine'/exp
#66. 'vaccination'/exp
#65. #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64
#64. (polyethylene NEAR/1 glycol):ti,ab
#63. 'heplisav b':ti,ab
#62. ('hepatitis b' NEAR/1 vaccin*):ti,ab
#61. 'hepatitis b vaccine'/exp
#60. dynavax:ti,ab
#59. fluad:ti,ab
#58. pandemrix:ti,ab
#57. arepanrix:ti,ab
#56. nanocrystal*:ti,ab
#55. lnp:ti,ab
#54. nanoparticle*:ti,ab
#53. 'nanoparticle'/exp
#52. saponin*:ti,ab
#51. 'saponin'/exp
#50. (flu NEAR/1 vaccine*):ti,ab
#49. (influenza NEAR/1 vaccine*):ti,ab
#48. 'influenza vaccine'/exp
#47. (vector NEAR/1 expressing):ti,ab
#46. 'mrna lnp':ti,ab
#45. mrna*:ti,ab
#44. bnt162b2:ti,ab
#43. azd1222:ti,ab
#42. v591:ti,ab
#41. 'measles vector':ti,ab
#40. chadox1:ti,ab
#39. 'adenovirus 5':ti,ab
#38. ad5*:ti,ab
#37. 'adenovirus 26':ti,ab
#36. ad26*:ti,ab
#35. (replication NEAR/1 incompetent):ti,ab
#34. (full NEAR/1 length):ti,ab
#33. (molecular NEAR/1 clamp):ti,ab
#32. 's protein*':ti,ab
#31. (stabilized NEAR/1 spike):ti,ab

#30. baculo*:ti,ab
#29. (recombinant NEAR/1 'spike protein'):ti,ab
#28. cpg1:ti,ab
#27. mf59:ti,ab
#26. as03:ti,ab
#25. aluminum*:ti,ab
#24. alhydrogel:ti,ab
#23. 'matrix m*':ti,ab
#22. (immunologic* NEAR/1 adjuvant*):ti,ab
#21. immunoadjuvant*:ti,ab
#20. 'immunological adjuvant'/exp
#19. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18
#18. dart:ti,ab
#17. fetomaternal:ti,ab
#16. (materno NEAR/1 fetal):ti,ab
#15. maternofetal:ti,ab
#14. fetus:ti,ab
#13. fetal:ti,ab
#12. 'fetus'/exp
#11. partum:ti,ab
#10. parturition*:ti,ab
#9. childbirth*:ti,ab
#8. 'birth'/exp
#7. gestational:ti,ab
#6. miscarriage*:ti,ab
#5. abortion*:ti,ab
#4. 'spontaneous abortion'/exp
#3. 'pregnancy complication'/exp
#2. pregnan*:ti,ab
#1. 'pregnancy'/exp

Cochrane Library (Wiley)
#1 MeSH descriptor: [Pregnancy] explode all trees
#2 Pregnan*:ti,ab,kw
#3 MeSH descriptor: [Pregnancy Complications] explode all trees
#4 MeSH descriptor: [Abortion, Spontaneous] explode all trees

#5 Abortion*:ti,ab,kw
#6 Miscarriage*:ti,ab,kw
#7 Gestational:ti,ab,kw
#8 MeSH descriptor: [Parturition] explode all trees
#9 Childbirth*:ti,ab,kw
#10 Parturition*:ti,ab,kw
#11 Partum:ti,ab,kw
#12 MeSH descriptor: [Fetus] explode all trees
#13 Fetal:ti,ab,kw
#14 Fetus:ti,ab,kw
#15 Maternofetal:ti,ab,kw
#16 (Materno NEAR/1 Fetal):ti,ab,kw
#17 Fetomaternal:ti,ab,kw
#18 DART:ti,ab,kw
#19 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18
#20 MeSH descriptor: [Adjuvants, Immunologic] explode all trees

#21 Immunoadjuvant*:ti,ab,kw
#22 (Immunologic* NEAR/1 Adjuvant*):ti,ab,kw
#23 Matrix-M*:ti,ab,kw
#24 Alhydrogel:ti,ab,kw
#25 Aluminum*:ti,ab,kw
#26 AS03:ti,ab,kw
#27 MF59:ti,ab,kw
#28 CpG1:ti,ab,kw
#29 (Recombinant NEAR/1 Spike-Protein):ti,ab,kw
#30 Baculo*:ti,ab,kw
#31 (Stabilized NEAR/1 Spike):ti,ab,kw
#32 S-Protein*:ti,ab,kw
#33 (Molecular NEAR/1 Clamp):ti,ab,kw
#34 (Full NEAR/1 Length):ti,ab,kw
#35 (Replication NEAR/1 Incompetent):ti,ab,kw
#36 Ad26*:ti,ab,kw
#37 Adenovirus-26:ti,ab,kw
#38 Ad5*:ti,ab,kw
#39 Adenovirus-5:ti,ab,kw
#40 ChAdOx1:ti,ab,kw
#41 (Measles NEAR/1 Vector):ti,ab,kw
#42 V591:ti,ab,kw
#43 AZD1222:ti,ab,kw
#44 BNT162b2:ti,ab,kw
#45 mRNA*:ti,ab,kw
#46 mRNA-LNP:ti,ab,kw
#47 (Vector NEAR/1 Expressing):ti,ab,kw
#48 MeSH descriptor: [Influenza Vaccines] explode all trees
#49 (Influenza NEAR/1 Vaccine*):ti,ab,kw
#50 (Flu NEAR/1 Vaccine*):ti,ab,kw
#51 MeSH descriptor: [Saponins] explode all trees
#52 Saponin*:ti,ab,kw
#53 MeSH descriptor: [Nanoparticles] explode all trees
#54 Nanoparticle*:ti,ab,kw
#55 LNP:ti,ab,kw
#56 Nanocrystal*:ti,ab,kw
#57 Arepanrix:ti,ab,kw

#58 Pandemrix:ti,ab,kw
#59 FLUAD:ti,ab,kw
#60 Dynavax:ti,ab,kw
#61 MeSH descriptor: [Hepatitis B Vaccines] explode all trees
#62 (Hepatitis-B NEAR/1 Vaccin*):ti,ab,kw
#63 HEPLISAV-B:ti,ab,kw
#64 (Polyethylene NEAR/1 Glycol):ti,ab,kw
#65 #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64
#66 MeSH descriptor: [Vaccines] explode all trees
#67 MeSH descriptor: [Vaccination] explode all trees
#68 Vaccin*:ti,ab,kw
#69 #66 OR #67 OR #68
#70 #19 AND #65 AND #69

CINAHL (EBSCO)

S85	S72 OR S84
S84	S82 AND S83
S83	(MH "Animals+")
S82	S77 AND S81
S81	S78 OR S79 OR S80
S80	TI DART OR AB DART
S79	TI Pregnan* OR AB Pregnan*
S78	(MH "Pregnancy+")
S77	S73 OR S74 OR S75 OR S76
S76	TI Nanocrystal* OR AB Nanocrystal*
S75	TI LNP OR AB LNP
S74	TI Nanoparticle* OR AB Nanoparticle*
S73	(MH "Nanoparticles")
S72	S19 AND S67 AND S71
S71	S68 OR S69 OR S70
S70	TI Vaccin* OR AB Vaccin*
S69	(MH "Immunization+")
S68	(MH "Vaccines+")
S67	S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65 OR S66
S66	TI (Polyethylene N1 Glycol) OR AB (Polyethylene N1 Glycol)
S65	TI HEPLISAV-B OR AB HEPLISAV-B
S64	TI (Hepatitis-B N1 Vaccin*) OR AB (Hepatitis-B N1 Vaccin*)
S63	(MH "Hepatitis B Vaccines+")
S62	TI Dynavax OR AB Dynavax
S61	TI FLUAD OR AB FLUAD
S60	TI Pandemrix OR AB Pandemrix
S59	TI Arepanrix OR AB Arepanrix
S58	TI Nanocrystal* OR AB Nanocrystal*
S57	TI LNP OR AB LNP
S56	TI Nanoparticle* OR AB Nanoparticle*
S55	(MH "Nanoparticles")
S54	TI Saponin* OR AB Saponin*
S53	TI (Flu N1 Vaccine*) OR AB (Flu N1 Vaccine*)
S52	TI (Influenza N1 Vaccine*) OR AB (Influenza N1 Vaccine*)
S51	(MH "Influenza Vaccine")
S50	TI (Vector N1 Expressing) OR AB (Vector N1 Expressing)
S49	TI mRNA-LNP OR AB mRNA-LNP
S48	TI mRNA* OR AB mRNA*
S47	TI BNT162b2 OR AB BNT162b2
S46	TI AZD1222 OR AB AZD1222
S45	TI V591 OR AB V591
S44	TI V591 OR AB V591
S43	TI (Measles N1 Vector) OR AB (Measles N1 Vector)
S42	TI ChAdOx1 OR AB ChAdOx1
S41	TI Adenovirus-5 OR AB Adenovirus-5
S40	TI Ad5* OR AB Ad5*
S39	TI Adenovirus-26 OR AB Adenovirus-26
S38	TI Adenovirus-26 OR AB Adenovirus-26
S37	TI Adenovirus-26 OR AB Adenovirus-26
S36	TI Adenovirus-26 OR AB Adenovirus-26

S35 TI Ad26* OR AB Ad26*
S34 TI (Replication N1 Incompetent) OR AB (Replication N1 Incompetent)
S33 TI (Full N1 Length) OR AB (Full N1 Length)
S32 TI (Molecular N1 Clamp) OR AB (Molecular N1 Clamp)
S31 TI S-Protein* OR AB S-Protein*
S30 TI (Stabilized N1 Spike) OR AB (Stabilized N1 Spike)
S29 TI Baculo* OR AB Baculo*
S28 TI (Recombinant N1 Spike-Protein) OR AB (Recombinant N1 Spike-Protein)
S27 TI CpG1 OR AB CpG1
S26 TI MF59 OR AB MF59
S25 TI AS03 OR AB AS03
S24 TI Aluminum* OR AB Aluminum*
S23 TI Alhydrogel OR AB Alhydrogel
S22 TI Matrix-M* OR AB Matrix-M*
S21 TI (Immunologic* N1 Adjuvant*) OR AB (Immunologic* N1 Adjuvant*)
S20 TI Immunoadjuvant* OR AB Immunoadjuvant*
S19 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18
S18 TI DART OR AB DART
S17 TI Fetomaternal OR AB Fetomaternal
S16 TI (Materno N1 Fetal) OR AB (Materno N1 Fetal)
S15 TI Maternofetal OR AB Maternofetal
S14 TI Fetus OR AB Fetus
S13 TI Fetal OR AB Fetal
S12 (MH "Fetus+")
S11 TI Partum OR AB Partum
S10 TI Parturition* OR AB Parturition*
S9 TI Childbirth* OR AB Childbirth*
S8 (MH "Labor+")
S7 TI Gestational OR AB Gestational
S6 TI Miscarriage* OR AB Miscarriage*
S5 TI Abortion* OR AB Abortion*
S4 (MH "Abortion, Spontaneous+")
S3 (MH "Pregnancy Complications+")
S2 TI Pregnan* OR AB Pregnan*
S1 (MH "Pregnancy+")

Global Health (OVID)

1 exp Pregnancy/
2 Pregnan*.ti,ab.
3 exp Pregnancy Complications/
4 Abortion*.ti,ab.
5 Miscarriage*.ti,ab.
6 Gestational.ti,ab.
7 exp Parturition/
8 Childbirth*.ti,ab.
9 Parturition*.ti,ab.
10 Partum.ti,ab.
11 exp Fetus/
12 Fetal.ti,ab.
13 Fetus.ti,ab.
14 Maternofetal.ti,ab.
15 (Materno adj1 Fetal).ti,ab.
16 Fetomaternal.ti,ab.

17	DART.ti,ab.	
18	or/1-17	
19	Immunoadjuvant*.ti,ab.	
20	(Immunologic* adj1 Adjuvant*).ti,ab.	
21	Matrix-M*.mp.	
22	Alhydrogel.mp.	
23	Aluminum*.mp.	
24	AS03.mp.	
25	MF59.mp.	
26	CpG1.mp.	
27	(Recombinant adj1 Spike-Protein).mp.	
28	Baculo*.mp.	
29	(Stabilized adj1 Spike).mp.	
30	S-Protein*.mp.	
31	(Molecular adj1 Clamp).mp.	
32	(Full adj1 Length).mp.	
33	(Replication adj1 Incompetent).mp.	
34	Ad26*.mp.	
35	Adenovirus-26.mp.	
36	Ad5*.mp.	
37	Adenovirus-5.mp.	
38	ChAdOx1.mp.	
39	Measles-Vector.mp.	
40	V591.mp.	
41	AZD1222.mp.	
42	BNT162b2.mp.	
43	mRNA*.mp.	
44	(Vector adj1 Expressing).mp.	
45	(Influenza adj1 Vaccine*).mp.	
46	(Flu adj1 Vaccine*).mp.	
47	exp Saponins/	
48	Saponin*.mp.	
49	exp Nanoparticles/	
50	Nanoparticle*.mp.	
51	LNP.mp.	
52	Nanocrystal*.mp.	
53	Arepanrix.mp.	8.8
54	Pandemrix.mp.	
55	FLUAD.mp.	
56	Dynavax.mp.	
57	(Hepatitis-B adj1 Vaccin*).mp.	
58	HEPLISAV-B.mp.	
59	(Polyethylene adj1 Glycol).mp.	
60	or/19-59	
61	exp Vaccination/	
62	exp Vaccines/	
63	Vaccin*.ti,ab.	
64	or/61-63	
65	18 and 60 and 64	
66	Animal*.mp.	
67	exp Nanoparticles/	
68	Nanoparticle*.mp.	
69	LNP.mp.	
70	Nanocrystal*.mp.	

71 or/67-70
72 exp Pregnancy/
73 exp Pregnancy/
74 Pregnan*.ti,ab.
75 DART.ti,ab.
76 or/72-74
77 66 and 71 and 76
78 65 or 77

Appendix 2. Risk of bias assessment tools by study design

2.1 Criteria for judging risk of bias in the 'Risk of bias' assessment tool

RANDOM SEQUENCE GENERATION **Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence**	
Criteria for a judgement of 'Low risk' of bias.	The investigators describe a random component in the sequence generation process such as: • Referring to a random number table; • Using a computer random number generator; • Coin tossing; • Shuffling cards or envelopes; • Throwing dice; • Drawing of lots; • Minimization.* **Minimization may be implemented without a random element, and this is considered to be equivalent to being random.*
'High risk' of bias.	The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: • Sequence generated by odd or even date of birth; • Sequence generated by some rule based on date (or day) of admission; • Sequence generated by some rule based on hospital or clinic record number. [8.9] Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorization of participants, for example: • Allocation by judgement of the clinician; • Allocation by preference of the participant; • Allocation based on the results of a laboratory test or a series of tests; • Allocation by availability of the intervention.
'Unclear risk' of bias.	Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk'.
ALLOCATION CONCEALMENT **Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment**	

'Low risk' of bias.	Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: • Central allocation (including telephone, web-based and pharmacy-controlled randomization); • Sequentially numbered drug containers of identical appearance; • Sequentially numbered, opaque, and sealed envelopes.
'High risk' of bias.	Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: • Using an open random allocation schedule (e.g. a list of random numbers); • Assignment envelopes that were used without appropriate safeguards (e.g. if envelopes were unsealed, non-opaque, or not sequentially numbered); • Alternation or rotation; • Date of birth; • Case record number; • Any other explicitly unconcealed procedure.
'Unclear risk' of bias.	Insufficient information to permit judgement of 'Low risk' or 'High risk'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement – for example, if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque, and sealed.
BLINDING OF PARTICIPANTS AND PERSONNEL **Performance bias due to knowledge of the allocated interventions by participants and personnel during the study**	
'Low risk' of bias.	Any one of the following: • No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; • Blinding of participants and key study personnel is ensured and it is unlikely that the blinding could have been broken.
'High risk' of bias.	Any one of the following: • No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; 8.10 • Blinding of key study participants and personnel is attempted, but it is likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
'Unclear risk' of bias.	Any one of the following: • Insufficient information to permit judgement of 'Low risk' or 'High risk'; • The study did not address this outcome.
BLINDING OF OUTCOME ASSESSMENT **Detection bias due to knowledge of the allocated interventions by outcome assessors**	
'Low risk' of bias.	Any one of the following: • No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; • Blinding of outcome assessment is ensured and it is unlikely that the blinding could have been broken.

'High risk' of bias.	Any one of the following: • No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; • Blinding of outcome assessment, but it is likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
'Unclear risk' of bias.	Any one of the following: • Insufficient information to permit judgement of 'Low risk' or 'High risk'; • The study did not address this outcome.
INCOMPLETE OUTCOME DATA **Attrition bias due to amount, nature or handling of incomplete outcome data**	
'Low risk' of bias.	Any one of the following: • No missing outcome data; • Reasons for missing outcome data are unlikely to be related to true outcome (for survival data, censoring is unlikely to introduce bias); • Missing outcome data are balanced in numbers across intervention groups, with similar reasons for missing data across groups; • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; • For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size;
'High risk' of bias.	Any one of the following: • Reason for missing outcome data is likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; • For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; • 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization; • Potentially inappropriate application of simple imputation.
'Unclear risk' of bias.	Any one of the following: • Insufficient reporting of attrition/exclusions to permit judgement of 'Low risk' or 'High risk' (e.g. number randomized not stated, no reasons for missing data provided); • The study did not address this outcome.
SELECTIVE REPORTING **Reporting bias due to selective outcome reporting**	

'Low risk' of bias.	Any of the following: • The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; • The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
'High risk' of bias.	Any one of the following: • Not all of the study's pre-specified primary outcomes have been reported; • One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; • One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); • One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; • The study report fails to include results for a key outcome that would be expected to have been reported for such a study.
'Unclear risk' of bias.	• Insufficient information to permit judgement of 'Low risk' or 'High risk'. It is likely that the majority of studies will fall into this category.
OTHER BIAS **Bias due to problems not covered elsewhere in the table**	
'Low risk' of bias.	The study appears to be free of other sources of bias.
'High risk' of bias.	There is at least one important risk of bias. For example, the study: • Had a potential source of bias related to the specific study design used; or • Has been claimed to have been fraudulent; or • Had some other problem.
'Unclear' risk of bias.	There may be a risk of bias, but there is either: • Insufficient information to assess whether an important risk of bias exists; or • Insufficient rationale or evidence that an identified problem will

2.2 Criteria for judging risk of bias in quasi-experimental studies ('Cochrane EPOC' assessment tool

QUALITY CRITERIA FOR CONTROLLED BEFORE AND AFTER (CBA) DESIGNS

Seven standard criteria are used for CBAs included in EPOC reviews:

a) Baseline measurement:

LOW RISK if performance or patient outcomes were measured prior to the intervention, and no substantial differences were present across study groups (e.g. where multiple pre-intervention measures describe similar trends in intervention and control groups);

UNCLEAR RISK if baseline measures are not reported, or if it is unclear whether baseline measures are substantially different across study groups;

HIGH RISK if there are differences at baseline in main outcome measures likely to undermine the post-intervention differences (e.g. are differences between the groups before the intervention similar to those found post-intervention).

b) Characteristics for studies using second site as control:
LOW RISK if characteristics of study and control providers are reported and similar;
UNCLEAR RISK if it is not clear in the paper e.g. characteristics are mentioned in the text but no data are presented;
HIGH RISK if there is no report of characteristics either in the text or a table OR if baseline characteristics are reported and there are differences between study and control providers.

c) Blinded assessment of primary outcome(s)* (protection against detection bias):
LOW RISK if the authors state explicitly that the primary outcome variables were assessed blindly OR the outcome variables are objective e.g. length of hospital stay, drug levels as assessed by a standardised test;
UNCLEAR RISK if not specified in the paper;
HIGH RISK if the outcomes were not assessed blindly.
** Primary outcome(s) are those variables that correspond to the primary hypothesis or question as defined by the authors. In the event that some of the primary outcome variables were assessed in a blind fashion and others were not, score each separately and label each outcome variable clearly.*

d) Protection against contamination:
Studies using second site as control:
LOW RISK if allocation was by community, institution, or practice and is unlikely that the control group received the intervention;
UNCLEAR RISK if providers were allocated within a clinic or practice and communication between experimental and group providers was likely to occur;
HIGH RISK if it is likely that the control group received the intervention (e.g., cross-over studies or if patients rather than providers were randomised).

e) Reliable primary outcome measure(s):
LOW RISK if two or more raters with at least 90% agreement or kappa greater than or equal to 0.8 OR the outcome is obtained from some automated system e.g., length of hospital stay, drug levels as assessed by a standardised test;
UNCLEAR RISK if reliability is not reported for outcome measures that are obtained by chart extraction or collected by an individual;
HIGH RISK if agreement is less than 90% or kappa is less than 0.8. [8.13]
** In the event that some outcome variables were assessed in a reliable fashion and others were not, score each separately and label each outcome variable clearly.*

f) Follow-up of professionals (protection against exclusion bias):
LOW RISK if outcome measures obtained 80-100% subjects allocated to groups. (Do not assume 100% follow-up unless stated explicitly.);
UNCLEAR RISK if not specified in the paper;
HIGH RISK if outcome measures obtained for less than 80% of patients allocated to groups.

g) Follow-up of patients:
LOW RISK if outcome measures obtained 80-100% of patients allocated to groups or for patients who entered the study. (Do not assume 100% follow-up unless stated explicitly.);
UNCLEAR RISK if not specified in the paper;
HIGH RISK if outcome measures obtained for less than 80% of patients allocated to groups or for less than 80% of patients who entered the study.

QUALITY CRITERIA FOR INTERRUPTED TIME SERIES (ITS)

The following seven standard criteria should be used to assess the methodology quality of ITS designs included in EPOC reviews. Each criterion is scored DONE, NOT CLEAR or NOT DONE but here we use 'low risk', 'unclear risk', and 'high risk' respectively to be consistent with the 'Risk of bias' assessment tool for RCTs (Appendix 2.1).

Protection against secular changes:

a) The intervention is independent of other changes.

LOW RISK if the intervention occurred independently of other changes over time;
UNCLEAR RISK if not specified (will be treated as HIGH RISK if information cannot be obtained from the authors);
HIGH RISK if reported that intervention was not independent of other changes in time.

b) Data were analysed appropriately:

LOW RISK if ARIMA models were used OR time series regression models were used to analyse the data and serial correlation was adjusted or tested for;
UNCLEAR RISK if not specified (will be treated as HIGH RISK if information cannot be obtained from the authors);
HIGH RISK if it is clear that neither of the conditions above not met.

c) Reason for the number of points pre- and post-intervention given:

LOW RISK if rationale for the number of points stated (e.g. monthly data for 12 months post-intervention was used because the anticipated effect was expected to decay) OR sample size calculation performed;
UNCLEAR RISK if not specified (will be treated as HIGH RISK if information cannot be obtained from the authors);
HIGH RISK if it is clear that neither of the conditions above met.

d) Shape of the intervention effect was specified:

LOW RISK if a rational explanation for the shape of intervention effect was given by the author(s);
UNCLEAR RISK if not specified (will be treated as HIGH RISK if information cannot be obtained from the authors);
HIGH RISK if it is clear that the condition above is not met.

Protection against detection bias:

e) Intervention unlikely to affect data collection:

LOW RISK if reported that intervention itself was unlikely to affect data collection (for example, sources and methods of data collection were the same before and after the intervention);
UNCLEAR RISK if not reported (will be treated as HIGH RISK if information cannot be obtained from the authors);
HIGH RISK if the intervention itself was likely to affect data collection (for example, any change in source or method of data collection reported).

f) Blinded assessment of primary outcome(s)*:

LOW RISK if the authors state explicitly that the primary outcome variables were assessed blindly OR the outcome variables are objective e.g. length of hospital stay, drug levels as assessed by a standardised test;

UNCLEAR RISK if not specified (will be treated as HIGH RISK if information cannot be obtained from the authors);
HIGH RISK if the outcomes were not assessed blindly.
** Primary outcome(s) are those variables that correspond to the primary hypothesis or question as defined by the authors. In the event that some of the primary outcome variables were assessed in a blind fashion and others were not, score each separately and label each outcome variable clearly.*

g) Completeness of data set:
LOW RISK if data set covers 80-100% of total number of participants or episodes of care in the study;
UNCLEAR RISK if not specified (will be treated as HIGH RISK if information cannot be obtained from the authors);
HIGH RISK if data set covers less than 80% of the total number of participants or episodes of care in the study.

h) Reliable primary outcome measure(s)*:
LOW RISK if two or more raters with at least 90% agreement or kappa greater than or equal to 0.8 OR the outcome is obtained from some automated system e.g. length of hospital stay, drug levels as assessed by a standardised test;
UNCLEAR RISK if reliability is not reported for outcome measures that are obtained by chart extraction or collected by an individual (will be treated as HIGH RISK if information cannot be obtained from the authors);
HIGH RISK if agreement is less than 90% or kappa is less than 0.8.
** In the event that some outcome variables were assessed in a reliable fashion and others were not, score each separately.*

QUALITY CRITERIA FOR CONTROLLED INTERRUPTED TIME SERIES (CITS)

a) Protection against secular changes:
The intervention is independent of other changes.
LOW RISK if the intervention occurred independently of other changes over time;
UNCLEAR RISK if not specified (will be treated as HIGH RISK if information cannot be obtained from the authors);
HIGH RISK if reported that intervention was not independent of other changes in time.

b) Data were analysed appropriately:
LOW RISK if ARIMA models were used OR time series regression models were used to analyse the data and serial correlation was adjusted or tested for;
UNCLEAR RISK if not specified (will be treated as HIGH RISK if information cannot be obtained from the authors);
HIGH RISK if it is clear that neither of the conditions above not met.

c) Reason for the number of points pre- and post-intervention given:
LOW RISK if rationale for the number of points stated (e.g. monthly data for 12 months post-intervention was used because the anticipated effect was expected to decay) OR sample size calculation performed;
UNCLEAR RISK if not specified (will be treated as HIGH RISK if information cannot be obtained from the authors);
HIGH RISK if it is clear that neither of the conditions above met.

d) Shape of the intervention effect was specified:
LOW RISK if a rational explanation for the shape of intervention effect was given by the author(s);
UNCLEAR RISK if not specified (will be treated as HIGH RISK if information cannot be obtained from the authors);
HIGH RISK if it is clear that the condition above is not met.

Intervention unlikely to affect data collection:
e) Protection against detection bias:
LOW RISK if reported that intervention itself was unlikely to affect data collection (for example, sources and methods of data collection were the same before and after the intervention);
UNCLEAR RISK if not reported (will be treated as HIGH RISK if information cannot be obtained from the authors);
HIGH RISK if the intervention itself was likely to affect data collection (for example, any change in source or method of data collection reported).

f) Blinded assessment of primary outcome(s)*:
LOW RISK if the authors state explicitly that the primary outcome variables were assessed blindly OR the outcome variables are objective e.g. length of hospital stay, drug levels as assessed by a standardised test;
UNCLEAR RISK if not specified (will be treated as HIGH RISK if information cannot be obtained from the authors);
HIGH RISK if the outcomes were not assessed blindly.

* Primary outcome(s) are those variables that correspond to the primary hypothesis or question as defined by the authors. In the event that some of the primary outcome variables were assessed in a blind fashion and others were not, score each separately and label each outcome variable clearly.

g) Completeness of data set:
LOW RISK if data set covers 80-100% of total number of participants or episodes of care in the study;
UNCLEAR RISK if not specified (will be treated as HIGH RISK if information cannot be obtained from the authors);
HIGH RISK if data set covers less than 80% of the total number of participants or episodes of care in the study.

h) Reliable primary outcome measure(s)*:
LOW RISK if two or more raters with at least 90% agreement or kappa greater than or equal to 0.8 OR the outcome is obtained from some automated system e.g. length of hospital stay, drug levels as assessed by a standardised test;
UNCLEAR RISK if reliability is not reported for outcome measures that are obtained by chart extraction or collected by an individual (will be treated as HIGH RISK if information cannot be obtained from the authors);
HIGH RISK if agreement is less than 90% or kappa is less than 0.8.

* In the event that some outcome variables were assessed in a reliable fashion and others were not, score each separately.

For CITSs, as for CBAs, we will include three additional domains that assess design-specific threats to validity covered by the Cochrane EPOC group: imbalance of outcome measures at baseline;

comparability of intervention and control group characteristics at baseline; and protection against contamination.

i) Baseline measurement:
LOW RISK if performance or patient outcomes were measured prior to the intervention, and no substantial differences were present across study groups (e.g. where multiple pre-intervention measures describe similar trends in intervention and control groups);
UNCLEAR RISK if baseline measures are not reported, or if it is unclear whether baseline measures are substantially different across study groups;
HIGH RISK if there are differences at baseline in main outcome measures likely to undermine the post-intervention differences (e.g. are differences between the groups before the intervention similar to those found post-intervention).

j) Characteristics for studies using second site as control:
LOW RISK if characteristics of study and control providers are reported and similar;
UNCLEAR RISK if it is not clear in the paper e.g. characteristics are mentioned in the text but no data are presented;
HIGH RISK if there is no report of characteristics either in the text or a table OR if baseline characteristics are reported and there are differences between study and control providers.

Studies using second site as control:
k) Protection against contamination:
LOW RISK if allocation was by community, institution, or practice and is unlikely that the control group received the intervention;
UNCLEAR RISK if providers were allocated within a clinic or practice and communication between experimental and group providers was likely to occur;
HIGH RISK if it is likely that the control group received the intervention (e.g. cross-over studies or if patients rather than providers were randomised).

QUALITY CRITERIA FOR UNCONTROLLED BEFORE AND AFTER (UBA) DESIGNS
Four standard criteria are used for UBAs (Derived from CBAs EPOC criteria):

a) Blinded assessment of primary outcome(s)* (protection against detection bias):
LOW RISK if the authors state explicitly that the primary outcome variables were assessed blindly OR the outcome variables are objective e.g. length of hospital stay, drug levels as assessed by a standardised test;
UNCLEAR RISK if not specified in the paper;
HIGH RISK if the outcomes were not assessed blindly.
** Primary outcome(s) are those variables that correspond to the primary hypothesis or question as defined by the authors. In the event that some of the primary outcome variables were assessed in a blind fashion and others were not, score each separately and label each outcome variable clearly.*

b) Reliable primary outcome measure(s):
LOW RISK if two or more raters with at least 90% agreement or kappa greater than or equal to 0.8 OR the outcome is obtained from some automated system e.g. length of hospital stay, drug levels as assessed by a standardised test;
UNCLEAR RISK if reliability is not reported for outcome measures that are obtained by chart extraction or collected by an individual;
HIGH RISK if agreement is less than 90% or kappa is less than 0.8.

** In the event that some outcome variables were assessed in a reliable fashion and others were not, score each separately and label each outcome variable clearly.*

c) Follow-up of professionals (protection against exclusion bias):
LOW RISK if outcome measures obtained 80-100% subjects at baseline. (Do not assume 100% follow-up unless stated explicitly.);
UNCLEAR RISK if not specified in the paper;
HIGH RISK if outcome measures obtained for less than 80% of patients at baseline.

d) Follow-up of patients:
LOW RISK if outcome measures obtained 80-100% of patients who entered the study. (Do not assume 100% follow-up unless stated explicitly.);
UNCLEAR RISK if not specified in the paper;
HIGH RISK if outcome measures obtained for less than 80% of patients who entered the study.

2.3 NIH Quality Assessment Tool for observational studies
https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools

Criteria for cohort and cross-sectional studies	**Judgement***
1. Was the research question or objective in this paper clearly stated?	
2. Was the study population clearly specified and defined?	
3. Was the participation rate of eligible persons at least 50%?	
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	
5. Was a sample size justification, power description, or variance and effect estimates provided?	
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	
10. Was the exposure(s) assessed more than once over time?	
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	
12. Were the outcome assessors blinded to the exposure status of participants?	
13. Was loss to follow-up after baseline 20% or less?	
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	

***Yes, No, CD, cannot determine; NA, not applicable; NR, not reported**

Criteria for cohort and case-control studies	Judgement*
1. Was the research question or objective in this paper clearly stated and appropriate?	
2. Was the study population clearly specified and defined?	
3. Did the authors include a sample size justification?	
4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?	
5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?	
6. Were the cases clearly defined and differentiated from controls?	
7. If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?	
8. Was there use of concurrent controls?	
9. Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?	
10. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?	
11. Were the assessors of exposure/risk blinded to the case or control status of participants?	
12. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?	

***Yes, No, CD, cannot determine; NA, not applicable; NR, not reported**

Criteria for case-series studies	Judgement*
1. Was the study question or objective clearly stated?	
2. Was the study population clearly and fully described, including a case definition?	
3. Were the cases consecutive?	
4. Were the subjects comparable?	
5. Was the intervention clearly described?	
6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	
7. Was the length of follow-up adequate?	
8. Were the statistical methods well-described?	
9. Were the results well-described?	

***Yes, No, CD, cannot determine; NA, not applicable; NR, not reported**

Appendix 3. List and exclusion reasons of excluded studies

Author	Title	Exclusion reason
Alguacil-Ramos 2015[1]	[Safety of influenza vaccines in risk groups: analysis of adverse events following immunization reported in Valencian Community from 2005 to 2011]	Wrong exposure
Arriola 2017[2]	Association of influenza vaccination during pregnancy with birth outcomes in Nicaragua	Wrong exposure
Beau 2014[3]	Pandemic A/H1N1 influenza vaccination during pregnancy: a comparative study using the EFEMERIS database	Wrong exposure
Carcione 2013[4]	Safety surveillance of influenza vaccine in pregnant women	Wrong exposure
Chambers 2013[5]	Risks and safety of pandemic H1N1 influenza vaccine in pregnancy: birth defects, spontaneous abortion, preterm delivery, and small for gestational age infants	Wrong exposure
Chambers 2015[6]	Safety of seasonal influenza vaccines in pregnancy: VAMPSS update	Wrong exposure
Chambers 2016[7]	Safety of the 2010-11, 2011-12, 2012-13, and 2013-14 seasonal influenza vaccines in pregnancy: birth defects, spontaneous abortion, preterm delivery, and small for gestational age infants, a study from the cohort arm of VAMPSS	Wrong exposure
Choe 2011[8]	Active surveillance of adverse events following immunization against pandemic influenza A (H1N1) in Korea	Wrong exposure
Conlin 2013[9]	Safety of the pandemic H1N1 influenza vaccine among pregnant U.S. military women and their newborns	Wrong exposure
Covington 2019[10]	PIN66 VACCINE PREGNANCY REGISTRIES: METHODS AND IMPACT ON FINDINGS	Wrong exposure
Cross 2020[11]	Adverse events of interest vary by influenza vaccine type and brand: Sentinel network study of eight seasons (2010-2018)	Wrong patient population
Dodds 2011[12]	Influenza vaccination in pregnancy	Wrong exposure
Donahue 2017[13]	Association of spontaneous abortion with receipt of inactivated influenza vaccine containing H1N1pdm09 in 2010-11 and 2011-12	Wrong exposure
Donahue 2019[14]	Inactivated influenza vaccine and spontaneous abortion in the Vaccine Safety Datalink in 2012-13, 2013-14, and 2014-15	Wrong exposure
Durrieu 2011[15]	Safety surveillance of influenza A(H1N1)v monovalent vaccines during the 2009-2010 mass vaccination campaign in France	Wrong exposure
Eaton 2018[16]	Birth outcomes following immunization of pregnant women with pandemic H1N1 influenza vaccine 2009-2010	Wrong exposure
Goldman 2013[17]	Comparison of VAERS fetal-loss reports during three consecutive influenza seasons: was there a synergistic fetal toxicity associated with the two-vaccine 2009/2010 season?	Wrong exposure
Kankawinpong 2012[18]	Immunogenicity and safety of an inactivated pandemic H1N1 vaccine provided by the Thai ministry of public health as a routine public health service	Wrong exposure
Kharbanda 2013[19]	Inactivated influenza vaccine during pregnancy and risks for adverse obstetric events	Wrong exposure
Kharbanda 2017[20]	First trimester influenza vaccination and risks for major structural birth defects in offspring	Wrong exposure
Kozuki 2018[21]	Impact of maternal vaccination timing and influenza virus circulation on birth outcomes in rural Nepal	Wrong exposure
Louik 2013[22]	Risks and safety of pandemic H1N1 influenza vaccine in pregnancy: exposure prevalence, preterm delivery, and specific birth defects	Wrong exposure
Louik 2016[23]	Safety of the 2011-12, 2012-13, and 2013-14 seasonal influenza vaccines in pregnancy: preterm delivery and specific malformations, a study from the case-control arm of VAMPSS	Wrong exposure
Lylianou 2012[24]	Adverse events following immunization from pandemic influenza A (H1N1)-Laos 2010	Wrong exposure
McHugh 2017[25]	Birth outcomes for Australian mother-infant pairs who received an influenza vaccine during pregnancy, 2012-2014: the FluMum study	Wrong exposure
McHugh 2019[26]	Influenza vaccination in pregnancy among a group of remote dwelling Aboriginal and Torres Strait Islander mothers in the Northern Territory: The 1+1 Healthy Start to Life study	Wrong exposure
Mohammed 2020[27]	Safety and protective effects of maternal influenza vaccination on pregnancy and birth outcomes: A prospective cohort study	Wrong exposure
Moro 2017[28]	Surveillance of Adverse Events After Seasonal Influenza Vaccination in Pregnant Women and Their Infants in the Vaccine Adverse Event Reporting System, July 2010-May 2016	Wrong exposure
Moro 2020[29]	Monitoring the safety of high-dose, trivalent inactivated influenza vaccine in the vaccine adverse event reporting system (VAERS), 2011 - 2019	Wrong exposure
Nordin 2013[30]	Maternal safety of trivalent inactivated influenza vaccine in pregnant women	Wrong exposure
Ohfuji 2020[31]	Safety of influenza vaccination on adverse birth outcomes among pregnant women: A prospective cohort study in Japan	Wrong exposure

Omer 2011[32]	Maternal influenza immunization and reduced likelihood of prematurity and small for gestational age births: a retrospective cohort study	Wrong exposure
Peppa 2020[33]	Seasonal influenza vaccination during pregnancy and the risk of major congenital malformations in live-born infants: A 2010-2016 historical cohort study	Wrong exposure
Phengxay 2015[34]	Introducing seasonal influenza vaccine in low-income countries: an adverse events following immunization survey in the Lao People's Democratic Republic	Wrong exposure
Regan 2014[35]	Using SMS to monitor adverse events following trivalent influenza vaccination in pregnant women	Wrong exposure
Regan 2016[36]	Seasonal trivalent influenza vaccination during pregnancy and the incidence of stillbirth: population-based retrospective cohort study	Wrong exposure
Regan 2018[37]	Birth outcomes associated with seasonal influenza vaccination during first trimester of pregnancy	Wrong exposure
Richner 2017[38]	Vaccine mediated protection against Zika virus-induced congenital disease	Wrong outcomes
Shatla 2016[39]	Effect of maternal antenatal influenza vaccination on adverse neonatal outcomes in terms of premature birth, small-for-gestational age and low birth weight: a comparative study	Wrong exposure
Vazquez-Benitez 2016[40]	Risk of preterm or small-for-gestational-age birth after influenza vaccination during pregnancy: caveats when conducting retrospective observational studies	Wrong exposure
Walsh 2019[41]	Health outcomes of young children born to mothers who received 2009 pandemic H1N1 influenza vaccination during pregnancy: retrospective cohort study	Wrong exposure
Wijnans 2017[42]	Bell's palsy and influenza(H1N1)pdm09 containing vaccines: a self-controlled case series	Wrong patient population

Appendix 4. COVID-19 and Pregnancy Registries

Registry	Registered countries	Consent needed for enrollment	Obstetric/pregnancy data						Neonatal and infant outcome				Samples collected	Study population		Registry start date (mm/dd/yy)	Vaccination Data		
			SARS-CoV-2 infection	COVID-19	Early pregnancy loss	Fetal Growth Restriction	Stillbirth	Delivery outcome	Birth condition	Neonatal outcome	Vertical transmission	Infant outcome		COVID+ Pregnant w.	COVID- Pregnant w.		General population	Pregnant women	Post-vaccination outcomes
UKOSS (National)	UK	No	X	X		X	X	X	X	X	X	X	No	X		03/01/20		X	
PAN-COVID (International)	42 countries	Yes	X	X	X	X	X	X	X	X	X		No	X	N/A	N/A	N/A	N/A	N/A
BPSU (National)	UK	No		X				X	X	X	X	X	No		N/A	N/A			
NPC-19 (SONPM/AAP) (National)	USA	No		X		X	X	X	X	X	X	X	No	X		N/A	No	No	No
EPICENTRE (International)	23 European countries Australia	No	X	X				X	X	X	X	X	No	X	N/A	N/A	N/A	N/A	N/A
periCOVID (International)	7 in Africa 7 in Europe	Yes	X	X		X	X	X	X	X	X	X	Yes*	X		N/A	No	No	No
INTERCOVID (International)	29 registered countries (South America & Africa)	Yes	X	X	X	X	X	X	X	X	X	X	No	X	X	04/20/20	N/A	N/A	N/A
PregCOV-19LSR (International)	Live systematic reviews	No	X	X	X	X	X	X	X	X	X	X	No	X	X	N/A	N/A	N/A	N/A
PRIORITY (National)	USA	Yes	X	X	X	X	X	X	X	X	X	X	No	X	X	03/22/20	No	No	No
COVI-PREG (International)	23 countries in Asia, Africa, Europe, the Americas and Oceania	Yes	X	X	X	X	X	X	X	X	X	X	No	X	X	N/A	N/A	N/A	N/A
OTIS/MotherToBaby (Multi-national)	North America (USA and Canada)	Yes	X	X	X	X	X	X	X	X	X	X	No	X	X	N/A	N/A	N/A	N/A
CHOPAN (Multi-national)	Australia, New Zealand	No#	X	X	X	X	X	X	X	X	X	X	No	X	No	N/A			
vsafe pregnancy registry	USA	Yes	X	X	X	X	X	X	X	X	X	X	No	X	X	N/A		X	X

*blood, throat/NPA swab, urine, stool, cord blood, placenta, amniotic fluid, breast milk; # Women can opt out

Appendix 5. PRISMA checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	2-3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	4-5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	5 and Appendix 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Appendix 2
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	6

Section and Topic	Item #	Checklist item	Location where item is reported
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	6-7
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	6
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	6
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	NA
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Not described
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not described
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Appendix 3
Study characteristics	17	Cite each included study and present its characteristics.	Table 2, 3 and 4
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table 5 and 6
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table 2 and 3
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	NA
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	NA

Section and Topic	Item #	Checklist item	Location where item is reported
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Not described
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not described
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Not described
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	17
	23b	Discuss any limitations of the evidence included in the review.	18
	23c	Discuss any limitations of the review processes used.	18
	23d	Discuss implications of the results for practice, policy, and future research.	18-19
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	7
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	7
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	19
Competing interests	26	Declare any competing interests of review authors.	19
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	NA

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