Safety of COVID-19 vaccines, their components or their platforms for pregnant women: A rapid review

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ABSTRACT

Background

Pregnant women with COVID-19 are at an increased risk of severe COVID-19 illness as well as adverse pregnancy and birth outcomes. Many countries are vaccinating or considering vaccinating pregnant women with limited available data about the safety of this strategy. Early identification of safety concerns of COVID-19 vaccines, including their components, or their technological platforms is therefore urgently needed.

Methods

We conducted a rapid systematic review, as the first phase of an ongoing full systematic review, to evaluate the safety of COVID-19 vaccines in pregnant women, including their components, and their technological platforms (whole virus, protein, viral vector or nucleic acid) used in other vaccines, following the Cochrane methods and the PRISMA statement for reporting (PROSPERO- CRD42021234185).

We searched literature databases, COVID-19 and pregnancy registries from inception February 2021 without time or language restriction and explored the reference lists of relevant systematic reviews retrieved. We selected studies of any methodological design that included at least 50 pregnant women or pregnant animals exposed to the vaccines that were selected for review by the COVAX MIWG in August 2020 or their components or platforms included in the COVID-19 vaccines, and evaluated adverse events during pregnancy and the neonatal period.

Pairs of reviewers independently selected studies through the COVIDENCE web software and performed the data extraction through a previously piloted online extraction form. Discrepancies were resolved by consensus.

Results

We identified 6768 records, 256 potentially eligible studies were assessed by full-text, and 37 clinical and non-clinical studies (38 reports, involving 2,397,715 pregnant women and 56 pregnant animals) and 12 pregnancy registries were included.

Most studies (89%) were conducted in high-income countries. The most frequent study design was cohort studies (n=21), followed by surveillance studies, randomized controlled trials, and registry analyses. Most studies (76%) allowed comparisons between vaccinated and unvaccinated pregnant women (n=25) or animals (n=3) and reported exposures 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), followed by aluminum-based adjuvants (n=11). Aluminum phosphate was used in Respiratory Syncytial Virus Fusion candidate vaccines (n=3) and Tdap vaccines (n=3). Different aluminum-based adjuvants were used in hepatitis vaccines. The replication-deficient simian adenovirus ChAdOx1 was used for a Rift Valley fever vaccine. Only one study reported exposure to messenger RNA (mRNA) COVID-19 vaccines that also used lipid nanoparticles. 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 that were selected for review by the COVAX MIWG 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 women 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, the Vaccine Alliance, 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 women, and only limited human data on their safety during pregnancy was available at the time of emergency use authorization[4]. However, pregnant women with COVID-19 are at increased risk of adverse pregnancy and birth outcomes and severe illness compared to non-pregnant women[5-9]. Many countries are vaccinating or considering vaccinating pregnant women especially if they are at risk of being exposed and 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.

The main characteristics of the vaccines that were selected for review by the COVAX MIWG in August 2020 are presented in **Table 1**. To assist pregnant women, make a more fully informed decision, we aimed to identify safety concerns for pregnant women associated with these exposures 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.

Table 1 Main characteristics of the vaccines that were selected for review by the COVAX MIWG in August 2020.

Platform	Developer/ manufacturer	Vaccine candidates	Construct	Adjuvant	Dose / Schedule
Protein / subunit	Novavax	SARS-CoV-2 rS	Recombinant Spike Protein Nanoparticle vaccine Baculovirus Expressed trimeric Stabilized Spike, ∆F	Matrix-M™	Two doses at 5 µg with/wo Matrix M (0,21 days)
	Sanofi/GSK	Recombinant protein vaccine	Baculovirus Expressed trimeric Stabilized Spike	AS03	5 µg + AS03 (0, 21 days)
	Biological E (Bio E) Coalition for Epidemic Preparedness Innovations (CEPI)	Protein antigen	SARS-CoV-2 Spike receptor binding domain (RBD)	Alhydrogel (Alum) / CpG 1018	Two doses (0,28d)
	Clover Xiamen Innovax Biotech & GSK	Recombinant protein vaccine	S-protein trimer	ASO3 / CpG1018 (in CHO cells)	Two doses (0,21d)
Vectored	Merck Sharp & Dohme Corp.*	Recombinant replicating virus	Recombinant Vesicular stomatitis virus (rVSV)- ∆G-spike, (in MRC or Vero cells)	No	One dose (TBD)
	Johnson & Johnson/Janssen	Non-replicating viral vector	Replication Incompetent Ad26; Stab. Spike; ∆F; TM	No	One dose at 5×10^{10} vp; 2 doses at 5×10^{10} (0-56)
	U Oxford / AstraZeneca	Non-replicating viral vector	ChAdOx1 wild type Spike; TM	No	Two doses at 5×10^{10} vp, (0-28 days)
Nucleic acid / mRNA-LNP	Moderna	Encapsulated mRNA-1273	mRNA: encodes 2P-stabilized Spike, TM, FI	No	Two doses at 100 µg (0,28 days)
	BioNTech / Pfizer	BNT162a b2	mRNA: encodes stabilized SARS-CoV-2 Spike	No	Two doses X 30 µg (0, 21 days)
	CureVac	mRNA nCoV-19	mRNA/LNP full-length S-protein stabilized	No	Two doses at 12 ug (0,28d)

* Merck discontinued the development of this vaccine on January 25, 2021
LNP: lipid nanoparticle; **AS:** Adjuvant System; **CpG**: Cytosine phosphoGuanosine; **MRC**: Human Fetal Lung Fibroblast Cells; **CHO**: Chinese hamster ovary; **TM**: transmembrane domain; **S**: Spike; **FI**: formalin-inactivated; **rS**: recombinant Spike

OBJECTIVES

To evaluate the effects of COVID-19 the vaccines that were selected for review by the COVAX MIWG 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 and non-comparative study designs. Case series were included only if they reported on more than 50 exposed pregnant women. We included also experimental studies of any size with exposed pregnant animals. We excluded systematic reviews (SRs) but explored their reference lists as an additional primary study source.

The interventions or exposures of interest are the COVID-19 candidate vaccines that were selected for review by the COVAX MIWG in August 2020 or vaccine platforms (protein/subunit, vectored, nucleic acid/mRNA-LNP) or components (antigen, vehicle, construct, adjuvants, lipid nanoparticles or other components) used by COVID-19 vaccines. It was considered mandatory that at least one of these exposures was explicitly reported 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.

Safety outcomes were 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) was 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 $\geq 38^{o}$C or 100.4^{o}F, headache, malaise, myalgia, fatigue, etc.). We also considered other post-vaccination medical events (unsolicited in the studies, reported by organ system as per Medical Dictionary for Regulatory Activities - MedDRA)[16].

We used the following classification to grade the severity of AEs:

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- Mild (Grade 1): Events require minimal or no treatment and do not interfere with the subject's daily activities.
- Moderate (Grade 2): Events result in a low level of inconvenience or concern with therapeutic measures. Moderate events may cause some interference with functioning and daily activities.
- Severe (Grade 3): Events interrupt the subject's daily activities and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.
- Potentially Life Threatening (Grade 4): Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death.

We also considered other classifications of AEs commonly reported in safety studies, including:
-Medically attended adverse events (MAEs): events 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): resulted in death, were life-threatening, required hospitalization or prolongation of existing hospitalization, resulted in disability/incapacity, or a congenital anomaly/birth defect in the child of a study participant)
-Adverse events of special interest (AESIs): events worthy closer follow-up over 6 months post-vaccination. These include vaccine associated enhanced disease such as multisystem inflammatory syndrome (MIS-C/A).

The operative definitions of each specific AEs were reported elsewhere (PROSPERO-CRD42021234185). For this rapid review we considered the integrative outcome "safety concerns" as any statistically significant adverse outcome reported in the comparative studies or unexpected figures, with respect to the published incidences in the peer-reviewed literature, reported in uncontrolled studies.

Search strategy

We searched published and unpublished studies without restrictions on language or publication status from inception to February 2021 (See **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, pre-print 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 adverse events/safety reported in active COVID-19 and pregnancy registries. Additionally, we reviewed information collected in COVID-19 and pregnancy registries. The Food and Drug Administration (FDA), the European Medicines Agency (EMA), 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 to capture any new evidence in databases between March 2021 and current date and time.

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

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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 eligible studies. We resolved any disagreements by discussion. We documented the selection process with a 'PRISMA' flow chart[12]. This process was 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. We resolved any disagreements 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 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); 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. Data from non-comparative studies, including numerous registries, were collected and analyzed in the context of the expected global or country incidences of neonatal or obstetric outcomes.

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) or (for very rare events) Peto ORs. For continuous data, we calculated mean difference (MD) or standardized mean difference (SMD) between treatment groups depending on the use of the same or different scales, respectively. We treated large ordinal data as continuous data. We present 95% confidence intervals (CIs) for all outcomes. Where data to calculate RRs/ORs or MDs/SMDs were not available, we utilized the most detailed numerical data available that may facilitate similar analyses of included studies (e.g., test statistics, P values). We assessed whether the estimates calculated in the review for individual studies are compatible in each case with the estimates reported in the study publications. For randomized controlled trials (RCTs), we analyzed the data on an intention to treat basis as far as possible (i.e., including all randomized participants in analysis, in the groups to which they were randomized). For this rapid review we tabulated the study intervention/exposition characteristics and compared against the unexposed. We analyze the results of each study to determine any safety concerns as 'Yes', 'No' or 'Unclear'.

We planned to conduct subgroup analyses by the trimester of exposure and sensitivity analysis restricted to studies with low risk of bias. However, these were not pursued for this rapid review

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given the lack of safety concerns identified. We plan to perform meta-analysis and present GRADE 'Summary of findings' tables[10, 21] for the full review as was previously stated (PROSPERO- CRD42021234185).

RESULTS

We identified 6756 records, 265 potentially eligible studies were assessed by full-text and we included 37 clinical and non-clinical studies, involving 2,397,715 pregnant women and 56 pregnant animals from 38 reports[4, 22-58] (**Fig 1**).

Description of studies

The characteristics of included studies are described in **Table 2**. The most frequent study design was cohort studies (n=21) followed by surveillance studies (n=8), controlled trials (n=5) and registry analyses (n=3). Twenty-eight of the included studies (76%) allowed comparisons between vaccinated and unvaccinated pregnant women (n=25) or were conducted in animals (n=3). Nine out of the 37 studies (24%) were abstracts.
The most frequent study location was the USA (n=6), followed by Sweden and 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 low-to-middle-income countries (LMICs)[27, 35, 44, 49].
Only 3 out of 37 studies were conducted in animals (8%)[28, 32, 57]. 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). In six studies the time of exposure was not reported.
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]. The aluminum phosphate was used in the testing of candidate Respiratory Syncytial Virus Fusion (RSV F) vaccines in pregnant women [28, 44, 48] (n=3). Aluminum phosphate was also used in Tdap vaccines[35, 45, 54] (n=3). Different aluminum salts were used in Hepatitis vaccines[23, 29, 36, 46, 47]. One study reported on the use of the ChAdOx1 vector for a Rift Valley fever vaccine[57]. Only one study specific to COVID-19 was identified, reporting exposure to mRNA-LNP from Pfizer & Moderna COVID-19 vaccines[4].

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 vsafe registries) are presented in **Table 4**. The list of excluded studies and the reasons for exclusion is presented in **Appendix 3**.

Risk of bias in included studies

The risk of bias for the included controlled trials are presented in **Table 5** and for the included observational studies in **Table 6**.
We assessed the 38 included reports. Among the five RCTs two (40%) presented high risk of bias in the randomization process and one (20%) in blinding of participant and personnel.

Among the 33 observational study reports, 14 were classified as "good" (43%), 12 as "fair" (36%) and 7 as "poor" (21%).

Outcomes of exposures

The results of included studies are described in **Table 2**. There were 13 pregnancy-related outcomes (26 reports), 8 neonatal outcomes (19 reports) and 9 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), fetal death (n=6). The most reported neonatal outcomes were congenital anomalies (n=9), low birth weight (n=8) and the most reported maternal outcomes were local reactions (n=7), systemic reactions (n=5), serious adverse event (n=6).

The adjusted relative effects comparing exposed vs. no exposed pregnant participants were summarized in **Table 3**. None of the available exposure, including AS03, aluminum phosphate or aluminum salts only, was statistically associated with adverse outcomes. Only 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) [53]; and aluminum salts with lower stillbirth aHR 0.49 (95%CI 0.29 to 0.84)[54]. 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[55], 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 and that some misclassification of outcome may have occurred or residual confounding after adjusting for age and chronic comorbidity may have been present. In fact the full-text manuscript reported one year later by these authors[56] included 9,445 women vaccinated before or during pregnancy and 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 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 of the WHO, the Milken Institute and clinicaltrials.gov. databases[59]. One phase-2

trial is assessing the Ad26.COV2.S vaccine (a monovalent vaccine composed of a recombinant, replication-incompetent adenovirus type 26 vector)[60], and a phase-2/3 trial assessing the BNT162b2 vaccine (an RNA vaccine)[61] 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 demonstrated in blood serum and milk of lactating mothers vaccinated with the CX-024414 vaccine (mRNA vaccine)[62].

Fig 1. Study flow diagram (PRISMA 2020)
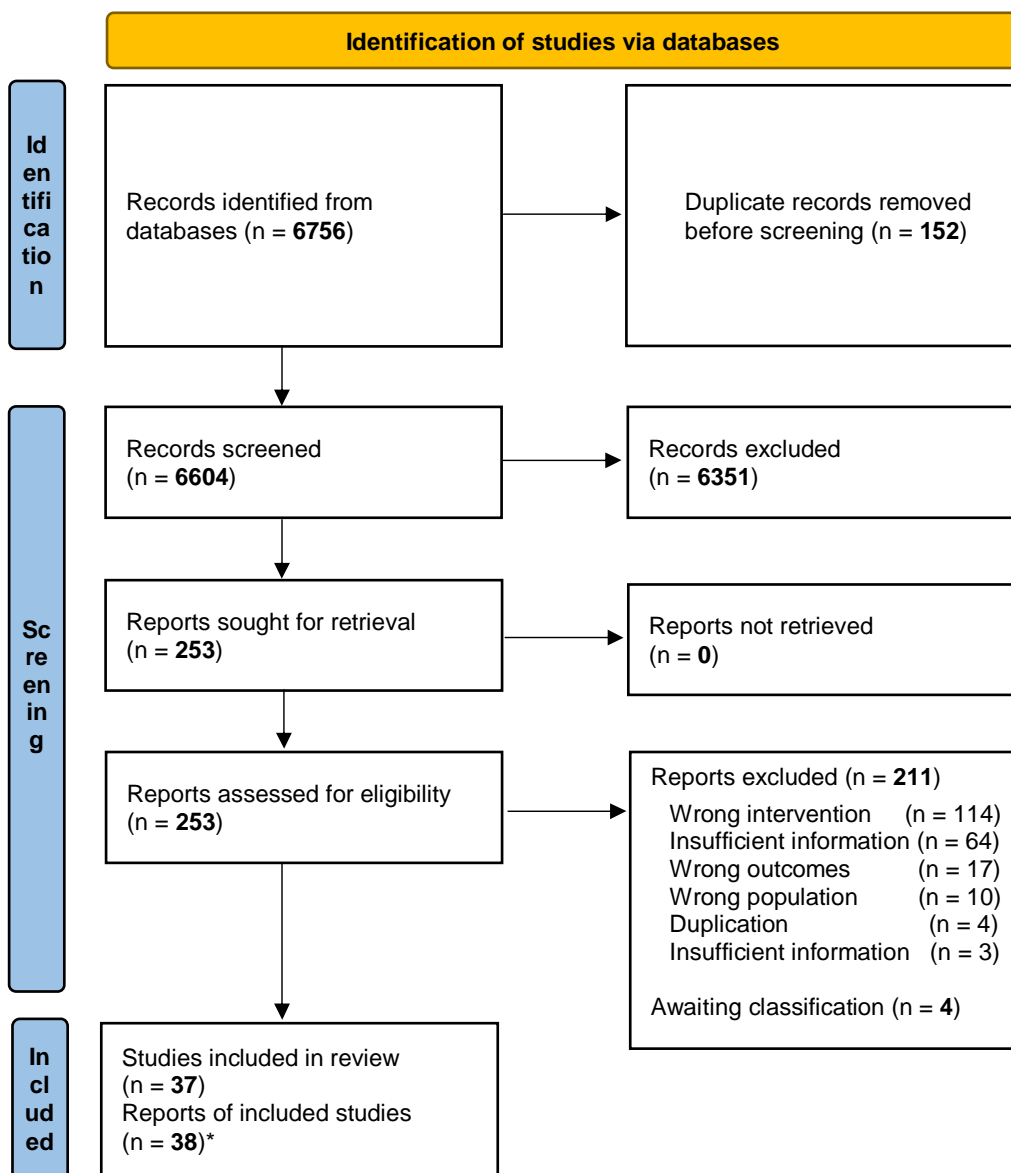
*Two reports for the study Pasternak 2012

Table 2 Main characteristics and results of included studies

Study ID	N	Study design	Country	Population	Trimester exposure	Brand names	Exposure*	Control	Results (vaccinated vs. non-vaccinated pregnant women for comparative studies)	Authors' conclusion	Safety concerns
Baum 2015[22]	34,241	Cohort studies	Finland	Pregnant women	2+3	Pandemrix	AS03	No Intervention	Stillbirth: aHR 1.05 (95% Confidence Interval [CI] 0.66–1.65) Early neonatal death: aHR 1.02 (0.43–2.40) Moderately preterm (28–36 weeks): aHR 1.00 (0.89–1.12) Very preterm (<28 weeks): aHR 0.90 (0.55–1.45) Moderately low birth weight (1500 g–2499 g): aHR 1.05 (0.90–1.21) Very low birth weight (<1500 g): aHR 0.84 (0.61–1.16) Fetal growth restriction: aHR 1.17 (0.98–1.40)	The risk of adverse pregnancy outcomes was not associated with the exposure to the AS03 adjuvanted pandemic influenza vaccine.	No
Celzo 2020[23]	1,676	Surveillance	Belgium	Pregnant women	1+2+3	Havrix, Engerix-B or Twinrix	Alhydrogel (Alum) / CpG 1018	No control	Pregnancy-related adverse event (Havrix 64/378; Engerix-B 23/339; Twinrix 103/199) Congenital anomalies/birth defects (Havrix 19/378; Engerix-B 29/339; Twinrix 10/199) Major birth defects (Havrix 17/19; Engerix-B 20/29; Twinrix 7/10) Spontaneous abortions (Havrix 43; Engerix-B 57; Twinrix 26)	No indication of any concerning pattern of adverse pregnancy outcomes following exposure to any of the 3 vaccines during pregnancy	No
Chavant 2013[24]	2,415	Surveillance	France	Pregnant women	NR	Pandemrix	AS03	No control	Fever and Flu-like symptoms: 37/56 (65.9%) Headaches: 9/56 (17.6%) Local reactions: 37/56 (65.9%) Congenital anomalies: 1/56 (1.4%)	Exposure to the A(H1N1)v2009 pandemic influenza vaccine during pregnancy does not increase the risk of adverse pregnancy outcomes.	No
Fell 2012[25]	23,340	Safety registry	Canada	Pregnant women	2+3	Pandemrix	AS03	No Intervention	Preterm birth (< 37 weeks): aRR (95% CI) 0.95 (0.88, 1.02) Very preterm birth (< 32 weeks): aRR 0.73 (0.58, 0.91) Small for gestational age: below 10th percentile: aRR 0.90 (0.85, 0.96) Small for gestational age: below 3rd percentile: aRR 0.81 (0.72, 0.92) 5-minute Apgar score below 7: aRR 0.97 (0.82, 1.14) Fetal death: aRR 0.66 (0.47, 0.91)	Second- or third-trimester H1N1 vaccination was associated with improved fetal and neonatal outcomes during the recent pandemic.	No
Folkenberg 2011[26]	5,772	Surveillance	Denmark	Pregnant women	NR	Pandemrix	AS03	No control	Uterine contractions: 2/12 Spontaneous abortions: 4/12 Stillbirth:1/12	No strong signals of any unknown or serious adverse events associated with influenza A/H1N1v vaccination in Denmark.	No
Galindo Santana 2011[27]	80,317	Cohort studies	Cuba	Pregnant women	1+2+3	Pandemrix	AS03	No control	Adverse effects 615/80,317 (0.8%) of the vaccinated pregnant women (fever 32,4%; headache 30,3%; vomiting 12%; local reactions 9%; arthralgia 6,9%; dizziness 5%; allergic manifestations 3%; spontaneous abortions 0.3%; increase in uterine contractions 0.3%)	No safety problem is associated to the Pandemrix vaccine.	No
Glenn 2015[28]	71	RCT	USA	Animals	3	RSV F vaccine	Protein/subunit; Nanoparticles; aluminum phosphate	Another intervention & placebo	Delivery rate Placebo: 80%; RSV F: 80% and RSV F + AIP04: 90% 3 stillbirths placebo vs 3 stillbirths in the adjuvanted RSV F group	The RSV F vaccine was safe. The rates of pregnancy and stillbirth were similar between controls and vaccinees.	No
Gray 2021[4]	84	Cohort studies	USA	Pregnant women	1+2+3	COVID-19 (Pfizer & Moderna)	Nucleic acid / mRNA	Not pregnant	Vaccine-related fevers/chills: 25/77 (32%) (8/16 [50%] in non-pregnant women; p=0.25). Fetal growth restriction: 0/13; Preeclampsia/gestational hypertension: 0/13 Preterm delivery: 1/13; Death: 0/13 The cumulative symptom score after the 1st dose in all groups was low and after the 2nd dose, the cumulative symptom score (median (IQR) 2 (1-3), 3 (2-4), and 2.5 (1-4.5) in pregnant, lactating, and non- pregnant groups respectively, p = 0.40).	There was no significant difference between pregnant, lactating, and non- pregnant groups respectively with respect to cumulative symptom score.	No
Groom 2018[29]	1,399	Cohort studies	USA	Pregnant women	1+2+3	Recombivax, Engerix or Twinrix	Aluminum hydrophosphate sulphate (Alum) Alhydrogel (Alum) Aluminum phosphate	Not Hep B vaccinated (other vaccines or unvaccinated)	Gestational hypertension aOR (95%CI) 1.02 (0.80–1.30). Gestational diabetes: aOR 1.06 (0.91–1.23) Pre-eclampsia/eclampsia: aOR 1.07 (0.84–1.36) Cesarean delivery: aOR 1.01 (0.91–1.13) Pre-term birth (<37 weeks): aOR 1.14 (0.94–1.39) Low birth weight (<2500 g): aOR 1.21 (0.96–1.52) Small for gestational age at birth: aOR 1.13 (0.94–1.37)	There were no significant associations between HepB exposure during pregnancy and maternal and neonatal outcomes. No increased risk for the adverse events that were observed among women or their offspring.	No
Guo 2010[30]	875	Cohort studies	Canada	Pregnant women	NR	Arepanrix	AS03	No Intervention	Fetal loss: 7/550 (1.3%) vaccinees vs 11/325 (3.3%) unvaccinated, P=0.06 Premature birth: 31/359 (8.6%) vaccinated vs 23/185 (12%) unvaccinated P=.21 Of 261 vaccinees reporting weekly data, 11 (4.2%) reported an adverse event requiring missed work or an MD visit within 7 days of vaccination, most commonly acute respiratory illness (N=7). Only one event (arm numbness) was thought to be vaccine related. No serious adverse events were reported.	Results to date suggest that pandemic vaccines were safe.	No
Haberg 2013[31]	63,367	Safety registry	Norway	Pregnant women	2+3	Pandemrix	AS03	No Intervention	Fetal death HR IC95% 0.88 (0.66-1.17) Preterm delivery HR 1.00 (0.93-1.09) Low birth weight at term HR 0.90 (0.76-1.08) Low Apgar score at term HR 1.08 (0.91-1.28)	There is no evidence of association between vaccination and fetal death, preterm delivery, low birth weight at term, and low Apgar score at term	No
Heldens 2009[32]	10	CT	Netherlands	Animals	3	Equilis Prequenza T	ISCOM-Matrix	No Intervention	Local reaction (swelling): 3/10 (in each dose) Pyrexia: 0/10 Systemic reactions: 0/10 The effects in the non-intervention was not reported	The vaccine was shown to be safe in pregnant mares, foals and is used safely since 2 years as a commercial vaccine in Europe.	No
Jonas 2015[33]	41,183	Cohort	Sweden	Pregnant	1+2+3	Pandemrix	AS03	No	Stillbirth: aHR IC95% 0.88 (0.59 to 1.30)	AS03 adjuvanted H1N1 vaccination during	No

Study	N	Study type	Country	Population	Dose	Vaccine	Adjuvant	Control	Results	Conclusion	
		studies		women				Intervention	Early neonatal death: aHR 0.82 (0.46 to 1.49) Later death: aHR 0.78 (0.52 to 1.19)	pregnancy does not affect the risk of stillbirth, early neonatal death, or later mortality in the offspring.	
Källén 2012[34]	18,612	Cohort studies	Sweden	Pregnant women	1+2+3	Pandemrix	AS03	No Intervention & pre-vaccination group	Gestational diabetes aOR (IC95%) 0.94 (0.81–1.09) Pre-eclampsia: aOR 0.99 (0.92–1.07) Stillbirth: aOR 0.77 (0.57–1.03) Preterm birth: aOR 0.86 (0.77–0.96) Low birthweight: aOR 0.86 (0.77–0.96) Congenital malformations: aOR 1.01 (0.83–1.23) Small-for-gestational-age: aOR 1.04 (0.92–1.17)	Vaccination during pregnancy with Pandemrix appeared to have no ill effects on the pregnancy.	No
Katz 2016[35]	1,845,379	Safety registry	Argentina	Pregnant women	1+2+3	Tdap	Protein / subunit & aluminum phosphate	No control	Adverse events following immunization (pregnant women): 1.46/100.000 Adverse events following immunization vaccine 0.43/100.000	Both vaccines presented a suitable safety profile. Since 2012 a downward trend in pertussis mortality was evident and no deaths from influenza in vaccinated were notified in pregnant women	No
Kushner 2020[36]	59	Cohort studies	Australia	Pregnant women	1	Heplisav B	Aluminum phosphate / CpG1018	Engerix-B	Healthy term deliveries: 24 (60%) Heplisav-B vs 11 (55%) Engerix-B Spontaneous abortions: 3 (7.5%) Heplisav-B vs 2 (10%) Engerix-B Congenital anomaly: 1 (2.5%) Heplisav-B vs 1 (5%) Engerix-B Stillbirths: 1 (2.5%) Heplisav-B vs 0 (0%) Engerix-B	Heplisav-b shows similar fetal outcomes compared with Engerix-B.	No
Lacroix 2010[37]	100,000	Surveillance	France	Pregnant women	NR	Pandemrix	AS03	No control	The French National Pharmacovigilance of A(H1N1) vaccination in pregnant women between October 2009 and March 2010, reported 13 intra-uterine deaths and 12 spontaneous abortions.	No causal relationship between immunization and in utero fetal death or spontaneous abortion was established.	No
Läkemedelsverket 2010[38]	30,000	Report	Sweden	Pregnant women	1+2	Pandemrix	AS03	No control	Suspected adverse events: 50/30.000 (0.17%) Miscarriages: 31/30.000 (0.10%) Intrauterine fetal deaths: 7/30.000 (0.02%)	The low number of reports with no defined risk profile would indicate that the vaccination with Pandemrix does not increase the risk for miscarriage or intrauterine fetal death.	No
Layton 2011[39]	92	Cohort studies	United Kingdom	Pregnant women	1+2+3	Pandemrix	AS03	No control	Miscarriages: 4/92 (4.3%) Congenital problems: 6/92 (6.5%)	No safety conclusion	No
Levi 2012[40]	6,989	Cohort studies	Denmark	Pregnant women	1+2+3	Pandemrix	AS03	No Intervention	Serious congenital malformation (1st trimester): 5.5% vs 4.5% unvaccinated Premature birth or low birth weight was also equally common in both groups, regardless of it time of vaccination.	It appears to be safe even during the pregnancy to be vaccinated against the H1N1-virus.	No
Ludvigsson 2013[42]	13,297	Cohort studies	Sweden	Pregnant women	1+2+3	Pandemrix	AS03	No Intervention	Low birth weight <2,500 g: aOR (IC95%) 0.91 (0.79–1.04) Preterm birth <37 weeks: aOR 0.99 (0.89–1.10) Small for gestational age: aOR 0.97 (0.90–1.05) Low Apgar score at 5 min<7: aOR 1.05 (0.84–1.31) Caesarean section: aOR 0.94 (0.89–0.99)	H1N1 AS03-adjuvanted vaccine during pregnancy, does not appear to adversely influence maternal or neonatal outcomes when used in different stages of pregnancy.	No
Ludvigsson 2016[41]	40,983	Cohort studies	Sweden	Pregnant women	1	Pandemrix	AS03	Siblings	Congenital malformation: aOR (IC95%) 0.98 (0.89–1.07) Congenital heart disease: aOR 0.98 (0.84–1.15) Oral cleft: aOR 1.14 (0.67–1.94) Limb deficiency: aOR 0.90 (0.36–2.28)	When intrafamilial factors were taken into consideration, H1N1 vaccination during pregnancy did not seem to be linked to overall congenital malformation in offspring.	No
Mackenzie 2012[43]	128	Cohort studies	United Kingdom	Pregnant women	1+2+3	Pandemrix	AS03	No Intervention	Miscarriages: 4/97 (4.1%) Potentially congenital abnormalities: 6/97 (6.2%) Stillbirths: 0/97 (0%)	Overall, no significant safety issues were identified.	No
Madhi 2020[44]	4,636	RCT	Multi-country#	Pregnant women	2+3	RSV F vaccine	Nanoparticle vaccine Baculovirus / Aluminum phosphate	Placebo	Local injection-site reactions: 40.7% vs. 9.9% placebo; P<0.001 Fever within 7 days: 1.2% vs 1.6% Systemic reaction: 41.2% vs 38.6% Serious adverse event: 29.8% vs 28.8% Any infant adverse event 82.3% vs 83% Serious adverse event: 44.3% vs 46.4% Serious adverse event with outcome of death: 0.6% vs 0.8%	RSV F protein nanoparticle vaccination in pregnant women was safe	No
McHugh 2019[45]	2,706	Cohort studies	Australia	Pregnant women	1+2+3	Tdap	Protein/subunit & aluminum phosphate	No Intervention	Preterm birth (<37 weeks): aRR (95% CI) 0.99 (0.75–1.32) Low birth weight at term (<2500 g): aRR 1.19 (.61–1.11) Small for gestational age (<10th percentile): aRR 1.09 (.86–1.37)	No significant associations were found between pertussis vaccination in pregnancy and adverse birth outcomes, regardless of the trimester of pregnancy.	No
Moro 2014[46]	139	Surveillance	USA	Pregnant women	1	Havrix, Vaqta, Twinrix	Aluminum hydrophosphate sulphate, Alhydrogel (Alum) Aluminum phosphate	No control	Pregnancy AEs: 41/139 (29.4%) Non-pregnancy specific outcomes: 21/139 (15.1%) Infant/neonatal outcomes: 12/139 (8.6%) No AE reported: 65/139 (46.8%)	This review of VAERS reports did not identify any concerning pattern of AEs in pregnant women or their infants following maternal Hep A or Hep AB immunizations during pregnancy	No
Moro 2018[47]	192	Surveillance	USA	Pregnant women	1+2+3	Recombivax Engerix-b, Twinrix, Comvax, Pediarix	Aluminum hydrophosphate sulphate, Alhydrogel (Alum) Aluminum phosphate	No control	Pregnancy-specific AEs: 61 (55.4%) Non-pregnancy specific AEs: 35 (31.8%) Infant outcomes: 22 (20.0%)	Our analysis of VAERS reports involving hepatitis B vaccination during pregnancy did not identify any new or unexpected safety concerns.	No
Muñoz 2019[48]	50	RCT	USA	Pregnant women	3	RSV F vaccine	Nanoparticle vaccine	Placebo	Solicited AEs: 15/22 (68.2%) vs 10/28 (35.7%) Severe solicited AEs 0/22 vs 0/28	The vaccine was well tolerated; no meaningful differences in pregnancy or infant outcomes	No

Author Year	N	Study type	Country	Population	Trimester	Vaccine	Adjuvant	Intervention	Results	Conclusion	A
							Baculovirus / Aluminum phosphate		Local solicited AEs 13/22 (59.1%) vs1/28 (3.6%) Systemic solicited AEs 6/22 (27.3%) vs10/28 (35.7%) Any unsolicited AE 22/22 (100.0%) vs 28/28 (100.0%) Severe unsolicited AE 3/22 (13.6%) vs 4/28 (14.3%) Severe & related unsolicited AE 0/22 vs 0/28 Any medically attended AE 18/22 (81.8%) vs 25/28 (89.3%) Any serious AE (SAE) 3/22 (13.6%) vs1/28 (3.6%)	were observed between study groups. Suggesting good tolerability of the RSV F vaccine among pregnant women and safety in their infants sufficient to justify larger trials.	
Núñez Rojas 2010[49]	451	Cohort studies	Cuba	Pregnant women	1	Pandemrix	AS03	No Intervention	34/451 Vs control group 21/205 (OR:0.71) for some condition, minor or major. 64,7% of findings in the vaccinated group were located in the kidneys (62,2% were renal ecstasy, either unilateral or bilateral)	Vaccination against influenza virus A H1N1 did not increase the risk of birth defects when applied during the first trimester of gestation in the sample studied	No
Oppermann 2012[50]	90	Cohort studies	Germany	Pregnant women	1	Pandemrix	AS03	No Intervention	Systemic adverse reactions: 23/90 (25.6%) Local reactions: 64/90 (71.1%) Spontaneous abortions: 3/90 (3.3%)	The results of our study do not indicate a risk for the pregnant woman and the developing embryo/fetus after H1N1 vaccination.	No
Pasternak 2012[51, 52]	54,585	Cohort studies	Denmark	Pregnant women	1+2+3	Pandemrix	AS03	Propensity score	Major birth defects in gestational weeks 4 to 10: prevalence OR (POR) 1.24 (0.57-2.71) Preterm birth: POR: 0.99 (0.84-1.17) Small size for gestational age: POR: 0.97 (0.86-1.09) Fetal death: HR (95%CI) 0.79 (0.53-1.16) Spontaneous abortion HR 1.11 (0.71-1.73) Stillbirth: HR 0.44 (0.20-0.94)	Exposure to an adjuvanted influenza A(H1N1) pdm09 vaccine during pregnancy was not associated with a significantly increased risk of major birth defects, preterm birth, or fetal growth restriction.	No
Ray 2014[53]	509	Cohort studies	Canada	Pregnant women	NR	Pandemrix	AS03	Inactivated non-adjuvanted H1N1 vaccine	Peripartum complications: 83/199 (41.7%) nonadjuvated vs 127/509 (25.1%) adjuvanted (aOR 1.55; IC95% 1.01–2.39)	The composite outcome of peripartum complications was more common in women who received the nonadjuvanted vaccine	No
Rega 2016[54]	5,155	Unclear	Australia	Pregnant women	NR		Aluminum phosphate	TIV & unvaccinated	Local reaction. 7.1% Tdap and 3.2% TIV	Active vaccine safety monitoring has not identified clinically significant issues. Pregnant woman vaccinated against influenza are less likely to experience stillbirth.	No
Sammon 2011[55]	9,282	Cohort studies	United Kingdom	Pregnant women	1+2+3	Influenza v. pandemic & seasonal	AS03	No Intervention	Spontaneous loss adjusted for age and chronic comorbidity: aRR 1.54; CI95% 1.36–1.74)	We identified an increased miscarriage risk associated with influenza vaccination during pregnancy possibility due to residual confounding	Unclear
Sammon 2012[56]	9,445	Cohort studies	United Kingdom	Pregnant women	1+2+3	Pandemrix	AS03	No Intervention	Fetal death 9 to 12 weeks unadjusted HR 0.56; CI95 0.43 to 0.73) Fetal death 13 to 24 weeks unadjusted HR 0.45; CI95 0.28 to 0.73) Fetal loss 9 to 12 weeks unadjusted HR 0.74; CI95 0.62 to 0.88) Fetal loss 13 to 24 weeks unadjusted HR 0.59; CI95 0.45 to 0.77)	Influenza vaccination during pregnancy does not appear to increase the risk of fetal death.	No
Stedman 2019[57]	16	RCT	Netherlands	Animals	2	ChAdOx1 RVF	Vectored	Placebo	All ewes and does in the ChAdOx1 RVF (n = 8) and mock-vaccinated groups (n = 8) were in good health, with no clinical signs or other adverse events following vaccination	When administered to pregnant sheep and goats, ChAdOx1 RVF is safe	No
Tavares 2011[58]	267	Cohort studies	United Kingdom	Pregnant women	1+2+3	Pandemrix	AS03	No Intervention	At least 1 MAE within the 31-daypost-vaccination: 59 (22.1 %) SAEs during the 181-day post-vaccination: 34 (12.7%) Observed / expected number of pregnancy outcomes by subgroup at vaccination: Spontaneous abortion: 4 (3.3%) (expected in the general population: 10–16%) Stillbirth :0 (expected in the general population: 0.51%) Congenital anomaly: 5 (1.9%) (expected in the general population: 2.09%) Preterm delivery (<37 weeks' gestation): 14 (5.4%) (expected in the general population: 5.6%) Very pre-term delivery (<32 weeks' gestation): 3 (1.1%) (expected in the general population: 1.7%) Low birth weight (<2.5 kg): 21 (8.1%) (expected in the general population: 7.1%) Very low birth weight (<1.5 kg): 4 (1.5%) (expected in the general population: 1.2%)	The results of this analysis suggest that exposure to the AS03 adjuvanted H1N1 (2009) vaccine during pregnancy does not increase the risk of adverse pregnancy outcomes including spontaneous abortion, congenital anomalies, preterm delivery, low birth weight neonates, or maternal complications.	No

* See adjuvants, platforms and constructs in table 1; # Argentina, Australia, Chile, Bangladesh, Mexico, New Zealand, the Philippines, South Africa, Spain, the United Kingdom, and the United States.

A: Only available as abstract; **RCT:** Randomized Controlled Trial; **aHR:** adjusted Hazard Ratio; **aRR:** adjusted Relative Risk; **aOR** adjusted Odds Ratio; **USA:** United States of America; **AE:** Adverse Event; **SAE:** Serious AE; **MAE:** medically attended adverse event;

RSV F: Respiratory Syncytial Virus Fusion

Alhydrogel is an aluminum hydroxide (referred to as alum)

Table 3. Exposure to vaccine components/platforms

Exposure References	Pregnant participants	studies (%)	Adjusted relative effects[#][$] (exposed vs no exposed)
AS03[22, 24-27, 30, 31, 33, 34, 37-43, 49-53, 55, 56, 58]	536,240	23 (62%)	Congenital malformation: 0.98 to 1.01 Fetal death 0.66 to 0.88 Early neonatal death: 0.82 to 1.02 Later death: 0.78 Preterm delivery 0.86 to 1.00 (Very preterm 0.73[$] to 0.90) Low birth weight/small at term 0.86 to 1.04 (<10th & 3rd percentile: 0.90 & 0.81; very low birth weight 0.84) Low Apgar score at term 0.97 to 1.08 Gestational diabetes 0.94 Pre-eclampsia: 0.99 Stillbirth: 0.77 to1.05 Caesarean section: 0.94 Peripartum complications: 0.65[$]
*Aluminum phosphate[28, 35, 44, 45, 48]	1,852,842	5 (14%)	Preterm birth: 0.99 Low birth weight at term: 1.19 Small for gestational age (<10th percentile): 1.09
*Aluminum salts only[29, 46, 47, 54]	6,885	4 (11%)	Stillbirth: 0.49[$] Gestational hypertension 1.02 Gestational diabetes: 1.06 Pre-eclampsia/eclampsia: 1.07 Cesarean delivery: 1.01 Pre-term birth (<37 weeks): 1.14 Low birth weight (<2500 g): 1.21 Small for gestational age at birth: 1.13
*CpG 1018 & Aluminum salts[23, 36]	1,735	2 (5%)	Not available
ISCOM-Matrix[32]	10	1 (3%)	Not available
mRNA-LNP[4]	84	1 (3%)	Not available
ChAdOx1 RVF[57]	16	1 (3%)	Not available

* Any aluminum exposure 1,861,462 pregnant participants from 11 studies; LNP: lipid nanoparticle
# Adjusted Hazard Ratio; Relative Risk or Odds Ratio; $ statistically significant

Table 4. COVID-19 and Pregnancy Registries

Registry	Registered countries	Consent needed for enrollment	SARS-CoV-2 infection	COVID-19	Early pregnancy loss	Fetal Growth Restriction	Stillbirth	Delivery outcome	Birth condition	Neonatal outcome	Vertical transmission	Infant outcome	Samples collected	COVID+ Pregnant w.	COVID- Pregnant w.	Registry start date (mm/dd/yy)	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

Table 4. Risk of bias of clinical trials

Study ID	Adequate sequence generation	Allocation concealment	Blinding of participant & personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias
Glenn 2015	Unclear	Unclear	Low	Low	Low	Unclear	Unclear
Heldens 2009	High	High	Unclear	Unclear	Low	Unclear	High
Madhi 2020	High	High	Unclear	Unclear	Low	Unclear	Unclear
Muñoz 2019	Unclear	Unclear	High	Low	Low	Unclear	Unclear
Stedman 2019	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear

Table 5. Risk of bias of observational studies

Study ID	Study design	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Global Quality
Baum 2015	Cohort studies	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	No	Yes	No	Yes	Yes	Good
Galindo Santana 2011	Cohort studies	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	No	Yes	No	NR	No	Fair
Gray 2021	Cohort studies	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NR	Yes	No	Fair
Groom 2018	Cohort studies	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NR	Yes	Yes	Good
Guo 2010	Cohort studies	Yes	CD	CD	CD	CD	Yes	Yes	NA	CD	NA	CD	NR	Yes	No	Fair
Jonas 2015	Cohort studies	Yes	Yes	Yes	Yes	NR	Yes	Yes	NA	Yes	NA	Yes	NR	Yes	Yes	Good
Källén 2012	Cohort studies	Yes	Yes	Yes	Yes	NR	Yes	Yes	NA	Yes	NA	Yes	NR	Yes	NR	Fair
Kushner 2020	Cohort studies	Yes	Yes	Yes	NR	No	Yes	Yes	No	Yes	Yes	NR	NR	NR	No	Fair
Layton 2011	Cohort studies	Yes	CD	CD	CD	CD	Yes	CD	NA	CD	NA	CD	CD	NR	No	Fair
Levi 2012	Cohort studies	Yes	Yes	CD	CD	CD	Yes	Yes	NA	CD	NA	CD	CD	NR	CD	Fair
Ludvigsson 2013	Cohort studies	Yes	Yes	Yes	Yes	NR	Yes	Yes	NA	Yes	NA	Yes	NR	No	Yes	Good
Ludvigsson 2016	Cohort studies	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NR	Yes	Yes	Good
Mackenzie 2012	Cohort studies	Yes	Yes	Yes	Yes	NR	Yes	Yes	NA	Yes	No	Yes	NR	Yes	No	Fair
McHugh 2019	Cohort studies	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NR	Yes	Yes	Good
Núñez Rojas 2010	Cohort studies	Yes	Yes	NR	No	No	Yes	Yes	NA	Yes	NA	No	NR	NR	No	Poor
Oppermann 2012	Cohort studies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	No	Yes	Yes	Good
Pasternak 2012	Cohort studies	Yes	Yes	Yes	Yes	NR	Yes	Yes	NA	Yes	No	Yes	NR	Yes	Yes	Good
Pasternak 2012	Cohort studies	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NA	NA	Yes	Good
Ray 2014	Cohort studies	No	No	CD	Yes	NR	Yes	CD	NA	No	No	No	NR	CD	NR	Poor
Sammon 2011	Cohort studies	Yes	Yes	Yes	Yes	No	Yes	CD	NA	Yes	NA	No	NA	NA	No	Poor
Sammon 2012	Cohort studies	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	No	Yes	No	NR	Yes	Good
Tavares 2011	Cohort studies	Yes	Yes	CD	Yes	No	Yes	Yes	NA	Yes	No	Yes	No	No	No	Fair
Fell 2012	Registry analysis	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NA	Yes	Yes	Good
Haberg 2013	Registry analysis	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NA	No	Yes	Good
Katz 2016	Registry analysis	Yes	Yes	CD	Yes	No	Yes	CD	NA	Yes	NA	Yes	NA	NA	NA	Fair
Celzo 2020	Surveillance	Yes	Yes	CD	No	No	Yes	NR	NR	Yes	NA	Yes	NA	NA	No	Fair
Chavant 2013	Surveillance	Yes	Yes	NA	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No	CD	No	Poor
Folkenberg 2011	Surveillance	Yes	Yes	CD	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NA	NA	NA	Good
Lacroix 2010	Surveillance	Yes	Yes	CD	Yes	No	No	Yes	NA	Yes	NA	Yes	NA	NA	No	Fair
Läkemedelsverket 2010	Surveillance	Yes	Yes	CD	CD	No	Yes	Yes	NA	Yes	NA	No	NA	No	No	Poor
Moro 2014	Surveillance	Yes	Yes	CD	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NA	NA	NA	Good
Moro 2018	Surveillance	Yes	Yes	NA	Yes	No	Yes	Yes	NA	No	No	Yes	NA	NA	NA	Poor
Rega 2016	Surveillance	No	No	Yes	NR	No	Yes	NR	NA	Yes	NA	NR	NA	NA	No	Poor

NA: not applicable, **NR**: not reported, **CD**: cannot be determined

*Signaling questions
1. Was the research question or objective clearly stated in this study?
2. Was the study population clearly specified and defined?
3. Was the participation of eligible persons at least 50%?
4. Were all subjects selected or recruited from the same or similar populations (including the same time frame)? Were the inclusion and exclusion criteria pre-specified and applied to participate in the study of uniformly to all participants?
5. Was a justification of the sample size, a description of the power, or estimates of variance provided and effect?
6. For the analysis in this study, were the exposure (s) of interest measured before the outcome (s) were measured?
7. Was the follow-up period long enough for one to reasonably expect to see an association between exposure and result if it exists?
8. For exposures that can vary in quantity or level, did the study examine different levels of exposure in relation to with the outcome (for example, exposure categories or exposure measured as a continuous variable)?
9. Were the exposure measures (independent variables) clearly defined, valid, reliable and implemented consistently across all study participants?
10. Were the exposure (s) evaluated 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 the participants?
13. Was the loss to follow-up after the start of the study 20% or less?
14. Were potential key confounding variables statistically measured and adjusted for their impact on the relationship between exposure (s) and outcome (s)?

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DISCUSSION

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

None of the adjusted relative effects comparing exposed vs. no exposed pregnant participants of the available exposure results was statistically associated with adverse outcomes Only AS03 showed a statistically lower frequency of very preterm[25] and peripartum complications[53] and aluminum salts showed lower stillbirth aHR 0.49 (95%CI 0.29 to 0.84)[54]. Uncontrolled studies in general reported low frequencies of adverse outcomes. One study[55], 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 more complete analysis they concluded that there is no evidence of safety concerns.

Nine systematic reviews consistently supported the safety of influenza vaccines during pregnancy[63-71]. In general, cohort studies showed the benefits of vaccinating during pregnancy such as significantly decreased risks for preterm birth, small for gestational age and fetal death. However, after adjusting for season at the time of vaccination and countries' income level, only reduction of fetal death remained significant[67]. There is no evidence of an association between influenza vaccination and serious adverse events in the comparative studies[68]. 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[70].

Other systematic reviews also assessed the safety of different vaccines. One SR evaluated the safety of hepatitis B, pneumococcal polysaccharide vaccine and meningococcal polysaccharide vaccines administration during pregnancy and found no clear association with a teratogenic effect on the fetus, preterm labor or spontaneous abortion[72]. Another SR evaluated safety of vaccines frequently given to travelers on pregnant women such as yellow fever, MMR (mumps, measles and rubella), influenza, Tdap (tetanus, diphtheria and pertussis), meningococcus or hepatitis A and B[73]. The authors concluded the safety of influenza vaccine is supported by high-quality evidence. For 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, hepatitis B vaccines during pregnancy. In summary primary and secondary evidence described 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 women, published after this rapid review was finalized, reinforced these findings[74-76]. Shimabukuro el al, published preliminary results from the U.S. surveillance review of the safety of mRNA COVID-19 vaccines during pregnancy[75]. The solicited local and systemic reactions reported were similar among persons who identified as pregnant and non-pregnant women. Prabhu et al, studied the antibody response of 122 pregnant women, and their neonates at time of birth, who had received one or both doses of a mRNA-based COVID-19 vaccine[74]. COVID-19 vaccination in pregnancy induced a robust maternal immune response, with transplacental antibody transfer detectable as early as 16 days after

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the first dose. Rottenstreich et al, 20 pregnant women who received two doses of SARS-CoV-2 BNT162b2 (Pfizer/BioNTech) mRNA vaccine and found 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[77-83].

This rapid review has several strengths. First, we included reports without time, language, or publication type restriction, in human 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 exposition to the vaccine components and platforms, which was a challenging issue that demanded frequently to explore 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 were selected for review by the COVAX MIWG in August 2020. The vaccines availability has changed over time[84] 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. 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 women and only five of them were RCTs. Therefore, most of this evidence is observational. Nevertheless, the absence of safety concerns regardless the study design and publication type suggest that this could not be a major limitation. We are aware that the cut-off of 50 animals for non-human studies could be too high, but allowed us to provide timely answers through a rapid review in the context of the pandemics.

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[75]. Regardless of the exposure, all reported a rates of spontaneous abortion in exposed pregnant women described in Table 2 are below the reported the highest global incidence of 31%, or 10% when considering only losses occurring in clinically recognized pregnancies[77]. 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 livebirths[78-82]. 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)[85]. None of the included studies conducted in LMICs reported stillbirth rates, which has been reported to be higher than in HIC: approximately 21 deaths per 1000 live births in low income countries[85].

We are aware that the list of Tdap vaccines included our review is incomplete due to the focus of our research question. This vaccine contains aluminum phosphate as 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, clinical trials registers or to contact authors and experts in the field to obtain additional data. For the same reason we could not conduct a meta-analysis that are planned for the full review phase. Regarding COVID-19 and pregnancy registries we identified 12 national or international databases with potentially

useful 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 components, or the technological platforms used for pregnant women. It is reasonable to consider COVID-19 vaccination in pregnant women, because their higher risk of adverse outcomes. The next full review phase will add stronger evidence over this important 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 an extremely useful evidence from the real-world data.

Author contributions: All authors contributed to 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 critically the first draft, and signed off on the final version.

Supporting information
Appendix 1. Search strategy
Appendix 2. Risk of bias assessment tools by study design
Appendix 3. List of excluded studies
Appendix 4. PRISMA checklist

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