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Data Analytics and Methods

# Safety and effectiveness of COVID-19 maternal immunisation

## An update of the available evidence

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## 1. Background

Emerging evidence has shown that pregnant women are at increased risk of COVID-19-related morbidity and mortality compared to their uninfected counterparts or nonpregnant women of reproductive age. Observational studies have reported increased risk of preeclampsia/eclampsia, hospitalisation, intensive care unit (ICU) admission, and death from COVID-19. [1-7] Moreover, the infants of women infected with SARS-CoV-2 during pregnancy are more likely to be preterm, stillbirth, and are at higher risk of severe neonatal morbidity. [1-8] Vaccination presents an important strategy for preventing adverse outcomes due to SARS-CoV-2 infection in this population. However, there are still relatively limited data on the safety and effectiveness of COVID-19 vaccines during pregnancy, because pregnant women were not initially included in vaccine clinical trials and observational evidence remains to be further complemented. Even scarcer are data on how vaccination during pregnancy or lactation protects the infant during the first months of life against SARS-CoV-2 infection or health complications, although some evidence is starting to build. Transplacental transfer of maternal vaccine-derived antibodies against other infections (e.g., pertussis, influenza) has been demonstrated following vaccination during pregnancy, which provides passive protection to infants.[9,10] Few studies have suggested that lactating women exhibit detectable human milk anti-SARS-CoV-2 IgG up to six weeks after the second dose of mRNA COVID-19 vaccines.[11-13] However, whether these antibodies are critical for neonatal protection against SARS-CoV-2 infection or health complications remains unclear.

The objective of this scoping literature review was to identify and compile the most recent evidence on the safety and effectiveness of COVID-19 vaccination during pregnancy and breastfeeding.

## 2. Methods

### *2.1. Information source and search strategy*

A literature search was conducted to include studies published between January 1, 2021, through June 7, 2022. The information sources were EMBASE and PubMed database. The key terms included in the search are shown in Table 1. Search results were exported to EndNote™ 20 (Clarivate, Philadelphia, PA).

**Table 1. Electronic database search terms**

| Date | Database | Search query | Filters | Results |
|---|---|---|---|---|
| 07-06-2022 | EMBASE | ('pregnancy'/exp OR 'pregnancy' OR 'pregnant wom?n' OR 'maternal'/exp OR 'maternal' OR 'maternal'/exp OR maternal OR f?etal OR 'birth'/exp OR 'birth' OR 'birth'/exp OR birth OR perinatal OR neonatal OR 'new born'/exp OR 'new born' OR new?born OR 'infant'/exp OR 'infant' OR 'infant'/exp OR infant OR 'breastfeeding'/exp OR breastfeeding OR 'lactation'/exp OR 'lactation') | [humans]/lim AND [2021-2022]/py | 1059 |

| | | | | |
|---|---|---|---|---|
| | | AND<br>('covid-19 vaccine'/exp OR 'covid-19 vaccine' OR 'covid-19 vaccination' OR 'sars-cov-2 vaccination' OR 'sars-cov-2 vaccine'/exp OR 'sars-cov-2 vaccine') | | |
| 07-06-2022 | PubMed | (pregnancy OR 'pregnant woman' OR 'pregnant women' OR maternal OR fetal OR foetal OR birth OR perinatal OR neonatal OR 'new born' OR new-born OR newborn OR infant OR breastfeeding OR lactation)<br>AND<br>('covid-19 vaccine' OR 'covid-19 vaccination' OR 'sars-cov-2 vaccination' OR 'sars-cov-2 vaccine') | [humans]/lim AND [2021-2022]/py | 1135 |

### *2.2. Study selection and data extraction*

Studies were included if they presented a comparison group (e.g., unvaccinated women) or used background rates, and if they addressed at least one of the following topics: (1) Safety of COVID-19 vaccines during pregnancy with pregnancy, delivery, or neonatal outcomes, or (2) effectiveness of COVID-19 vaccines against SARS-CoV-2 infection, severe COVID-19 illness, or COVID-19-related complications or death, in pregnant women or their infants. Additionally, we included studies looking at the potential protective effect of COVID-19 vaccination during breastfeeding of infants. The exclusion criteria included research on AEFIs (adverse events following immunisation) published only as abstracts, case-studies, or animal-models.

Based on inclusion criteria, an initial screening of titles and abstract was conducted, which was followed by full-text screening of potential studies addressing the objective of this scoping review. Finally, we carried out a full-text review of included studies (Figure 1).

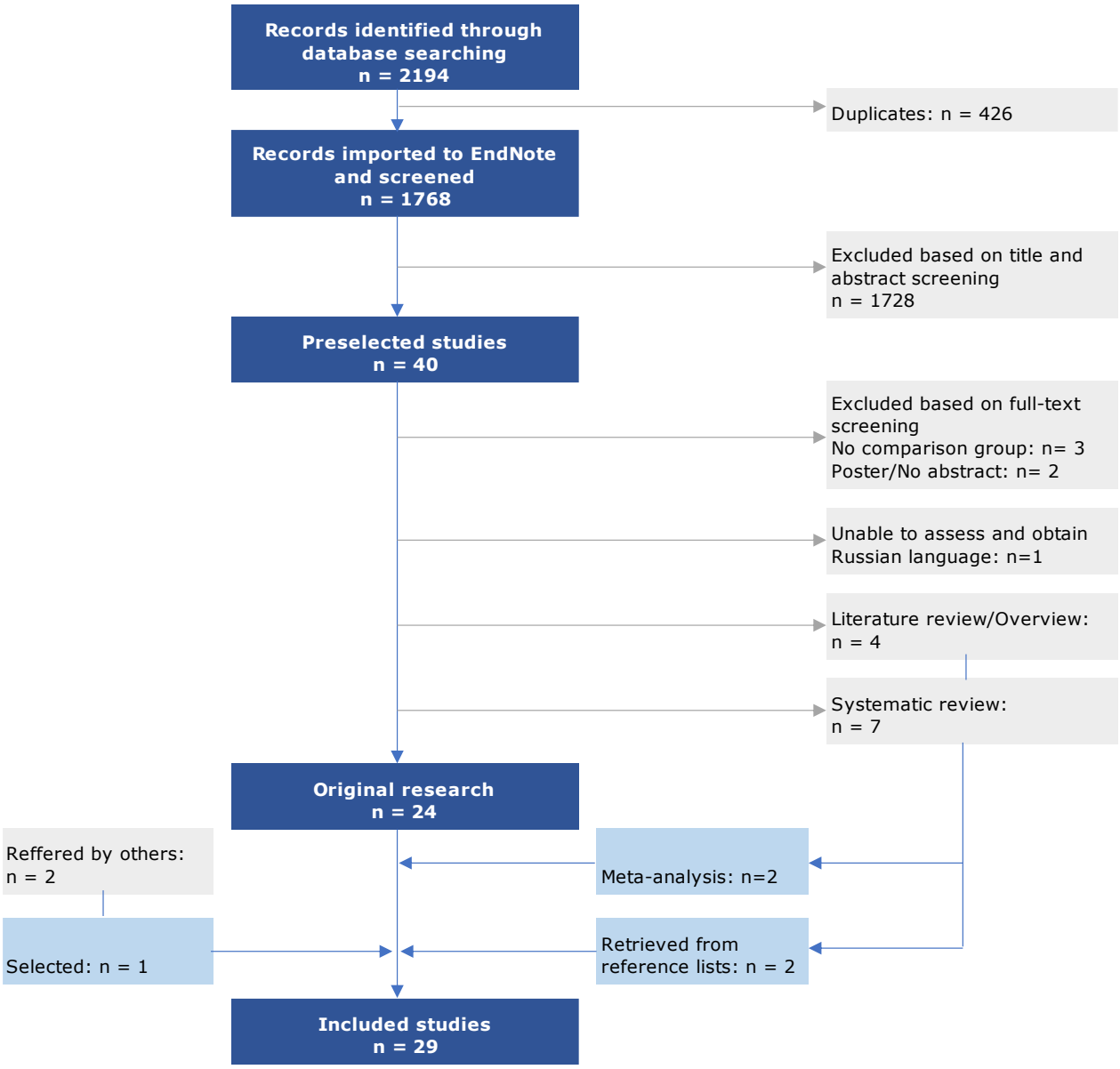


**Figure 1. Flowchart of included studies**

### *2.3. Data synthesis*

A data extraction form was used to collect the following information: first author, year of publication, title, status, coordinating centre, countries covered, data sources, study period, study design, sample size, n subject exposed, follow-up, type of vaccine, exposure, outcomes, confounders, summary of findings, limitations, strength, quality/usefulness, URL or DOI (Supplementary Table 1 and Table 2).

## 3. Results

### *3.1. Overview*

A total of 2194 studies were retrieved from EMBASE and MEDLINE databases and 1768 were imported into EndNote software after removal of 426 duplicates. Of these, 1728 were excluded based on inclusion criteria during the title/abstract screening. The remaining 40 studies were screened for full-

text review. Of these, three studies were excluded because they did not present reference group or background rates for comparison,[14-16] one was a poster whose results are already published as an article,[17] one was available only as abstract,[18] one did not have an available abstract to assess further,[19] four were literature review/overview,[20-23] and seven were systematic reviews.[24-29]

Published systematic reviews were conducted between June to November 2021. Of these, one was carried out in February 2022 with a focus on pregnant women in the United States,[24] and two conducted a meta-analysis.[26,30] This yielded to the selection of 24 original research papers [31-51] and two meta-analyses.[26,30] Reference lists of the reviews and the original research were screened to identify additional studies, which led to select two more studies.[52,53] In addition, two studies were published online recently but not yet indexed in the searched databases.[54,55] Of these, one was a meta-analysis (pre-print) on safety of COVID-19 vaccines, including their components and technological platforms used in other vaccines during pregnancy.[54] This meta-analysis included seven studies already identified in this review but did not show pooled estimates for COVID-19 vaccines and was therefore excluded. Finally, 29 studies were included in this review (Figure 1).

Of the 29 included studies, 21 reported results on vaccine safety[26,30-41,43-45,47-49,56] and 12 reported results on vaccine effectiveness[26,30,33,42,46,48,50,52,53,55,57,58] during pregnancy (four studies reported on both types of outcomes). [26,30,33,48] None of the studies reported on the potential protective effect of maternal immunisation during lactation of breastfed infants. There were five case-control studies (including three test-negative case control studies), two meta-analyses, and the remaining were cohort studies.

The included studies were carried out in Norway and Sweden (n=2), Norway (n=1), England (n=1), Scotland (n=1), Romania (n=1), Israel (n=8), Qatar(n=1), USA (n=8), Canada (n=2), and Brazil (n=2). The meta-analyses included studies from England, Norway, Israel, USA, Canada, and Qatar. Six studies had sample sizes <1000 individuals, six 1000 to 4999, three 5000 to 9999, and 12 ≥10000. Ten studies linked hospital electronic medical records, prenatal and birth registries to national/regional registries regarding COVID-19 vaccines, SARS-CoV-2 tests, COVID-19-related hospitalizations, and death. Most of studies (n=25) reported the use of Pfizer-BioNTech vaccine, 19 reported the use of Moderna vaccine, four included Janssen vaccine, four AstraZeneca vaccine, one CoronaVac[57] and one was not clear on the type of COVID-19 vaccine examined. However, those with additional data on AstraZeneca or Janssen vaccines had very small sample size in these groups which precluded from reporting separate results for these vaccines. Three studies reported results stratified by number of doses. Only two studies reported on the use of COVID-19 vaccine boosters in pregnant women.[47,56]

### *3.2. COVID-19 vaccine safety*

Detailed description of the methodological characteristics and key findings of the studies are shown in Supplementary Table 1. Sixteen of the 21 studies on vaccine safety discussed the risk of adverse pregnancy and delivery outcomes and 17 assessed the risk of adverse neonatal outcomes after COVID-19 vaccination during pregnancy.

Among the 16 studies with a focus on pregnancy and delivery (Table 2), 20 outcomes were identified. The most frequently studied outcome was spontaneous abortion and postpartum haemorrhage. Nine studies reported on the risk of spontaneous abortion before 14- or 20-weeks' gestation after COVID-19 vaccination during pregnancy, involving a total of around 31000 vaccinated and 258000 unvaccinated pregnant women. Nine and eight studies assessed the risk of postpartum haemorrhage and caesarean section, respectively, involving around 27000 vaccinated and 43000 unvaccinated pregnant women. Five studies evaluated the risk for instrumental/operative delivery, involving around 1800 vaccinated and 6600 unvaccinated pregnant women. Five studies examined the risk of pregnancy-related hypertensive disorders and three specifically explored preeclampsia and eclampsia, involving around

3300 vaccinated and 8600 unvaccinated pregnant women. Four studies used composite outcomes to include pregnancy-related morbidities or complications given the low prevalence of some these conditions, involving around 6600 vaccinated and 3300 unvaccinated pregnant women. Other outcomes were explored less frequently (1 to 2 studies) such as chorioamnionitis, antepartum bleeding, meconium-stained amniotic fluid, maternal postpartum fever, pyrexia, oligohydramnios, polyhydramnios, placental abruption, gestational diabetes, non-reassuring foetal monitoring, pathological presentation, emergency caesarean delivery, and ICU admission (Table 2). The sample size of most of these studies was <1700 vaccinated and <3500 unvaccinated pregnant women.

Among the 17 studies with a focus on adverse consequences in newborns (Table 3), 31 outcomes were identified. The most frequently studied outcome was preterm birth (<37 weeks' gestation). Eleven studies reported on the risk of preterm birth involving around 50000 vaccinated and 179000 unvaccinated pregnant women. Nine studies assessed the risk of being born small-for-gestational age (SGA) and eight studies examined the risk of stillbirth, involving around 37000-44000 vaccinated and 135000-175000 unvaccinated pregnant women. Eight studies looked at low 5-minutes Apgar score, involving 54000 vaccinated and 168000 unvaccinated pregnant women. Seven studies assessed admission to neonatal intensive care (NICU), involving around 52000 vaccinated and 162000 unvaccinated pregnant women. Six studies reported on the risk for congenital anomalies, involving around 5700 vaccinated and 4600 unvaccinated pregnant women. Other outcomes were explored less frequently (1 to 3 studies) such as low birth weight (<2500 g), extended perinatal mortality, early and late preterm birth, specific congenital malformations, jaundice requiring phototherapy, neonatal hospitalization, newborn postpartum fever, neonatal severe morbidities, among others (Table 3). Most of these studies involved a range of 100-2000 vaccinated and 500-5000 unvaccinated pregnant women.

In short, review of the 21 studies on vaccine safety does not suggest evidence of an increased risk of adverse pregnancy or neonatal outcomes following COVID-19 maternal immunisation when compared with no vaccination. Findings were mostly based on mRNA vaccines administered in the second and third trimester. Results appear to be consistent across studies despite differences in study design, analytical approach, and data source limitations.

Most of studies failed to consider time-varying confounders such as time of vaccination during pregnancy, and gestational age, or other potential confounders such as socioeconomic factors, health-seeking behaviours, pre-existing morbidities, and obstetric conditions which may influence the propensity for both vaccination and adverse outcomes. The internal and external validity of some studies might have been undermined due to the small sample size of exposed individuals or small number of adverse events. It is worth noting that five studies [38-40,43,44] provided a good level of evidence considering the large population-based sample size, the use of multiple data sources to have a comprehensive data on vaccination, SARS-CoV-2 infection, maternal comorbidities, socio-demographic factors, and maternal and neonatal outcomes (two of which used mother-offspring linkage); the analytical strategy to account for potential influence of unmeasured time-related factors, time-dependent vaccine exposures and propensity to be vaccinated.

### *3.3. COVID-19 vaccine effectiveness (VE)*

Detailed description of the methodological characteristics and key findings of the studies are shown in Supplementary Table 2. Among the 12 studies with a focus on VE, eight outcomes were identified (Table 4). Six studies reported VE against SARS-CoV-2 infection, involving a total of around 21000 vaccinated and 38000 unvaccinated pregnant women. Three studies assessed VE against COVID-19-related hospitalisation, involving around 18000 vaccinated and 18000 unvaccinated pregnant women. Two studies examined COVID-19-related severe illness involving around 14000 vaccinated and 37000

unvaccinated pregnant women. Only one study examined COVID-19-related intensive care unit admission, intubation, and death, including around 200 vaccinated and 2000 unvaccinated women.

These studies suggested that vaccination was effective in preventing SARS-CoV-2 infection, COVID-19-related hospitalisation, COVID-19-related severe illness among pregnant women. However, only two studies[46,50] conducted in Israel provided a good level of evidence, considering: the large population-based sample size; the matching process which accounted for vaccination date; the use of documented vaccination status, SARS-CoV-2 infection and disease; the analytical strategy to account for potential influence of time-related (age, gestational age), socioeconomic and behaviour-related (e.g., influenza vaccination) factors and comorbidities, which affect the propensity to be vaccinated and the risk for infection/disease. Goldshtein *et al*[50] reported 78% (95%CI 57-89%) VE for SARS-CoV-2 infection after 27 days of receiving the first dose of vaccine. Dagan *et al*[46] reported VE in the range of 71% (95%CI 33-94%) for SARS-CoV-2 infection after 21 days of first dose, and 96% (95CI% 89-100%) after seven days of second dose. Given the low incidence of COVID-19-related hospitalisation and severe disease, Dagan *et al* could not provide precise VE estimates for these outcomes.

Regarding VE in infants after maternal immunisation, only two studies were found. One study explored COVID-19-related hospitalisation in infants aged <6 months following COVID-19 maternal immunisation in the US, involving around 170 infants hospitalised with COVID-19 as the primary reason for admission and with positive SARS-CoV-2 RT-PCR or antigen test results, and 200 infants hospitalised with negative SARS-CoV-2 RT-PCR or antigen test results.[42] Another study assessed the association between COVID-19 vaccination in pregnancy and reduced risk of COVID-19 in infants up to age 4 months during COVID-19 pandemic periods dominated by Delta and Omicron variants in Norway.[55] This study involved 9739 infants born to women who received a second and third dose of a COVID-19 vaccine during pregnancy and 11904 infants born to women who did not receive vaccines before or during pregnancy. Halasa *et al*[42] conducted a test-negative, case-control study in the US to assess effectiveness of maternal immunisation (completion of a 2-dose mRNA COVID-19 vaccination series during pregnancy) on COVID-19-related hospitalisation in infants. Results suggest a protective effect of maternal immunisation however more evidence is needed given the small sample size and methodological constraints such as the lack of information on SARS-CoV-2 infection during pregnancy which might have provided maternal antibodies to the infants. Also, data on health- and behaviour-related factors which affect the propensity to vaccinate were not available; and the potential for misclassification of vaccination status cannot be ruled out given that data was obtained by self-report for few participants. On the other hand, Carlsen *et al*[55] provided a good level of evidence considering the large population-based sample size, the large number of women vaccinated during pregnancy, the detailed information on clinical and sociodemographic variables obtained by using multiple data sources and the analytical approach including several sensitivity analyses. This study suggests a lower risk of a positive test for SARS-CoV-2 during the first four months of life among infants born to mothers who were vaccinated during the second and third trimester of pregnancy.

It is worth noting that the results from all 12 studies reflect the effectiveness of mRNA vaccines mainly against the SARS-CoV-2 Alpha, Beta or Delta variants.

# 4. Conclusions

We presented an updated overview of the evidence on COVID-19 maternal immunisation including studies published between January 1, 2021, through June 7, 2022.

Vaccine safety outcomes of interest included pregnancy, delivery, and neonatal outcomes and vaccine effectiveness outcomes included protection against SARS-CoV-2 infection, COVID-19-related disease, and hospitalisation. Findings from included studies suggest that mRNA COVID-19 vaccines are not associated with an increased risk of adverse outcomes in pregnant women and their neonates and are

effective in reducing the incidence of SARS-CoV-2 infection in both mothers and infants. Regarding COVID-19-related hospitalisation and severe disease, the low incidence of these events precluded the studies that looked at these outcomes from providing precise VE estimates.

Despite the number of published studies, there remain major gaps in our knowledge of how COVID-19 vaccines impact pregnancy and newborns. First, strong evidence is needed based on large population-based studies that use rigorous methods and include diverse populations that could confirm these initial findings. Although several studies have been published since the approval of COVID-19 vaccines, these have been mostly small, regional, hospital-based studies. Second, some observational studies that have examined time-specific outcomes (e.g., spontaneous abortion) might have neglected the timing of pregnancy when selecting the comparison groups, introducing selection bias. As a result, these studies might underestimate the risks of pregnancy outcomes or overestimate the protective effect of vaccines. Third, most of studies failed to properly address methodological challenges commonly faced by studies of vaccination during pregnancy.[59,60] For instance, some studies failed to account for time-varying exposure status, time-dependant (i.e., gestational and calendar time) factors, or socioeconomic, health- and behaviour-related variables. All of which can affect the probability of being vaccinated and the probability of experiencing the outcome. Also, many studies did not consider data on SARS-CoV-2 infection in their analysis which is associated with both adverse outcomes during pregnancy and the probability of being vaccinated. The use of self-reported data in some studies might have led to invalid estimates due to misclassification of vaccination status and/or outcomes. Finally, evidence is still scarce on ideal timing of immunisation and number of doses to provide protection to the pregnant women and their infants, vaccine safety during the first trimester of pregnancy, vaccine effectiveness of boosters and against emerging SARS-CoV-2 variants as well as evidence on safety and effectiveness of viral vector vaccines or inactivated vaccines. Additionally, whether COVID-19 vaccine-derived antibodies transferred from the mothers to their infants during breastfeeding provide protection against SARS-CoV-2 infection or health complications remains to be elucidated.

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**Table 2. Studies on COVID-19 vaccine safety with focus on pregnancy and delivery outcomes**

| Pregnancy and delivery outcomes (n=20) | N studies | Shimabukuro, 2021 | Kharbanda, 2021 | Zauche, 2021 | Wainstock, 2021 | Theiler, 2021 | Bleicher, 2021 | Rottenstreich, 2021 | Magnus, 2021 | Blakeway, 2022 | Fell, 2022 | Dick, 2022 | Citu, 2022 | Sadarangani, 2022 (preprint) | Ma, 2022 (meta-analysis) | Dick, 2022 | Prasad, (2022) (meta-analysis) | Total vaccinated | Total unvaccinated | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Spontaneous abortion/miscarriage | 9 | X | X | X | | | X | | X | | | | X | X | X | | X | 31614 | 258651 | 290265 |
| Postpartum hemorrhage | 9 | | | | X | X | | X | | X | X | X | | | X | X | X | 27430 | 43606 | 71036 |
| Cesarean delivery | 8 | | | | X | X | | X | | X | X | X | | | X | X | | 27430 | 43606 | 71036 |
| Instrumental delivery/ Vacuum delivery | 5 | | | | X | X | | X | | X | | | | | X | | | 1898 | 6630 | 8528 |
| Pregnancy related hypertensive disorders | 5 | | | | X | X | | | | | | X | | | X | | X | 3346 | 8661 | 12007 |
| Composite outcome [a] / Composite adverse maternal outcome [b] / Adverse outcome inde (AOI) [c] /Any adverse pregnancy outcome [d] | 4 | | | | | X | X | X | | | | | | X | | | | 6651 | 3388 | 10039 |
| Pre-eclampsia/ Eclampsia | 3 | | | | | X | | | | | | | | | X | | X | 7670 | 9392 | 17062 |
| Chorioamnionitis | 2 | | | | | | | | | X | X | | | | | | | 23372 | 31178 | 54550 |
| Meconium stained amniotic fluid | 2 | | | | X | | | X | | | | | | | | | | 1625 | 4549 | 6174 |
| Maternal postpartum fever | 2 | | | | X | | | X | | | | | | | | | | 1625 | 4549 | 6174 |
| Antepartum bleeding | 2 | | | | | | X | | | | | | | X | | | | 5799 | 463 | 6262 |
| Placental abruption | 2 | | | | | | | | | X | | | | | | | X | 712 | 1063 | 1775 |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| High-dependency/intensive care unit admission | 2 | | | | | | | | | X | | | | | | | X | 133 | 399 | 532 |
| Pyrexia | 1 | | | | | | | | | X | | | | | | | | 133 | 399 | 532 |
| Oligohydramnios | 1 | | | | X | | | | | | | | | | | | | 913 | 3486 | 4399 |
| Polyhydramnios | 1 | | | | X | | | | | | | | | | | | | 913 | 3486 | 4399 |
| Gestational diabetes | 1 | | | | | | | | | | | X | | | | | | 2293 | 3313 | 5606 |
| Non-reassuring fetal monitoring | 1 | | | | X | | | | | | | | | | | | | 913 | 3486 | 4399 |
| Pathological presentation | 1 | | | | X | | | | | | | | | | | | | 913 | 3486 | 4399 |
| Emergency cesarean delivery | 1 | | | | | | | | | | X | | | | | | | 22660 | 30115 | 52775 |

**a** Any of the following: vaginal bleeding at any point of gestation, 1st trimester pregnancy loss (up to 13 weeks of gestation), 2nd trimester loss (14–28 weeks of gestation), fetal growth restriction, gestational and or diabetes mellitus, hypertensive disease, fetal malformations that were observed on first or second anatomy scan (usually performed between 14 and 16 and 20–24 weeks of gestation, respectively), premature labor and premature contractions.

**b** Any of the following: chorioamnionitis, postpartum haemorrhage (PPH, estimated blood loss of >1000 ml and/or haemoglobin drop of ≥3 g/dl), endometritis, blood transfusion, caesarean delivery (CD), ICU admission, maternal hospital length of stay of >5 days for vaginal delivery and >7 days for cesarean delivery (the usual postpartum hospital lengths of stay for vaginal delivery and CD are 48–72 hours and 96–120 hours, respectively).

**c** Any of the following: maternal death during hospitalization; intrapartum neonatal death within 7 days of birth with a birthweight of ≥2500 g and ≥37 weeks' gestation; hypoxic-ischemic encephalopathy; uterine rupture; unplanned maternal ICU admission; return to the operating room within 72 hours of delivery; postpartum hemorrhage with blood transfusion; third- or fourth-degree laceration; 5-minute Apgar score of <7 with a birthweight of ≥2500 g and ≥37 weeks' gestation; admission to the neonatal ICU within 1 day of birth for >1 day with a birthweight of ≥2500 g and ≥37 weeks' gestation; or neonatal birth trauma.

**d** Any of the following: high blood pressuare, vaginal bleeding, abnormal fetal heart rate, other pregnancy complications such as lower abdominal pain, reduce fetal movement, cramp, vomiting, etc.

**Table 3. Studies on COVID-19 vaccine safety with focus on neonatal outcomes**

| **Neonatal outcomes (n=31)** | N studies | Shimabukuro, 2021 | Wainstock, 2021 | Theiler, 2021 | Bleicher, 2021 | Rottenstreich, 2021 | Blakeway, 2022 | Magnus, 2022 | Goldshtein, 2022 | Lipkind, 2022 | Fell, 2022 | Dick, 2022 | Stock, 2022 | Ruderman, 2022 | Sadarangani, 2022 (preprint) | Ma, 2022 (meta-analysis) | Dick, 2022 | Prasad, (2022) (meta-analysis) | Total vaccinated | Total unvaccinated | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Preterm birth (<37 weeks' gestation) | 9 | X | | X | | X | | X | X | X | | X | X | | | X | X | X | 50429 | 179838 | 230267 |
| Stillbirth (≥20 weeks) | 7 | X | | X | | X | | X | | | | X | | | X | X | | X | 37973 | 135592 | 173565 |
| Small-for-gestational-age (SGA) | 7 | X | X | | | | X | X | X | X | | X | | | | | X | X | 44959 | 179166 | 224125 |
| Neonatal Intensive Care Unit (NICU) admission | 6 | | | X | | X | X | X | | | X | | | | | X | | X | 52237 | 162448 | 214685 |
| Low newborn 5-minute Apgar score (<7) | 6 | | | X | | X | | X | | | X | X | | | | X | X | X | 54279 | 168209 | 222488 |
| Congenital anomalies [a] | 5 | X | | | X | | X | | X | | | | | X | | | | X | 5713 | 4627 | 10340 |
| Low birth weight (<2500 g) | 3 | | | X | | | | | X | | | | | | | X | | X | 2172 | 5432 | 7604 |
| Gestational age at delivery | 3 | | X | | | X | | | | | | X | | | | | | X | 3918 | 7862 | 11780 |
| Birth weight (g) | 3 | | X | | | X | | | | | | | | | | | | X | 3918 | 7862 | 11780 |
| Very low birth weight (<1500 g) | 2 | | | X | | | | | X | | | | | | | | | | 2172 | 5432 | 7604 |
| Early preterm birth (<32 weeks' gestation) | 2 | | | | | | | X | X | | | | | | | | | X | 30538 | 132585 | 163123 |
| Jaundice requiring phototherapy | 2 | | | | | X | | | X | | | | | | | | | | 2744 | 4633 | 7377 |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Newborn respiratory complications/ Transient tachypnoea of the newborn (TTN) | 2 | | X | | | X | | | | | | | | | | | | | 1625 | 4549 | 6174 |
| Heart malformations | 1 | | | | | | | | X | | | | | | | | | | 2032 | 3570 | 5602 |
| Major heart malformations [b] | 1 | | | | | | | | X | | | | | | | | | | 2032 | 3570 | 5602 |
| Extended perinatal mortality (stillbirth and neonatal deaths) [c] | 1 | | | | | | | | | | | | X | | | | | | 5766 | 1635 | 7401 |
| Late preterm birth (32-36 weeks' gestation) | 1 | | | | | | | | X | | | | | | | | | | 2032 | 3570 | 5602 |
| Birth weight Z-score | 1 | | | | | | X | | | | | | | | | | | X | 133 | 399 | 532 |
| Umbilical artery pH<7.1 | 1 | | | | | | | | | | | X | | | | | X | | 2587 | 6681 | 9268 |
| Neonatal hospitalization (1-28 days after birth) | 1 | | | | | | | | X | | | | | | | | | | 2032 | 3570 | 5602 |
| Newborn postpartum fever | 1 | | X | | | | | | | | | | | | | | | | 913 | 3486 | 4399 |
| Neonatal hypoxic-ischemic encephalopathy | 1 | | | | | | | | | | | | | | | X | | | 140 | 1862 | 2002 |
| Neonatal birth trauma | 1 | | | | | | | | | | | | | | | X | | | 140 | 1862 | 2002 |
| Postneonatal hospitalization (28 days after birth) | 1 | | | | | | | | X | | | | | | | | | | 2032 | 3570 | 5602 |
| Neonatal death | 1 | X | | | | | | | | | | | | | | | | | 724 | 0 | 724 |
| Composite adverse neonatal outcome [d] | 1 | | | | | X | | | | | | | | | | | | | 712 | 1063 | 1775 |

| | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Infant death over the study period | 1 | | | | | | | | X | | | | | | | | | | 2032 | 3570 | 5602 |
| Birthweight >4000 g | 1 | | | | | X | | | | | | | | | | | | | 712 | 1063 | 1775 |
| Large for gestational age (LGA) | 1 | | | | | X | | | | | | | | | | | | | 712 | 1063 | 1775 |
| Hypoglycaemia | 1 | | | | | X | | | | | | | | | | | | | 712 | 1063 | 1775 |
| Mechanical ventilation | 1 | | | | | X | | | | | | | | | | | | | 712 | 1063 | 1775 |

a Nervous system, eye, orofacial, cardiovascular, respiratory system, gastrointestinal, genitourinary, musculoskeletal, and chromosomal anomalies

b Congenital heart malformations other than ventricular spetal defect and patent foramen ovale.

c per 100 live births

d Any of the following: intrauterine fetal death (IUFD), Apgar score of ≤7 at 1 minute, Apgar score of ≤7 at 5 minutes, admission to neonatal intensive care unit (NICU), neonatal asphyxia, intracranial haemorrhage, meconium aspiration syndrome, hyperbilirubinaemia, neonatal seizures, neonatal hypoglycaemia, neonatal sepsis, use of mechanical ventilation

**Table 4. Studies on COVID-19 vaccine effectiveness**

| Outcome (n=8) | N studies | Theiler, 2021 | Bleicher, 2021 | Butt, 2021 | Dagan, 2021 | Morgan, 2022 | Goldshtein, 2022 | Halasa, 2022 | Ma, 2022 (meta-analysis) | Paixao, 2022 | Paganoti, 2022 | Carlsen, 2022 | Prasad, 2022 (meta-analysis) | Vaccinated | Unvaccinated | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SARS-CoV-2 infection | 6 | X | X | X | X | | X | | X | X | | | X | 21173 | 38619 | 59792 |
| COVID-19-related hospitalization | 3 | | | | X | | X | | X | | | | | 18391 | 18391 | 36782 |
| COVID-19-related severe illness | 2 | | | | X | X | | | | X | | | | 14226 | 37426 | 51652 |
| COVID-19-related intensive care unit admission | 1 | | | | | | | | | | X | | | 200 | 2084 | 2284 |
| COVID-19-related intubation | 1 | | | | | | | | | | X | | | 200 | 2084 | 2284 |
| COVID-19-related mortality | 1 | | | | | | | | | | X | | | 200 | 2084 | 2284 |
| COVID-19-related hospitalization in infants (<6 mo) | 1 | | | | | | | X | | | | | | 176 | 203 | 379 |
| SARS-CoV-2 infection within 1 and 122 days after birth (4 months of age) | 1 | | | | | | | | | | | X | | 9739 | 11904 | 21643 |