Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
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EVIDENCE SUMMARY

Is COVID-19 vaccination effective and safe among pregnant and lactating individuals and their infants in the prevention of COVID-19 infections?: A Rapid Review

Evidence Reviewers: Christdianzen Grace Saroca, MD, Marie Carmela Lapitan, MD, Mary Anne Castor, MD

RECOMMENDATIONS

We suggest the use of following vaccines, after the first trimester, for the prevention of COVID-19 infection in pregnant and lactating women.

a. **BNT162b2 (Pfizer)** *(Low certainty of evidence; Weak recommendation)*
b. **mRNA-1273 (Moderna)** *(Low certainty of evidence; Weak recommendation)*
c. **ChAdOx1 (AstraZeneca)** *(No direct evidence; Weak recommendation)*
d. **Ad26.CoV2.S (Janssen/Johnson&Johnson)** *(No direct evidence; Weak recommendation)*
e. **CoronaVac (Sinovac)** *(No direct evidence; Weak recommendation)*
f. **BBIBP-CorV (Sinopharm)** *(No direct evidence; Weak recommendation)*
g. **BBV152 (Covaxin)** *(No direct evidence; Weak recommendation)*

We suggest <u>against</u> the use of the following vaccines for the prevention of COVID-19 infection in pregnant and lactating women:

a. **Gam-CoV-Vac (Sputnik V)** *(No direct evidence; Weak recommendation)*
b. **NVX-2373 (Novavax)** *(No direct evidence; Weak recommendation)*

Consensus Issues

The Panel took into consideration that pregnant and lactating women are at a higher risk for severe COVID infection and are a particularly vulnerable population to recommend COVID-19 vaccination for them. Despite the absence of direct evidence of the efficacy of some vaccines for this population, the Panel still recommended their use using indirect evidence of efficacy and safety from the other vaccines and from the general adult population. The decision to recommend against the use of Gam-COVID-Vac (Sputnik V) was made based on the manufacturer's restriction of their product among pregnant women, in the absence of direct evidence of its effect. On the other hand, the decision to recommend against the use of NVX-2373 for pregnant women was mainly due to its low efficacy seen in the immunocompromised population and a higher risk of adverse reaction.

Key Findings

The current evidence base includes forty-two reports that investigated the effectiveness, immunogenicity, and safety of COVID-19 vaccination among pregnant and lactating women and their infants. Three were systematic reviews and 39 were observational studies. Available evidence demonstrates that COVID-19 vaccination provides sufficient protection against COVID-19 disease for pregnant and lactating women, with transfer of antibody protection to the newborn, without significant increase in the risk of maternal and neonatal adverse events nor adverse pregnancy and delivery outcomes.

Introduction

Pregnancy has been designated as a risk factor for severe COVID-19 infection by the Centers for Disease Control and Prevention (CDC) and the American College of Obstetricians and Gynecologists (ACOG). Physiologic changes in pregnancy such as increased metabolic and cardiovascular demands, reduced lung capacity and immune modulation contribute to increased hospital and intensive care unit admission, and mortality in pregnant individuals with COVID-19 related illness. Subsequently, maternal infection in pregnancy correlates with increased neonatal respiratory distress and hospitalization, supporting the need for COVID-19 prevention.

As of July 30, 2021, the ACOG recommends that both pregnant and lactating individuals, as well as eligible people who consider any future pregnancy, be vaccinated against COVID-19. However, only one randomized clinical trial on the use of a COVID-19 vaccine versus placebo in pregnant women has been reported and Pfizer-N-Biotech is still in the recruitment phase as of October 28, 2021. Subsequently, there has been vaccine hesitancy among pregnant and lactating individuals. This review thus aims to synthesize existing real-world data on the effectiveness, immunogenicity and safety of COVID-19 vaccines in pregnancy and lactation.

Review Methods

Search Results

As of December 8, 2021, forty-two studies, including three systematic reviews were identified by the search. All studies in these systematic reviews, apart from case reports reporting on efficacy outcomes with sample sizes less than 10, were included in this review.

Characteristics of Included Studies

This review involves information provided by 39 observational studies. Twenty of these involved pregnant women, 15 involved lactating women and 4 involved both. No completed randomized controlled trial (RCT) comparing the efficacy of a COVID-19 vaccine to placebo/no vaccination in pregnant or lactating women was found.

Of the 24 studies included in the vaccinated pregnant women review, 13 were comparative cohort studies, three were case control studies, and the rest were cross-sectional or single cohort studies. Eleven studies compared the outcomes of the vaccinated with the unvaccinated pregnant women, of which one was a matched cohort study. Four of the studies specifically included previously infected pregnant women in the unvaccinated control group. One study included only vaccinated pregnant women and compared the outcomes across the three vaccines used. Four studies compared the outcomes of the vaccinated pregnant women with vaccinated non-pregnant and/or lactating women.

Seventeen studies used BNT162b2 vaccine, seven used mRNA-1273, four mentioned using mRNA vaccines, two included pregnant women vaccinated with Ad26.CoV2.S and another with ChAdOx1, and two studies did not specify the vaccine used. No study reported on the outcomes of vaccination among pregnant women with CoronaVac, Gam-COVID-Vac, BBV152, BBIBP-CorV or NVX2373.

Of the 19 studies included in the vaccinated lactating women review, nine were comparative cohort studies, one was a cross sectional study and the rest were single cohort non-comparative studies. Comparisons were among unvaccinated lactating women, unvaccinated pregnant women, non-lactating healthy women or vaccinated pregnant women.

Seventeen studies included women who received the BNT162b2, eight included those who received mRNA-1273, one included those who had CoronaVac and one included women who received ChAdOx1. One study did not specify the vaccine received by the participants. No study among vaccinated lactating women received Gam-COVID-Vac, BBV152, BBIBP-CorV or NVX-2373.

Details of the studies are in Appendix 2.

Methodological Quality Assessment of Included Studies

All available primary studies included in this review were observational studies. Majority of the comparative studies failed to control for confounders, and nearly all had missing data and short follow up. Thus, methodological assessment of the studies uniformly showed serious risk of bias. In addition, studies on efficacy were mostly immunologic studies, and those on safety were cross-sectional, non-comparative. Hence, the certainty of evidence for this review is generally low.

Details of the methodological quality assessment are in Appendix 3.

COVID-19 Vaccination in Pregnant Women and their Children

Results of Efficacy

Real World Evidence: Effectiveness

Four studies provided information on infection rates after vaccination among pregnant women.[1-4] All studies reported significantly lower COVID-19 infection rates associated with vaccination, with two studies reporting vaccine effectiveness rates that reflect sufficient to excellent protection.

A test-negative case-control study of pregnant women in Qatar matched three RT-PCR negative controls for every woman who tested positive. The vaccinated group received either BNT162b2 or mRNA-1273. Vaccine effectiveness was at 40.3% (95% CI 0.0-80.4) 14 days or more after being given the first dose but prior to second dose administration. At 14 days or more after the second dose was given, vaccine effectiveness was at 67.7% (95% CI 30.5-86.9).[1]

Another case-control study of pregnant women with no prior SARS-CoV-2 infection was done in Israel where 10,861 pregnant women given BNT162b2 were matched to unvaccinated pregnant controls. Median age of the participants was 30 years with majority in their third trimester at 48%, while 26% were in their first and second trimesters. With a follow-up of 7 to 56 days after the

second dose, estimated vaccine effectiveness for any documented SARS-CoV-2 infection was 96% (95% CI 89-100). For symptomatic COVID-19 infection, vaccine effectiveness was 97% (95% CI 91-100), while for COVID-19 related hospitalization it was 89% (95% CI 43-100). During a longer follow up, estimated vaccine effectiveness for documented COVID-19 infection was at 93% with narrower confidence interval of 91-94% and 96% for symptomatic infection with a more precise CI of 94-97%. Cumulative incidences of documented COVID-19 infections were similar in both vaccinated and unvaccinated groups until day 14 after the first dose when incidence in the vaccinated group started to have a steep decline. No deaths were observed in both groups and only one case of severe illness was noted in the unvaccinated group. Due to low incidence of severe outcomes, vaccine effectiveness was not estimated for severe infection and mortality.[2]

In a sequential questionnaire survey from among 326 pregnant women, the unvaccinated were 4.5 times more likely to report testing positive for COVID-19 since the survey one month prior (OR=4.5 [95% CI 1.19-17.6]) compared to those who received at least one dose of vaccine.[3]

A comprehensive vaccine registry from Mayo Clinic showed that vaccinated pregnant women were significantly less likely to have COVID-19 infection before delivery compared to unvaccinated pregnant women, (2/140, 1.4% vs 210/1862, 11.3%, p<0.001, computed VE 87.3% [95% CI 49.6-96.8]). No maternal COVID-19 infections occurred after vaccination during the pregnancy (both cases occurred prior to vaccination).[4]

Immunogenicity

Maternal Immune Response

Thirteen studies provided information on the maternal immune response to COVID-19 vaccination. Six studies showed significant rise in antibody titers (IgM, IgG and IgA) after vaccination compared to baseline.[5-10] Two cohort studies comparing vaccinated and unvaccinated pregnant women showed higher antibody IgM and IgG titers in the vaccinated group.[5,11] Four studies were consistent in showing higher antibody titers among vaccinated pregnant women when compared with titers from those who were unvaccinated previously infected.[5-6,12-13] Four studies compared the maternal antibody responses of pregnant, non-pregnant and lactating women after vaccination. Two comparative cohort studies showed similar titers across the three groups[6,12] while one showed lower titers in the pregnant women when compared to the lactating mothers.[14] A matched cohort study found lower serum IgG signal to cutoff ratio in pregnant compared to non-pregnant vaccinees.[15]

One study compared antibody titers at delivery after early versus late trimester vaccination. It showed lower titers in the early trimester vaccination group.[8]

Three studies compared responses to the different vaccines. Two studies showed higher rises in antibody titers after mRNA-1273 vaccination compared to BNT162b2.[12,14] Similar higher titers for anti-spike IgG2 with mRNA-1273 were seen.[16] This study also showed significantly lower antibody titers among those who received Ad26.CoV2.S compared to those who received the mRNA vaccine.

The mRNA COVID-19 vaccines were seen to produce maternal antibodies as early as 5 days after the first dose while transplacental transfer occurred as early as 16 days.[10] The follow up

study by Rottenstreich et al. showed a significantly negative association between maternal IgG concentrations and time elapsed since immunization.[8]

Two cohort studies showed that immunologic response was rapid after vaccination in contrast to a more gradual response during COVID-19 infection,[5,12] producing higher anti-spike IgG titers.[12] Collier et al. also reported median IgG levels to the Receptor Binding Domain (RBD) of the S protein of SARS-CoV-2 as a useful tool to estimate individual protection against infection.[6] Similar to the other studies, vaccinated pregnant women had higher anti-RBD IgG titers and neutralizing antibody titer than infected pregnant women. Gray et al. also showed that anti-spike and anti-RBD IgG titers both significantly increased after the first dose. This was followed by a further significant increase in both titers after the second dose.[12]

T-cell response to COVID-19 vaccination was evaluated in peripheral blood mononuclear cells by comparative cohort study.[6] Pregnant, lactating, and non-pregnant participants were seen to have similar spike-specific IFN-gamma production by CD4 T-cells, CD4 central memory T-cells, CD8 T-cells, and CD8 central memory T-cells post-vaccination.

Antibody response to the variants of concern by BNT162b2 vaccination was compared among non-pregnant, pregnant, and lactating women in a study from Israel.[6] Serum anti-RBD IgG binding and neutralizing antibody titers to the wildtype USA-WA1/2020 and B.1.1.7 (Alpha) RBD proteins were similar in all three groups but less to the B.1.351 (Beta) RBD protein. Median neutralizing antibody titers across all groups were 3.5-fold lower for the Alpha variant and 6-fold lower for the Beta variant than for the USA-WA1/2020 variant.

Antibody Transfer to the Fetus/Newborn (Via Placenta or Cord Blood)

Twelve observational studies investigated the potential transfer of immunity/protection of maternal vaccination during pregnancy to the child, through the identification of binding and neutralizing antibodies in the placenta or cord blood. Consistent findings across the studies were presence of antibodies in the cord blood, albeit at a lower level with a positive correlation between the maternal and cord blood antibody titers. Prabhu et al. showed that 44% of cord blood samples after the first vaccination dose had IgG detected which then increased to 99% of samples after both vaccine doses. Higher titers in the cord blood at the time of delivery were seen in those who received the vaccination earlier in the pregnancy.[8] Significantly higher IgG levels were seen in maternal serum and cord blood of vaccinated women as compared to recovered COVID-19 pregnant women. Significantly greater antibody persistence was also seen at 6 months among infants of vaccinated women compared to those with natural infection.[13]

Binding and neutralizing antibodies (IgG RBD) were analyzed in nine paired maternal and cord blood samples by Collier et al. and it was found that vaccinated maternal-infant dyads had a more robust response compared to non-vaccinated dyads.[6] Prabhu et al. showed that 44% of cord blood samples after the first vaccination dose had IgG detected which then increased to 99% of samples after both vaccine doses.[10] Cord blood IgG levels were seen to increase as maternal IgG levels increased, with positive correlation seen only after the second dose. Rottenstreich et al. showed that all 20 maternal-infant dyads in their study had detectable anti-S and anti-RBD specific IgG levels with significant positive correlations between maternal sera and cord blood concentrations, a finding replicated in 33 maternal-infant pairs in their follow-up cohort.[8] Similarly, the prospective cohort observed by Nir et al. showed a significant positive correlation between maternal serum levels of SARS-CoV-2 and cord blood IgG. Also, significantly higher IgG levels were seen in maternal serum and cord blood of vaccinated women as compared to

recovered COVID-19 patients.[17] In a prospective case series by Mithal et al., IgG was higher than IgM, and only IgG was seen in cord blood among pregnant, vaccinated women.[7] Further support is seen in the study by Zdanowski et al. where high anti-S total IgG antibody titers were seen in cord serum at birth in 16 analyzed mother-infant pairs post-vaccination with BNT162b2.[9] Significant positive correlation was seen between week of gestation of first dose and week of gestation for second dose and the respective cord-to-maternal ratio. The follow-up cohort by Rottenstreich et al. showed significantly higher anti-RBD-specific IgG concentrations in neonatal sera and placental transfer ratios among mothers vaccinated early in the third trimester compared with those vaccinated later on.[8] These data show that there is efficient maternal antibody transplacental transfer.

Shook et al. further compared the durability of anti-Spike IgG antibodies in the infants of vaccinated and infected women. Significantly higher maternal and cord titers were seen at delivery and significantly greater antibody persistence was seen at 6 months among infants of vaccinated women compared to those with natural infection.[13]

Results of Safety

Maternal Reactogenicity and Adverse Events

Eight observational studies reported maternal reactogenicity and adverse events post-vaccination. Shimabukuro and Kadali reported injection site pain as the most common adverse event after receiving either mRNA vaccines.[18-19] This was seen more in pregnant patients while non-pregnant patients had more systemic symptoms such as fatigue, myalgia, chills, fever, and nausea. All occurred more commonly after the second dose for both mRNA vaccines in the study by Shimabukuro. Meanwhile, the online survey questionnaire conducted by Kadali et al. on female healthcare workers showed no differences between pregnant and non-pregnant populations for adverse events reported. Similarly, rates of rash, fever, and severe fatigue were similar after vaccination in pregnant and non-pregnant women in the study by Peretz et al.[15] Timing of vaccine administration during pregnancy also did not significantly affect rate of side effects.

Incidences of post-vaccine symptoms were similar across pregnant, lactating, and non-pregnant women in the study by Gray et al.[12]

Collier et al. reported no severe adverse events or any complications in both mothers and neonates post-vaccination in pregnancy.[6]

In a prospective observational cohort, composite pregnancy complications in the short term were not increased following vaccination using BNT162b2, in comparison to the non-vaccinated group.[3] Another large retrospective cohort showed no differences in the incidence of pregnancy related hypertensive disorder and cesarean delivery rates in the vaccinated versus unvaccinated groups.[22] A composite of adverse maternal pregnancy-related events (eclampsia/pre-eclampsia, gestational hypertension, thromboembolism) and delivery outcomes such as uterine rupture, hemorrhage with transfusion, mode of delivery and stillbirth were also not significantly different between the vaccinated and unvaccinated groups in a delivery database registry.[4] Pregnancy or delivery outcomes were not significantly affected among the vaccinated as seen in the study by Beharier.[5] Obstetric complications (uterine contractions, vaginal bleeding, pre-labor rupture of membranes) were seen by Peretz et al. to be very low after vaccination.[15]

In the largest cohort by Shimabukuro et al., spontaneous abortion, stillbirth, preterm birth, small size for gestational age, congenital anomalies and neonatal death were all seen to be similar to or lower than published incidences.[18] In a study by Magnus et al. based on Norwegian registries, among 13,956 pregnant women (5.5% vaccinated) and 4521 women with miscarriages (5.1% vaccinated), no evidence was found of an increased risk for early pregnancy loss after COVID-19 vaccination.[21] Zauche et al. showed from v-safe registry data that there is no increased risk of spontaneous abortion (SAB) following mRNA COVID-19 vaccination and that the cumulative risk of SAB from 6-19 weeks' gestation is within the expected range based on previous SAB studies.[23]

Neonatal Outcomes

Seven studies provided neonatal outcomes after maternal vaccination during pregnancy.[12,15,18,20,22] Reported congenital anomaly rates ranged from 2.2 to 4.5%, and NICU admission rates from 1.5 to 15.1%. No neonatal deaths were reported by any study. The studies were consistent in their observation that outcomes were comparable known rates for the unvaccinated.

Gray et al. found that post-vaccination, 15% of neonates required NICU admission, 8% had transient tachypnea of the newborn (TTN), and 8% required supplemental oxygenation.[12] From the V-safe data set analysis, small size for gestational age, congenital anomalies and neonatal death were all seen to be similar to or lower than published incidences.[18] Similar results were seen in the cross-sectional study by Trostle et al. where rates of small for gestational age neonates and NICU admission rates were within expected rates for the general pregnant population.[20] Peretz et al. had no cases of preterm birth, fetal or neonatal death, and only 3.5% of cases needing NICU admission for respiratory support.(15) In the large retrospective cohort observed by Wainstock et al., slightly higher gestational age and birthweight was noted in women who received 2 doses of BNT162b2 but no differences in newborn characteristics and complications were found between vaccinated and unvaccinated women. There was even a lower risk of meconium stained amniotic fluid and non-reassuring fetal monitoring in the vaccinated group.[22]

Detailed outcomes are in Appendix 2b. The summary of findings tables for efficacy and safety are in Appendix 4.

COVID-19 Vaccination in Lactating Women and their Children

Results of Efficacy

Real World Evidence: Effectiveness

No study was identified reporting clinical effectiveness of COVID-19 vaccination among lactating women.

Immunogenicity

Maternal Immune Response

Six studies recorded antibody response among vaccinated lactating women. IgG was the dominant antibody noted in the maternal sera for all observational studies. Vaccinated lactating women had similar levels of antibody response with vaccinated pregnant women in the cohort study by Atyeo et al.[14] After their booster dose, the antibody response of lactating women increased more effectively than pregnant women, as seen in higher IgG and NK-cell activating antibodies, but with lower FcR binding levels.

Both lactating and non-lactating vaccinated women had increased sera IgG in the cohort study by Charepe et al., with lower detectable IgM and IgA levels.[24] Among lactating women, serum IgM and IgG both increased after the second dose but with slight reduction of IgA levels. Higher IgG levels were seen by Valcarce et al. in individuals given BNT162b2 than those given mRNA-1273.[25]

Peak antibody titers in lactating, vaccinated individuals were seen to appear as early as 7 days and lasted as long as 28 days after the second dose in the cohort by Esteve-Paula et al. Juncker et al. and Friedman et al. also looked at trends of IgG titers in lactating individuals at multiple timepoints, with a trend towards gradual increase without any declines.[26-28]

Antibody Transfer to the Breastmilk

Thirteen studies reported on detected antibody levels in the breastmilk of vaccinated lactating individuals. Similar to maternal sera, IgG was consistently seen as the predominant antibody while results on IgA detection were varied.

Majority (96.4%) of breast milk samples obtained from vaccinated women after birth were positive for IgG in the study by Nir et al.[17] Similarly, IgG levels in breast milk of vaccinated lactating women were positively correlated with maternal IgG serum levels as seen by Esteves-Paula et al and Schwartz et al.[26,29]
Fox et al. and Gray et al. both detected IgA, IgM and IgG titers in breast milk after the first dose, with significantly increasing IgG after both vaccine doses.[12,30] This trend was also present in the cohort seen by Charepe et al. where IgG levels noted in breastmilk after the first dose of BNT162b2 increased further after the second dose. Moreover, a positive correlation was seen between duration of breastfeeding and milk IgG levels after the second dose of BNT162b2, implying that higher IgG titers are seen with longer breastfeeding time.[24]

Fox et al. and Gray et al. both detected IgA, IgM and IgG titers in breast milk after the first dose, with significantly increasing IgG after both vaccine doses.[12,30] This trend was also present in the cohort seen by Charepe et al. where IgG levels noted in breastmilk after the first dose of BNT162b2 increased further after the second dose. Moreover, a positive correlation was seen between duration of breastfeeding and milk IgG levels after the second dose of BNT162b2, implying that higher IgG titers are seen with longer breastfeeding time.[24]

Meanwhile, IgA was also present after the first dose but decreased after the second dose in the same cohort by Charepe et al.[24] Binding and neutralizing antibodies were noted in lactating women post vaccination but IgA responses were also low compared to infected lactating individuals in both studies by Collier et al. and Selma-Royo et al.[6,31] No differences were noted by Golan et al. in the IgA levels of vaccinated and infected lactating individuals.[32] In contrast, higher IgA levels were found in lactating individuals post- vaccination in the studies by Low et al.

and Perl et al.[33-34] Furthermore, Perl et al. saw that SARS-CoV-2 specific IgA and IgG antibodies in breast milk remained elevated for 6 weeks post-vaccination and that IgA was secreted as early as two weeks after completion of doses. IgG levels only spiked four weeks from the second dose.[34] Valcarce et al. also showed that a predominant IgA response was seen in human milk with a significantly increasing trend from pre-vaccination, post-first dose and post-second dose. This was positively correlated with increased IgA in maternal plasma seen 7-10 days after vaccination completion. IgG also significantly increased throughout the three time points as seen in human milk samples.[25]

All studies previously mentioned reported findings from individuals given mRNA vaccines, with the exception of Selma-Royo et al. who included 24 lactating women given ChAdOx1.[31] A single Israeli cohort by Calil et al. observed 20 lactating employees given CoronaVac vaccine where an increase in mean anti SARS-CoV-2 specific IgA was seen in the first two weeks after the first dose, but with significantly higher mean values only 5 and 6 weeks after.[35] However, four months after the first dose, only 5 out of 20 mothers still had high specific IgA levels. Future studies should have larger sample sizes and matched controls for more definitive conclusions on effect of the different vaccines in breast milk antibody titers.

Antibody Transfer to the Newborn

Two studies examined antibody levels in the newborn of pregnant and lactating women.[17,29] In a study of 64 vaccinated parturients, 94% of the neonatal blood spots were found to have SARS-CoV-2 IgG, with titers correlated with the maternal serum levels.[17] In contrast, a study of 61 vaccinated lactating women showed that none of the neonatal blood spots had any detectable IgG but 60% of the saliva of infants did.[29]

Results of Safety

Reactogenicity and Adverse Events

Low et al. reported that among vaccinated lactating women, 6% had axillary or neck lymphadenitis with 3% experiencing mastitis. Pain/redness/swelling at injection site was the most common side effect in lactating vaccinated women but no serious adverse events were noted.[36]

Mclaurin-Jiang et al. saw that symptoms were more commonly reported after the second dose of mRNA vaccination for lactating individuals, with mRNA-1273 being the more common cause of fatigue, headache, pain at injection site, muscle pain, chills, fever and allergic reactions than BNT162b2. In contrast, Perl et al. saw that lactating individuals had a higher incidence of vaccine-related adverse events after the first dose instead of the second dose, but still had pain at injection site as the most reported symptom.[37] Selma-Royo et al. included lactating women who received ChAdOx1 and it was seen that more symptoms such as fever and headache were reported as opposed to those who had mRNA vaccines.[31] More than 85% of the vaccinated lactating women presented with local or systemic symptoms after either first or second dose of mRNA vaccines in the study by Bertrand et al., again with more frequent occurrence after the second dose.[38] No significant adverse reactions were reported by either lactating mothers or babies in the small cohort given CoronaVac vaccine in the study by Calil et al.[35]

Changes in Lactation / Breastmilk

No changes were noted to milk supply post-vaccination in the studies by Low et al.[36] and McLaurin-Jiang et al.[37] No adverse events were also noted in children who were breastfed by their mothers post-vaccination. Peretz et al. found reduced milk supply in a few of the population but production in all cases became normal within 72 hours.[15]

In summary, the available data shows an acceptable safety profile for vaccination in pregnant and lactating women, with majority of the data on mRNA vaccines.

Detailed outcomes are in Appendix 2c. The summary of findings tables for efficacy and safety are in Appendix 5.

Recommendations from Other Groups

As of June 2, 2021, in the interim, the World Health Organization (WHO) currently recommends vaccination in pregnant women when the benefits of vaccination to the pregnant women outweigh the potential risks, i.e. those with high risk of exposure to COVID-19 and those with comorbidities that place them in a high risk group for severe COVID-19.

The American College of Obstetrics and Gynecology (ACOG), as of July 30, 2021, recommends that pregnant and lactating individuals be vaccinated against COVID-19, including all eligible people who may consider future pregnancy. Pregnancy testing is not required prior to receiving any EUA-approved COVID-19 vaccine. In its updated recommendations on December 3, 2021, booster vaccination was also advised for pregnant individuals.[39]

The United Kingdom's Joint Committee on Vaccination and Immunisation (JCVI) has advised that pregnant women should be offered COVID-19 vaccines at the same time as people of the same age or risk group.

In its March 30, 2021 health update, the Department of Health stated that pregnancy is not a contraindication to COVID-19 vaccination and women are advised to get the vaccine after the first trimester of pregnancy. However, it stated that Gam-COVID-Vac should not be administered to pregnant women. Breastfeeding women may be vaccinated if they belong to the priority group by the WHO.[40] As of August 13, 2021, pregnant women were included in the national vaccination priority list.

The Philippine Obstetrical and Gynecological Society (POGS) practice bulletin updated on August 9, 2021 stated that COVID-19 vaccination is recommended for pregnant women, who should be given information about the risks of COVID-19 in pregnancy, the benefits of vaccination in the local epidemiologic context, and the current limitations of safety data in pregnant women. The POGS likewise recommended COVID-19 vaccination among breastfeeding women, noting that there is no need to avoid initiation or discontinue breastfeeding in those who receive the vaccine.[41]

Research Gaps

The following are identified research gaps regarding COVID-19 vaccination for pregnant and lactating women:

1. Efficacy and long-term safety for both mRNA vaccines and non-mRNA vaccines
2. Clinical efficacy / effectiveness and safety of heterologous vaccination
3. Clinical efficacy / effectiveness against infection with variants of concern

Ongoing Trials

The search performed on November 18, 2021 of the Clinicaltrials.gov registry showed one ongoing randomized, placebo-controlled trial on the safety, tolerability and immunogenicity of SARS CoV-2 RNA Vaccine Candidate (BNT162b2). It is currently in the recruitment phase.

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Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N=6)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (6)					
Benefits	Large (5)	Moderate	Small	Uncertain	Varies (1)		• VE COVID-19 infection: 96% (89-100) • VE symptomatic COVID-19: 97% (91,100) • VE hospitalization: 89% (43,100) OR COVID-19 infection: 4.5 (1.19-17.9) for unvaccinated
Harm	Large	Moderate	Small (5)	Trivial	Varies (1)	Uncertain	• No serious adverse events reported. Adverse reaction and event rates general similar to vaccinated non-pregnant women. • Pain at injection site as most common side effect • Symptoms more common after second dose of mRNA vaccines; higher incidence of fever and headache in those given ChAdOx1 versus mRNA

							vaccines.
Certainty of evidence	High	Moderate	Low (6)	Very low			• Low
Balance of effects	Favors vaccine (4)	Probably favors vaccine (2)	Does not favor diagnostic/treatment or no diagnostic/treatment	Probably favors no diagnostic/treatment	Favors no diagnostic/treatment	Don't know	
Values	Important uncertainty or variability (1)	Possibly important uncertainty or variability (3)	Possibly NO important uncertainty or variability (2)	No important uncertainty or variability			
Resources required	Varies (5)	Large cost	Moderate Cost	Negligible cost	Moderate savings / Large savings	Uncertain/Don't know (1)	• Varies per vaccine
Certainty of evidence of resources required	No included studies (5)	Very low	Low (1)	Moderate	High		
Equity	Uncertain (2)	Reduced	Probably no impact	Probably increased (3)	Increased	Varies (1)	
Acceptability	Uncertain (1)	No	Probably no	Probably yes (3)	Yes (2)	Varies	• Varies per vaccine
Feasibility	Uncertain (2)	No	Probably no	Probably yes (2)	Yes (2)	Varies	• Varies per vaccine

Appendix 2a: Characteristics of Included Studies

Author/Study ID	Country	Study design	Vaccine type	No. of doses administered before analysis	Timing of vaccination	N	Sample collection	Population type	Outcomes reported
PREGNANT WOMEN REVIEW									
Atyeo	USA	Observational cohort	Pfizer, Moderna	One and two	Unspecified but mentioned that participants who gave birth were all immunized in 3rd trimester	131	Serum antibody of pregnant/lactating women and non-pregnant women	Vaccinated pregnant, lactating women and non-pregnant women	Serum antibody titers, Fc-receptor (FCR) binding capacity, IgG subclass response, Fc-effector profiles, NK cell activation ability of antibodies
Atyeo2	USA	Observational cohort	Johnson, Moderna. Pfizer	One or two	First trimester: n=18 (11%), Second trimester: n=88 (56%), Third trimester: n=52 (33%)	158	Maternal serum antibodies, cord blood samples	Vaccinated pregnant, lactating women and non-pregnant women	Maternal serum antibody (Spike specific antibody, Fc-receptor (FCR) binding), Umbilical cord serum (spike specific antibody titers, Fc-receptor binding, functional antibody responses, absolute anti-Spike IgG titer), Transfer ratio
Beharier	Israel	Case-control	Pfizer	One and two, numbers not specified	Mean gestational age at first vaccine dose: 34.5 +/- 7.5 weeks (third trimester)	213	Maternal and fetal blood samples: sera: IgG and IgM titers	Pregnant, vaccinated (n=86) Pregnant, unvaccinated, infected (n=65). Pregnant, unvaccinated, non-infected (n=62)	Temporal dependence in pregnant women, temporal dependence in neonates, maternal IgG between vaccinated vs PCR-positive, and Maternal-fetal IgG response to infection and vaccination correlation
Bleicher	Israel	Prospective Observational cohort	Pfizer	Unspecified	First trimester: n=24 (30%), Second trimester: n=37 (46%), Third trimester: n=18 (24%)	313	Two subsequent questionnaires	Pregnant vaccinated, and pregnant non-vaccinated women	Composite pregnancy complications, vaccine side effects, COVID-19 infection incidence, prevalence of vaccinated participants, refusal to be vaccinated
Butt	Qatar	Case-control matched, unbalanced to nationality	Pfizer, Moderna (unspecified)	One and two	Not reported	1255	Pregnant women identified from the centralized hospital electronic medical records. RT-PCR	Pregnant, vaccinated; Pregnant, unvaccinated; Pregnant, PCR positive; Pregnant, PCR negative	Vaccine effectiveness
Collier	USA	Observational cohort	Pfizer and Moderna	Not reported	<14 weeks: n=5 (17%); 14-28 weeks: n=15 (50%); >= 28 weeks: n=10 (33%)	131	Participants recruited in hospital wide prospective data and tissue biorepository	Non-pregnant, nonlactating, vaccinated (n=57) Pregnant, vaccinated (n=30) Lactating, vaccinated (n=16) Non-pregnant, unvaccinated, infected (n=6) Pregnant, unvaccinated, infected (n=22)	Adverse events, Serum binding and functional antibody responses, Binding and Neutralizing Antibodies in cord blood, Binding and Neutralizing Antibodies in Breast milk, T cell Responses in peripheral blood, Humoral and Cellular Immune Responses to SARS-COV-2 Variants of Concern
Dagan	Israel	Case-control	Pfizer	One (14-20 days after, 21-27 days after); Two (7-56 days after)	First trimester: n=2814 (26%), Second trimester: n=5242 (48%), Third trimester: n=2805 (26%)	21722	Pregnant vaccinated women identified from Clalit Health Services matched to unvaccinated pregnant controls	Pregnant, vaccinated; Pregnant, unvaccinated	Vaccine effectiveness

Gray	USA	Cohort	Pfizer and Moderna	One and Two	Mean gestational age at first vaccine dose: 23.2 weeks (second trimester)	131	Antibodies in umbilical cord blood, maternal sera and breastmilk measured using ELISA, Adverse events measured using questionnaire	Pregnant and non pregnant vaccinated women	Maternal antibody titer, local and systemic adverse events, adverse pregnancy outcomes, composite infant morbidity
Kadali	USA	Cross-sectional study	Pfizer and Moderna	Two	Not reported	1029	Online survey questionnaire	Pregnant and non pregnant vaccinated women	Local and systemic adverse events
Mithal	USA	Prospective case series	Pfizer, Moderna, unspecified	One and Two	Mean gestational age at first vaccine dose: 33 +/- 2 weeks (third trimester)	27	Maternal and umbilical cord blood	Pregnant, vaccinated	Maternal antibody titer, positive IgM rate, positive IgG rate, IgG transfer outcomes, Infant IgG outcomes
Nir	Israel	Prospective Observational cohort	Pfizer	Two	All women in third trimester, mean age of 33.5+/-3 weeks	75	Maternal and cord blood samples, breastmilk	Pregnant vaccinated and COVID-19 recovered women	Maternal serum IgG, Neonatal cord blood IgG, Breastmilk IgG
Peretz	Israel	Observational case-control	Pfizer	One and Two	1ST DOSE First trimester: n=76 (19%), Second trimester: n=193 (50%), Third trimester: n=121 (31%); 2ND DOSE First trimester: n=52 (13%), Second trimester: n=154 (40%), Third trimester: n=184 (47%)	650	Pregnant women vaccinated between 2-40 weeks of gestation, recruited via social media and matched to a control group of non pregnant vaccinated females at Sheba Medical Center, Tel Hashomer	Pregnant and non pregnant vaccinated women	Adverse events, Serum binding and functional antibody responses, Binding and Neutralizing Antibodies in cord blood, Binding and Neutralizing Antibodies in Breast milk, T cell Responses in peripheral blood, Humoral and Cellular Immune Responses to SARS-COV
Prabhu	USA	Cohort	Pfizer and Moderna	One and Two	Not reported	122	Semi quantitative testing of maternal peripheral blood and	Pregnant vaccinated women	Maternal antibody, Neonatal IgG, Placental transfer ratio
Rotteinstrech	Israel	Cohort	Pfizer	One or Two	Interval from first vaccine to delivery (median): 33 (30-37 days) *(third trimester)*	20	Antibody in maternal and cord blood sera samples	Pregnant vaccinated women	Maternal IgG, cord blood IgG and placental transfer ratio
Rottenstreich2	Israel	Cohort	Pfizer	One and two	Interval from first vaccine to delivery (median): 33 (30-37 days) *(third trimester)*	171	Maternal and cord blood samples	Pregnant vaccinated women	Maternal IgG, Neonatal IgG, Placental transfer ratio
Shanes	USA	Cohort	mRNA vaccines	Two	Interval from first vaccine to delivery (mean): 45.96 +/- 24.3 days, *(second to third*	200	Antibody testing from plasma	Pregnant vaccinated and non vaccinated women	Maternal antibody titer, placental findings
Shimabukuro	USA	Observational cohort	Pfizer (n=19252), Moderna (n=16439)	One (n=16982), Two (n=12273)	Not reported	35961	Data from "v-safe and VAERS.	Pregnant, vaccinated	Infection rate, local adverse events, systemic adverse events, pregnancy loss, and neonatal outcomes
Shook	USA	Prospective cohort	Johnson (n=7), Moderna (n=28), Pfizer (n=55)	One or Two, unspecified	Interval from first vaccine to delivery (mean): 91 days (54 SD), *(second to*	102	Maternal and Neonatal blood samples	Pregnant women, COVID-19 recovered women, neonates of vaccinated women, neonates of women with recovered COVID-19 infection	Maternal and umbilical cord titers at birth, infant titer at 2 then 6 months, proportion of infants with detectable antibody after 2 or after 6 months

Theiler	USA	Case-control	Johnson (n=1), Moderna (n=12), Pfizer (n=127)	One (n=37), Two (n=103)	Mean gestational age at first vaccine dose: 32 (13.9 - 40.6) weeks, *(first to third*	2002	Medical records from Mayo Clinic	Pregnant, unvaccinated (n=1862), Pregnant, vaccinated (n=140)	Infection rate, Maternal and delivery outcome, length of hospital stay
Trostle	USA	Cross-sectional study	Pfizer, Moderna	One or Two	First trimester or <14 weeks: n=0, Second trimester or 14-27 weeks: n=14 (16.5%), Third trimester or >28 weeks: n=71 (83.5%)	424	Medical records	Pregnant, vaccinated	Fetal or neonatal demise, Gestational age at delivery, preterm delivery, mode of delivery, obstetrical complications, NICU admission, small for gestational age, congenital anomalies
Magnus 1	Norway	Case-control	Pfizer, Moderna, Astra Zeneca	One or Two	All women in first trimester	13956	Norwegian registry	Pregnant vaccinated and unvaccinated	
Wainstock	Israel	Retrospective observational cohort	Pfizer	One or Two	All women in third trimester, mean age of 30.6 +/- 5.3 weeks, *(third*	4860	HMO database	Pregnant vaccinated and pregnant unvaccinated	
Zauche	USA	Observational cohort	Pfizer, Moderna	One, Two	1ST DOSE Preconceptio n: n=380 (15.5%), First trimester or >=2 weeks and <14 weeks: n=1230 (50.1%), Second trimester or >=14 weeks and <20 weeks: n=846 (34.4%), 2ND DOSE Preconceptio n: n=188 (8.5%), First trimester or >=2 weeks and <14 weeks: n=885	2456	V-safe pregnancy registry	Pregnant, vaccinated	Self reported spontaneous abortion rates
Zdanowski	Poland	Observational cohort	Pfizer	One, Two	All women in third trimester, mean age of 31.75 +/- 2.05 weeks at first dose, mean age of 35.13 +/- 2.13	16	Maternal and cord blood samples	Pregnant vaccinated women	Anti-S total IgG antibody titers in maternal and cord serum

LACTATING WOMEN REVIEW									
Atyeo	USA	Observational cohort	Pfizer, Moderna	One and two	Unspecified but mentioned that participants who gave birth were all immunized in 3rd trimester	131	Serum antibody of pregnant/lactating women and non-pregnant women	Vaccinated pregnant Lactating women and non-pregnant women	Serum antibody titers, Fc-receptor (FCR) binding capacity, IgG subclass response, Fc-effector profiles, NK cell activation ability of antibodies
Bertrand	USA	Observational cohort	Moderna (n=52), Pfizer (n=128)	Moderna: both doses (n=52), Pfizer not clear	Post delivery	180	Records from Mommy's Human Milk Human Milk Research Biorepository at the University of California, San Diego	Lactating, vaccinated	Maternal symptoms and child events after vaccination
Caliii	Sao Paulo, Brazil	Observational cohort	Coronavac	One, Two	Post delivery	20	Human milk samples obtained from employee volunteers during immunization process in HC-FMUSP	Lactating, vaccinated	Anti-SARS-Cov-2 IgA Ratio
Charepe	Portugal	Observational cohort	Pfizer	One, Two	Unspecified	24	Maternal serum and breast milk	Lactating and non lactating vaccinated women	Maternal and breastmilk IgM, IgA and IgA antibodies
Collier	USA	Observational cohort	Pfizer and Moderna	Not reported	<14 weeks: n=5 (17%); 14-28 weeks: n=15 (50%); >= 28 weeks: n=10 (332%)	131	Participants recruited in hospital wide prospective data and tissue biorepository	Non-pregnant nonlactating vaccinated (n=57) Pregnant vaccinated (n=30) Lactating vaccinated (n=16) Non-pregnant unvaccinated infected (n=6) Pregnant unvaccinated infected (n=22)	Adverse events, Serum binding and functional antibody responses, Binding and Neutralizing Antibodies in cord blood, Binding and Neutralizing Antibodies in Breast milk, T cell Responses in peripheral blood, Humoral and Cellular Immune Responses to SARS-COV-2 Variants of Concern
Esteve-Palau	Spain	Observational cohort	Pfizer	Two	Post delivery	18	Breastmilk and maternal antibodies	Lactating, vaccinated	Antibodies in breast milk, seropositivity in maternal blood
Fox	USA	Observational cohort	Pfizer (n=6), Moderna (n=4)	Two	Post delivery	10	Breastmilk antibodies	Lactating vaccinated	Breastmilk SARS-CoV-2 Spike-specific IgA, SC, IgG reactivity
Friedman	Israel	Observational cohort	Pfizer	Two	5 months postpartum (mean 154 days, range 68-382)	10	Maternal serum and breast milk	Lactating vaccinated	Vaccine specific IgG/IgA ratio in breastmilk and serum
Golan	USA	Observational cohort	Moderna (n=9), Pfizer (n=14)	Two	Post delivery	23	Maternal serum and breast milk	Lactating vaccinated Lactating infected	anti-SARS-CoV2 IgG and IgM antibodies in maternal plasma, anti SARS-CoV2 IgA in human milk
Gray	USA	Cohort	Pfizer and Moderna	One and Two	Mean gestational age at first vaccine dose: 23.2 weeks, *(second to third*	131	Umbilical cord blood, maternal sera and breastmilk measured using ELISA, Adverse events measured using questionnaire	Pregnant and non pregnant vaccinated women Lactating vaccinated	Maternal antibody titer, local and systemic adverse events, adverse pregnancy outcomes, composite infant morbidity
Juncker	Netherlands	Observational cohort	Pfizer	One (n=6), Two (n=20)	Post delivery	26	Maternal serum and breast milk	Lactating vaccinated	Antibodies in breast milk, seropositivity in maternal blood
Low 1	Singapore	Observational cohort	Pfizer	Two	Post delivery	25	Breastmilk	Lactating vaccinated Lactating infected unvaccinated Lactatin unvaccinated	Antibodies in breast milk
Low 2 (singapore)	Singapore	Observational cohort	Pfizer	Two	Post delivery	88	Questionnaire	Lactating vaccinated	Maternal-child local, systemic and/or serious adverse events
McLaurin-Jiang	USA	Cross-sectional study	Pfizer (n=2702) Moderna	One (n=2627) Two (n=1828)	Post delivery	4455	Survey	Lactating vaccinated	Local and systemic maternal adverse events
Nir	Israel	Prospective Observational cohort	Pfizer	Two	All women in third trimester, mean age of 33.5+/-3 weeks	75	Maternal and cord blood samples, breastmilk	Pregnant vaccinated and COVID-19 recovered women	Maternal serum IgG, Neonatal cord blood IgG, Breastmilk IgG
Perl	Israel	Observational cohort	Pfizer	Two	Post delivery	84	Breastmilk	Lactatingvaccinated	Antibodies in breast milk

Schwartz	Israel	Observational cohort	Pfizer	Unspecified	Post delivery	61	Maternal sera and breastmilk	Lactating vaccinated women	SARS-CoV-2 IgG and IgA in serum and breastmilk
Selma-Royo	Spain	Observational cohort	Pfizer (n=30) Moderna (n=21) Astra Zeneca (n=24)	One, Two	Post delivery	131	Breastmilk	Lactating vaccinated (n=75) Lactating infected unvaccinated (n=19)	IgG, IgA antibodies in breast milk, maternal adverse events
Valcarce	USA	Observational cohort	Pfizer (n=14) Moderna (n=7)	Two	Post delivery	21	Maternal sera and breastmilk	Lactating vaccinated	Antibodies in breast milk, seropositivity in maternal blood

Appendix 2b. Detailed Data Extraction Tables for Pregnancy Reviews

STUDY ID	DESIGN	POPULATION	INTERVENTION (Vaccine) (Timing) (n)	CO	CONTROL/S Population (n)	IN	INFECTION RATE / VE post D2, post D1, by subgroup	MA	MATERNAL ANTIBODIES (Titers / %) post D2 vs baseline, vs control,	NA	NEONATAL ANTIBODIES (Titers / %) vs. maternal, vs control	PO	PREGNANCY OUTCOMES pre-eclampsia, PROM, gestational DM, fetal growth restriction (vs. unvaccinated)	DO	DELIVERY OUTCOMES preterm delivery spontaneous abortion FDU (vs. unvaccinated)	NO	NEONATAL OUTCOMES respiratory complications, APGAR, NICU admission, Sepsis, NEC, Death (vs. unvaccinated moms)	AE	LOCAL AR	SYSTEMIC AR	ADVERSE EVENTS
Atyeo (USA) preprint	comparative cohort Pregnant vs nonpregnant vs lactating Pfizer vs Moderna age matched	Vaccinated women: Pregnant women Non pregnant Lactating	Pfizer and Moderna: unspecified (Timing not specified, implied that all participants who gave birth were all immunized in the third trimester) Pregnant vaccinated (n=84)	NPLA	non-pregnant vaccinated (n=16) lactating vaccinated (n=31)		na	y	differences in titers among pregnant, non-pregnant and lactating women post vac : higher titers pD1 in non-pregnant vs pregnant and lactating; higher pD2 titers in lactating vs pregnant higher post D2 after Moderna vs Pfizer : ADNP, IgA, IgG2, IgG3, and NK cell activating antibodies higher IgG1 and FC-binding titers after Pfizer vs Moderna - lower antibody titers & FcR binding in P & L after dose 1 but no significant difference after dose 2 - after dose 2, lactating had	y	(cord blood) (+) variable transfer of IgG to cord blood: equivalent for IgGS1 but lower for IgGS3 higher levels of antibodies were observed in maternal blood compared to cord blood		na		na		na		na	na	na

									higher IgG titer & NK cell activity (similar to non-pregnant but still with lower FcR binding)											
Atyeo2 (USA) preprint	Comparative cohort (across vaccines)not all participants contributed to the outcomes	vaccinated pregnant womencomparable by vaccination to sampling, maternal age, gravidity, parity, BMI, race, insurance status, obesity, autoimmune disorder	Pfizer = 69 [86]Moderna = 61[62]JnJ = 28 [27]Timing:First trimester: n=18 (11%), Second trimester: n=88 (56%), Third trimester: n=52 (33%)maternal infant dyads = 175 : 123 with titers, +52 dyads who delivered	VC	across platforms		na	y	antibody titers and functions were significantly lower in those who received JnJ compared to mRNAshigher IgG2 and anti-S2 anti-spike response in those vaccinated with mRNA_1273 vs BNT162b2no trimester-specific differences in anti-Spike antibodies or FcR-binding, but 1st & 3rd trimester had higher functional antibody responsetime interval of extraction:mRNA: 62 [27-91] BNT162b2: 42 [22-74]Ad26.COV2.S: 58 [38-85]	y	cord blood titers significantly higher in mRNA recipients compared to JnJ correlating with maternal levelsspike-specific antibody response and response to variants mirrored maternal response-IgG2 against Spike was significantly higher in the cord blood of mRNA-1273recipients compared to either Ad26.COV2.S or BNT162b2 recipients-Functional antibody responses were lower in the cord blood of Ad26.COV2.S recipients compared to mRNA-1273 or BNT162b2 - ***similar maternal and cord blood antibody titers and functions -*** *higher TRs generated by first and*		na		na		na		na	na	na

											second trimester vaccination (median TR = 1.5 and 1.3) compared to third trimester vaccination (median TR = 1.0)- highest TRs for first trimester vaccination but lower absolute titers in cords of mothers vaccinated in the first trimester (waning maternal titers by delivery)										
Beharier et al. (Israel)	comparative cohort(vac vs unvac)younger infectedsimilar comorbidities	Pregnant women213 dyads	BNT162b2(n=86)Timing: Mean gestational age at first vaccine dose: 34.5 +/- 7.5 weeks (third trimester)	UV	Pregnant unvaccinated, infected(n=65)P regnant unvaccinated, non-infected(n=62)		na	y	IgG, IgMsignificant rise in anti-S1, anti-S2, and anti-RBD IgG from baseline to at least 15 days after D2 compared to unvacsimilar pattern for IgMlevels and pattern similar to infected unvaccinated; (but anti-N levels also rise; low seropositivity for anti-N-IgG for the vaccinated N-group)	y	IgG, IgM (fetal / cord blood)significant rise in anti-S1, anti-S2, and anti-RBD IgG from baseline to at least 15 days after D2, titers similar to maternal IgM levels significantly lower than maternal levels		na	y	Preterm delivery:Vaccinated: 4/92 (4.3%)UnVac noninfec: 5/66 (7.6%)UnVac Infec: 8/74 (10.8%)	y	NICU admission: Vac: 4/92 (4.3%)UnVac noninf: 1/66 (1.6%)UnVac Infec: 1/74 (1.6%)		na	na	na
Bleicher (Israel)	comparative cohort (online questionnaire, 2 instances) (vacc vs Unvac) vaccinated group more with flu vaccine, more were medical workers, less had no risk factors, less had	pregnant women who completed 2 online questionnaires n = 313	Pfizer Timing First trimester: n=24 (30%), Second trimester: n=37 (46%), Third trimester: n=18 (24%)	UV	unvaccinated	y	COVID-19 positive since the last questionnaire (Vaccinated vs unvac): 3/202 (1.5%) vs 8/124		na		na	y	no difference in composite pregnancy complications (15.8% vs 20.2%) Vaccinated vs	y	first trim pregnancy loss = 2/202 0.9%) vs 1/124 (0.8%) ns No preterm births in either group	y	anomaly on anatomy scan: 9 (4.5%) vs 6 (4,8%) ns	y	66% with local reaction at injection site	16.8% weakness 16.8% headache	na

	previous pregnancy loss						(6.5%) OR = 4.5 (95%CI 1.19-17.6)						Unvac : fetal grown restriction : 3/202 (1.5%) vs) (0.0), ns							
Butt (Qatar) **preprint**	TNCC matched by age and reason for testing	2020 pregnant women with RT-PCR results PCR (+) : 393 PCR (-) : 1074	pregnant, vaccinated mRNA vaccine unspecified (Timing not specified) PCR (+) = 23 PCR (-) = 109	UV	unvaccinated PCR (+) = 370 PCR (-) = 753	y	VE at least 14 days after D2: 67.7% (30.5, 86.9) VE at least 14 days after D1, before D2 : 40.3% (0, 80.4)		na		na		na		na					
Collier(USA)	Comparative Cohort(vaccinated pregnant/nonpregnant/lactating vs nonvaccinated nonpregnant infected, vs nonvaccinated pregnant infected)	pregnant, lactating and nonpregnant vaccinated, non-pregnant infected unvaccinated, pregnant-infected unvaccinated	Pfizer (n=56)Moderna (n=47)Vaccinated nonpregnant : 57Vaccinated pregnant : 30Vaccinated lactating : 16Timing <14 weeks: n=5 (17%); 14-28 weeks: n=15 (50%); >= 28 weeks: n=10 (33%)	UV NP	unvaccinated, pregnant, infectedunvaccinated, non-pregnant, infected		na	y	significant increase in RBD IgG and neutralizing antibody titers; equivalent between non-pregnant and lactating vaccinated, higher than infected unvaccinatedmedian RBD-IgG binding antibody titer:pregnant, vaccinated: 27 601pregnant, infected: 1321non-pregnant, vaccinated: 37839non-pregnant, infected: 771pseudovirus NT50:pregnant: 910non-pregnant: 901functional assays:ADNP:pregnant: 27non-pregnant: 58ADCD:pregnant: 402non-pregnant: 376ADCP:pregn	y	(cord blood)among vaccinated :similar RBD IgG titers between maternal sera and cord bloodRBD IgG:maternal: 14 953cord blood: 19 873Lower NABs in cord blood vs maternal sera NT50 (NAB):maternal: 1016 cord blood: 324among unvaccinated infected :similar levels of RBD and NABs between maternal sera and cord bloodRBD IgG:maternal: 1342 cord blood: 635NT50 (NAB):maternal: 151 cord blood: 164	y	no pregnancy complications		na	y	no neonatal complications	y	na	fever was reported in 27/52 nonpregnant (52%, SD; 7%), 4/29 pregnant (14%; SD, 6%), and 7/16 lactating (44%; SD, 12%) women	No severe adverse events

									ant: 282non-pregnant: 277Cellular response comparable in pregnant, lactating and nonpregnant vaccinated womenT cell responses (per million PBMCs):pregnant: 270non-pregnant: 435spike-specific IFN-γ production by CD4 T cells,CD4 central memory T cells, CD8 T cells, and CD8 central memory T cells were comparable in pregnant, lactating, and non-pregnant womenanti RBD IgG comparable with Alpha but lower with Beta strain, but NABs lower for both alpha (3.5-fold lower) and beta strain (6-fold lower) for pregnant and lactating, as with non-pregnant; nodifferences in ELISPOT responses , CD4 T-cell responses, CD4 central memory T-cell responses, CD8T-cell responses, or CD8central memory T-cell responses across these variants											

Dagan (Israel) Communication	Matched cohortby age, pregnancy trimester, population sector, CDC risk factorcovariates: age, sex, pregnancy trimester, place of residence, health care worker, long-term care facility resident, influenza vaccination, comorbidities	vaccinated pregnant 16 years and older, matched with unvaccinated pregnant	BNT162b2(n = 10, 861) Timing First trimester: n=2814 (26%), Second trimester: n=5242 (48%), Third trimester: n=2805 (26%)	UV	unvaccinated(n = 10,861)	y	7 days after D2 (56 days ffup)VE any infection : 96% (89-100) : 1 vs 37VE symptomatic infection : 97 (91-100) : 1 vs 26Hospitalization : 89% (43-100) 1 vs 7severe disease: 1 in unvaccinated vs 0 in vaccinated death : no events for both		na		na		na		na		na	na	na
Gray (USA)	comparative cohort (Pregnant vs lactating vs nonpregnant)	Vaccinated women Pregnant, lactating and nonpregnant vaccinated	pregnant (N=84) Pfizer: n=41 (49%), Moderna: n=43 (51%) first dose given at mean gestational age of 23.2 weeks, 46% in 2nd trimester, 40% in 3rd trimester	NP UV	non-pregnant vaccinated (N=16) Pfizer: n=8 (50%) Moderna: n=8 (50%) pregnant infected 4-12weeks prior (37)		na	y	antibody titers similar between pregnant, lactating and nonpregnant vaccinated, all higher than infected; did not differ by trimester of vaccination Higher S- and RBD-specific IgA responses were noted in Moderna vaccinees than Pfizer/BioNTech vaccinees IgG predominant by 2 weeks after dose 2	y	slightly lower NABs in the cord compared to maternal sera		na	y	13 deliveries: 1 spontaneous preterm delivery	y	13 deliveries: 1 (8%) - supplemental O2 1 (8%) - TTN 2 (15%) NICU admission 0 death 0 sepsis 0 NEC	y	na	na	cumulative symptoms scores of side effects in all 3 groups were low and with no significant difference

Kadali (USA) letter	cross sectional(Vac vs nonVac)	pregnant HCWs	mRNA vaccine(Timing not specified)(n = 38)Pfizer = 20Moderna = 18	NP	nonpregnant HCW = 991		na		na		na		na		na		na	y	na	na	no significant difference in side effect profile between the 2 groups
Mithal (USA) letter	single cohort (matched maternal and cord blood)	vaccinated pregnant (mostly HCW)	Pfizer, Moderna, unspecified (n= 27) Timing: Mean gestational age at first vaccine dose: 33 +/- 2 weeks (third trimester) Pfizer = 18 Moderna = 6 unknown = 4	NA	none		na	y	IgM: 15/27 IgG: 26/27	y	IgG transfer ratio : 1.0 ± 6 increased latency from vaccination to delivery associated with an increase in transfer ratio IgM: 0/28 IgG: 25/28 (2 mothers: dose 1 <3 weeks before delivery) -increased latency from vaccination to delivery (weeks) - associated with an increased transfer ratio (β=0.2; 95% CI, 0.1, 0.2) - having received the second vaccine dose before delivery - significantly associated with increased infant IgG levels (β=19.0; 95% CI, 7.1, 30.8) - latency from vaccination to delivery - associated with increased		na		na		na		na		na	na	na

											infant IgG levels (β=2.9; 95% CI, 0.7, 5.1)									
Nir	comparative cohort(vaccinated vs unvac infected)	parturients	BNT162b2(mean 21 days prior to delivery)(n=64) Timing: all women in third trimester, mean age of 33.5+/-3 weeks	UV	unvaccinated, had COVID during pregnancy(mean 92 days prior to delivery)(n=11)		na		na	y	cord blood: IgG titers higher in vaccinated (26.1 vs 20.2)good correlation between maternal and cord blood titers	y	no difference in gestational diabetes, gestational hypertensive disease between vac and unvac		na		na		na	na	na
Peretz (Israel)	comparative cohort (stated as case control in study but assessed as a matched cohort study) matched by age; comparable by BMI and comorbidities not all outcomes available for all recruited	vaccinated women excluded those who delivered and had an abortion before D2	pregnant Pfizer (2-40 weeks AOG) (n=390) immunogenicity (n=96) Timing: 1ST DOSE First trimester: n=76 (19%), Second trimester: n=193 (50%), Third trimester: n=121 (31%); 2ND DOSE First trimester: n=52 (13%), Second trimester: n=154 (40%), Third trimester: n=184 (47%)	NP	non-pregnant women (n=260)		na	y	lower serum IgG signal to cut off ratio in pregnant compared to non-pregnant (27.03 vs. 34.35)		na	y	gestational diabetes = 4 (7%) preeclampsia = 1 (1.8%)	y	n=91 deliveries, 57 with complete data no preterm delivery no fetal deaths no neonatal death no miscarriage	y	2/57 NICU admission for respiratory support	y	less local pain and swelling than non-pregnant	myalgia, arthralgia and headache and lymphadenopathy were less than non-pregnant rates of rash, fever and severe fatigue comparable to non-pregnant women; paresthesia more common (after dose 2)	no significant differences in the rates of side effects according to whether patients were vaccinated in the first, second or third trimester
Prabhu (USA) letter	single cohort	vaccinated pregnant who delivered	Pfizer or Moderna; at least 1 dose (Time not specified) (n=122)	NA	none/self		na	y	increasing maternal IgG starting 2 weeks after first vaccine; linearly associated with cord blood	y	cord blood IgG linearly associated with maternal levels placental transfer ratio correlated with the number of weeks elapsed since maternal vaccine dose 2		na		na		na		na	na	na

Rotteinstrech (Israel) Brief report	single cohort	vaccinated pregnant who delivered	Pfizer, two doses(n= 20) Timing: Interval from first vaccine to delivery (median): 33 (30-37 days) *(third trimester)*	NA	self		na	y	all women were positive for anti-S and Anti-RBD specific IgG; IgM in 6 mothers Anti-S: 319 [IQR 211–1033]Anti-RBD: 11 150 [IQR 6154–17 575]	y	all were positive for anti-S and anti-RBD IgG; no IgM Anti-S: 193 [IQR 111–260]Anti-RBD: 3494 [IQR 1817–6163]titers correlated with maternal sera; increasing titers with increased time since first dose of vaccinemedian placental transfer ratios:Anti-S: 0.44 [IQR 0.25–0.61]Anti-RBD: 0.34 [IQR 0.27–0.56]		na		na		na		na	na	na
Rottenstreich2	comparative cohort (early vs late 3rd trim vaccination)	pregnant women vaccinated in the 3rd trim	BNT162b2 early (27-31weeks) (n= 83) Timing: Interval from first vaccine to delivery (median): 33 (30-37 days) *(third trimester)*	OT	late (32-36wks) n=88		na	y	median anti-S and antiRBD titers at time of delivery lower in the early vs late group (S: 200 vs 292 AU/ml) (RBD : 3980 vs 8506)	y	Neonatal concentrations of anti-S IgG did not differ antiRBD IgG higher in the early vs late group (9620 vs 6697); positively correlated with increasing time since vaccination NAB titers reflected maternal activity; higher placental transfer ratio with early vs late (1.9 vs 0.8),	y	3rd vs 1st trim gestational DM: 7.2% vs 8.0% gestational HPN: 1.2% vs 2.3%		na		na		na	na	na

Shanes (USA)\ research letter	comparative cohort(vac vs unvac)timing of vaccination not known for all	pregnant	vaccine not specified(n = 84) Interval from first vaccine to delivery (mean): 45.96 +/- 24.3 days, *(second to third trimester)*	UV	unvaccinated (n= 116)		na	y	higher IgG and IgM titers after vaccination (compared to unvaccinated)		na		na	y	higher vaginal delivery in vaccinated (79% vs 65%)placental examination of vaccinated showed no increased decidual arteriopathy, fetal vascular malperfusion, low-grade chronic vasculitis or chronic histiocytic intervillositis		na	y	na	na	no increased incidence of decidual arteriopathy,fetal vascular malperfusion, low-grade chronicvillitis, or chronic histiocytic intervillositis
Shimabukuro (USA)	cross-sectional (historical control)	pregnant vaccinated 16-54 yo enrolled in v-safe and in registry n = 35691 v-safe pregnant: 3958 827 completed pregnancies	Pfizer (n=19252), Moderna (n=16439) Timing not specified	NP	non pregnant 16 to 54yo		na		na		na	y	SGA = 3.2% n= 827 115 (13.9%) pregnancy losses still birth 0.1% spon abortion 12.6% (96 occurred before 13 weeks) induced abortion/ectopic 1.2% 712 (86.1%) live births, mostly among participants vaccinated in the 3rd trim)	y	preterm birth = 9.4% SGA = 3.2% congenital anomalies = 2.2% n= 827 115 (13.9%) pregnancy losses still birth 0.1% spon abortion 12.6% (96 occurred before 13 weeks) induced abortion/ectopic 1.2% 712 (86.1%) live births, mostly among participants vaccinated in the 3rd trim)	y	major congenital anomalies = 2.2% no neonatal deaths Calculated proportions of pregnancy and neonatal outcomes appeared similar to incidences published in literature	y	(injection-site pain was reported more frequently among pregnant persons	overall reactogenicity profile was similar	221 pregnancy-related Aes, most commonws spontaneous abortion (46 cases)

Shook	comparative cohort(vaccinated vs infected_	deliveries	Johnson (n=7), Moderna (n=28), Pfizer (n=55) Timing: Interval from first vaccine to delivery (mean): 91 days (54 SD), *(second to third trimester)*	UV	previously infected median 71 days from infection to delivery (n=12)		na	y	maternal titers at birth significantly higher vs. infected (1.94 vs).65)	y	umbilical cord titers at birth significantly higher at birth vs infected (2.06 vs 1.0)infant titers at 2 months seen only in the vaccinated (1.19)at 60 months 0.33, also seen only in vaccinatedantibodies detected in 94% at 2 months (vs 0) and in 60% at 6 mos (vs 8%)		na		na		na		na	na	na
Theiler (USA) **preprint**	comparative cohort (vaccinated vs infected)	deliveries	Johnson (n=1), Moderna (n=12), Pfizer (n=127) (N=140) Timing: Mean gestational age at first vaccine dose: 32 (13.9 - 40.6) weeks, *(first to third trimester)*	UV	unvaccinated, infected (n=212)	y	infection prior to delivery: vac: 2/140 (1.4%) unvac : 210/1862 (11.3%) - 26 in first trim, 84 in 2n, 100 in 3rd no maternal COVID-19 infections after vaccination during pregnancy	y	na		na	y	no difference in gestational hypertension, eclampsia	y	no difference in preterm births, still births,	y	no difference in early neonatal deaths no difference in NICU admission, APGAR <7, low birth wight	y	na	na	Adverse outcomes index not different between groups: 5.0% (7/140) vs 4.9% (91/1862) no maternal or early neonatal deaths
Trostle	cross-sectional	pregnant vaccinated; at least 1 dose of mRNA vaccine	Pfizer: n = 332 (78.3%); Moderna: n = 92 (21.7%), N= 424 348 (82%) two doses76 (17.1%) one dose Timing: First trimester or <14 weeks: n=0, Second trimester or 14-27 weeks: n=14	NA	none		na		na		na	y	18.8% hypertensive disorder of pregnancy 2 (0.6%) intrauterine growth restriction	y	5.9% preterm birth9 spontaneous abortions, 8 in the first trim (6.5%)3 terminated pregnancies85 liveborn infantsno stillbirths	y	2 (0.6%) intrauterine growth restriction5 (1.5%) with anomalies 15.5% admission to NICU		na	na	na

			(16.5%), Third trimester or >28 weeks: n=71 (83.5%)																	
Magnus	Case control adjusted for age, country of birth, marital status, educational level, household income, number of children, employment as healthcare prof, underlying risk conditions for COVID, previous test positive for SARSCOV, calendar month	first trimester registrants cases: miscarriages control: continued pregnancy	Pfizer Moderna AstraZeneca unspecified N = 13956 Timing: all women in first trimester	OT	none		na		na		na		na	y	OR for miscarriages for vaccination : 0.91 (0.75, 1.10) for vaccination in the previous 3 weeks, 0.81 (0.69 , 0.95) for vaccination in the previous 5 weeks 5-week window Pfizer : 0.80 (0.67, 0.96) Moderna : 0.84 (0.56, 1.25) AZ : 0.84 (0.48, 1.48)		na		na	na	na
Wainstock	comparative cohort(vaccinated vs unvaccinated)vaccinated older, conceived following fertility treatments, had sufficient prenatal care, higher socioeconomic positionadjusted for age, fertility treatment, socioeconomic score	women who delivered, excluded women diagnosed with COVID-19 in the past, multiple gestation or unknown vaccination statusn = 4399	BNT162b2Timing: All women in third trimester, mean age of 30.6 +/- 5.3 weeks, *(third trimester)*	UV	unvaccinated		na		na		na	y	no difference in pregnancy complications except for meconium stained amniotic fluid, aOR 0.52 (0.32-0.83) for vaccinated	y	no difference in delivery outcomes (age at delivery, CS, placental abruption, postpartum hemorrhage)	y	no difference in APGAR <7 at 5 mins, birthweight, SGA, newborn respiratory complications, new born fever, length of newborn hospitalization compared to unvaccinated		na	na	na

Zauche	cross sectional / single cohortwith lost patients	v-safe pregnancy registry participants who received at least one dose of mRNA vaccine preconceptio n or prior to 20 weeks AOG, and who did not report pregnancy loss before 6 weeks gestation	(N=2456)Pfizer: n=1294 (52.7%), Moderna: n=1162 (47.3%)(prior to 20 weeks AOG)Timing: 1ST DOSE Preconception: n=380 (15.5%), First trimester or >=2 weeks and <14 weeks: n=1230 (50.1%), Second trimester or >=14 weeks and <20 weeks: n=846 (34.4%), 2ND DOSE Preconception: n=188 (8.5%), First trimester or >=2 weeks and <14 weeks: n=885 (40%), Second trimester or >=14 weeks and <28 weeks: n=1125 (50.9%)	NA	none		na		na		na		na	y	cumulative risk of spontaneous abortion from 6-19 weeks = 14.1% (95%CI 12.1-16.1%), risk increasing with age		na		na	na	na
Zdanowski (Poland)	single cohort	vaccinated mothers who delivered	BNT162b2,2 dosesn = 16Timing: All women in third trimester, mean age of 31.75 +/- 2.05 weeks at first dose, mean age of 35.13 +/- 2.13 weeks at second dose	NA	none		na	y	anti-S = 100%, 984.37 U/mL	y	anti-S = 100% in umbilical blood, 1062.51 U/mlcord/mat erna: 1.28positive correlation between weeks from first vaccine dose to delivery and antiS antibody titer in cord blood		na		na		na		na	na	na

Appendix 2c. Detailed Data Extraction Tables Lactating Women Reviews

STUDY ID	DESIGN	POPULATION	INTERVENTION (Vaccine) (Timing) (N)	CO	CONTROL/S (N)	INFECTION RATE / VE post D2, post D1, by subgroup	MA	MATERNAL ANTIBODIES post D2 vs baseline, vs control,	NA	NEONATAL ANTIBODIES vs. maternal, vs control	BA	BREASTMILK ANTIBODIES vs maternal	AE	OVERALL AR	LOCAL AR	SYSTEMIC AR	ADVERSE EVENTS
Atyeo	comparative cohort (lactating vs nonpregnant)	Vaccinated pregnant (n=84) vs Vaccinated lactating (n=31)	Pfizer and Moderna: unspecified (Timing not specified, implied that all participants who gave birth were all immunized in the third trimester) Vaccinated lactating (n=31)	NP	non-pregnant (n=16)	na	y	- lower antibody titers & FcR binding in P & L after dose 1 but no significant difference after dose 2 - after dose 2, lactating had higher IgG titer & NK cell activity (similar to non-pregnant) - lactating women induced significantly higher NK cell activating antibodies after boosting	y	higher levels of antibodies were observed in maternal blood compared to cord blood	y	robust transfer of FCR binding antibodies after the second dose; also with enriched transfer of IgM IgG and IgA to breast milk higher transfer with Moderna vs Pfizer		na	na	na	na
Bertrand	Comparative cohort (across vaccines)	Vaccinated lactating women	BNT162b2 = 128 mRNA-1273 = 52 Timing: post delivery	VA	none (with each other)	na		na		na		na	y	after D1: 89.4% Pfizer; 98.1% Moderna after D2 : 98.3 Pfizer, 100% moderna	after D1: 86.8% Pfizer, 96.2% Moderna after D2: 87.9% Pfizer, 98% after moderna signif higher with moderna at dose 2	after D1: 41.5% Pfizer, 53.8 moderna after D2: 87.1% Pfixer, 96.0% moderna signif higher with moderna at dose 2	reported significant reduction in mild production for both vaccines, but normalized after 72 hours; 5 women reported change in color of breast milk post vaccination few events for children reported post vaccination, including irritability, poor sleep
Caliil	Single cohort	vaccinated lactating women (N = 20) (n = 10 with 4-month sample)	CoronaVac N=20 Timing: post delivery	NA	self	na		na		na	y	siginificant rise in IgA titers in the first 2 weeks after the first dose, significantly higher mean values at weeks 5 and 6		na	na	na	na

												(21 days after the second dose); all determinations, including at 4 months showed levels above the cut off					
Charepe	comparative cohort (lactating vs non lactating)	healthcare workers, vaccinated	BNT162b2 N=24 (Timing not specified) Lactating	NL	non lactating vaccinated	na	y	all had positive serum antibodies after the second dose 1st dose igG levels higher in non-lactating group	y	IgG in 42.9% after D2 IgA in 21.4% after D2 (higher in D1) higher correlation between IgA maternal and serum IgG titers higher with longer breastfeeding time		na	y	no difference in vaccination side effects	na	most common AE was myalgia	na
Collier (USA)	comparative cohort (pregnant, lactating vaccinated vs unvaccinated)	pregnant, lactating and nonpregnant vaccinated, non-pregnant infected unvaccinated, pregnant-infected unvaccinated	Pfizer (n=56) Moderna (n=47) Timing: <14 weeks: n=5 (17%); 14-28 weeks: n=15 (50%); >= 28 weeks: n=10 (33%)	UV	unvaccinated, pregnant, infected unvaccinated, non-pregnant, infected	na	y	significant increase in RBD IgG and neutralizing antibody titers; equivalent between non-pregnant and lactating vaccinated, higher than infected unvaccinated pseudovirus NT50: lactating: 783 non-pregnant: 901 functional assays: ADNP: lactating: 12 non-pregnant: 58 ADCD: lactating: 333 non-pregnant: 376 ADCP: lactating: 249 non-pregnant: 277		na	y	lower IgG titers in breast milk among vaccinated compared to infected, despite higher titers in the maternal sera of vaccinated serum RBD IgG: vaccinated: 25 055 infected: 1593 breastmilk RBD IgG: vaccinated: 97 infected: 203 Same pattern with IgA titers and median NT50 (lower with vaccinated compared to infected) serum RBD IgA: vaccinated:		na	na	fever was reported in 27/52 nonpregnant (52%, SD; 7%), 4/29 pregnant (14%; SD, 6%), and 7/16 lactating (44%; SD, 12%) women	No severe adverse events

								Cellular response comparable in pregnant, lactating and nonpregnant vaccinated women T cell responses (per million PBMCs): pregnant: 185 non-pregnant: 435 anti RBD IgG comparable with Alpha but lower with Beta strain, but NABs lower for both alpha and beta strain for pregnant and lactating, as with non-pregnant				820 infected: 152 breastmilk RBD IgA: vaccinated: 25 infected: 1940 median breastmilk NT50: vaccinated: 75 infected: 153					
Esteve-Palau	Single cohort with missing samples	lactating, no previous infection,	Pfizer (n=18) Timing: post delivery	NA	none/self	na		na		na	y	median IgG levels for serum-milk pairs T1(14s p D1) : 410-1.7 T2(14d pD2) : 11505-52.2 T3 (28d pD2) : 8311-41.7 breast milk IgG(S1) levels dramatically increase after the second dose and that they are positively correlated with corresponding serum levels	y	adverse reactions were minor	na	na	no adverse events observed in the lactating infants

Fox	Single cohort	lactating, no history of SARS COV infection, negative IgA titers in milk prior to vaccination	Pfize (n=6), Moderna (n=4) Timing: post delivery	NA	none/ self at baseline	na		na		na	y	spike specific IgA % = 60^ secretory IgA = 50% spike specific IgG = 100%		na	na	na	na
Friedman	Single cohort	lactating	Pfizer (n=10) Timing: 5 months postpartum (mean 154 days, range 68-382)	NA	none/self	na		na		na	y	IgG and IgA at D7 and D14 pD1 and D1 and D14 pD2 first significant increase in titers noted at 14d pD1 and peaked at 7d pD2 with a slight decrease at 14dpD2 serum antibody response dominated by IgG and IgG/IgA was significantly higher in serum than in breast milk.		na	na	na	na
Golan	Comparative cohort	vaccinated lactating women	Moderna (n=9), Pfizer (n=14) Timing: post delivery	UV	Infected unvaccinated	na	y	significant rise in plasma IgG, peaking at 4 weeks post D2 from baseline		na	y	IgA levels in milk (anti RBD) increased with vaccination but lower than levels reached post-infection		na	na	na	na
Gray (USA)	comparative cohort	Pregnant, lactating and nonpregnant vaccinated	Lactating N=31 Pfizer: n=16 (52%), Moderna: n =15 (48%) first dose given at mean gestational age of 23.2 weeks, 46% in 2nd trimester, 40% in 3rd trimester	UV NP	non-pregnant vaccinated (16) pregnant infected 4-12weeks prior (37)	na		na		na	y	2nd dose boosted maternal sera and breastmilk IgG but not IgA breastmilk titer		na	na	na	na

Juncker	single cohort	lactating, vaccinated	Pfizer N=26 One dose (n=6), Two doses (n=20) Timing: post delivery	NA	none/self	na	y	steep rise in IgG in first 2 weeks after D1 with continued rise. All participants showed seroconversio n after D1		na	y	high inter-individual variability in IGA response in human milk rise after D1, sustained until 3d after D2, then decline 2d after D2 most had milk conversion after D1, but only some show milk conversion after D2 spike- and RBD-specific IgG low after 1 dose in 1 mother (2 doses may be essential to optimize humoral immune transfer to the neonate)		na	na	na	na
Low 1 **(Singapore)**	comparative cohort	lactating vaccinated; no prior exposure to COVID-19, excluded autoimmune disease, current infection, cancer, current immunomodulator y medication	Pfizer Timing: mean 10 months post-partum (n= 10)	UV	convalescent (n=6) healthy moms (n=9)	na		na		na	y	strong IgA and IgG response at 3-7days after D2; higher than convalescent; no levels seen with health unvaccinated cohort minimal transfer of BNT162b2 mRNA in milk samples of vaccinated women		na	na	na	no serious adverse events noted during the 28-day study period none of the infants breastfed within 72 hours of vaccination had any adverse events
Low 2 **(Singapore)**	single cohort	lactating vaccinated and children	Pfizer Timing: post-delivery (n=88)	NA	none/self	na		na		na		na	y	no serious adverse event no adverse events in children	64.8% with pain/redness/swellin g at injection site	na	5/88 (5.7%) lymphadenopath y 3 (3.4%) mastitis none with change in milk supply 1 with bluish-green tinge

McLaurin-Jiang	cross-sectional survey	breastfeeding mothers who underwent vaccination at least 2 days prior to survey	Pfizer (n=2702) Moderna (n=1714) Timing: post delivery	NA	none	na		na		na		na	y	77 (1.7%) reported negative impact on breastfeeding post vaccination - fatigue, headache, muscle pain, injection site pain, fever, allergic reactions	na	na	na
Nir	comparative cohort	parturients	BNT162b2 Timing: All women in third trimester, mean age of 33.5+/-3 weeks; mean 21 days prior to delivery (n=64)	UV	had COVID during pregnancy (mean 92 days prior to delivery) (n=11)	na		na	y	cord blood: IgG titers higher in vaccinated (26.1 vs 20.2)	y	IgG higher in vaccinated (11.0 vs 4.9) good correlation between neonatal blood spot samples and breast milk samples		na	na	na	na
Perl	single cohort	vaccinated lactating	Pfizer Timing: post-delivery (n=84)	NA	none/self	na		na		na	y	increased IgA in first 2 weeks after D1 (61.8% positive), increased to 86% at week 1 pD2, and 65% positive at week6. igG antibodies increase at week 4 (91%), and increased to 97% at week 5 and 6	y	55.9% at D1, 61.9% at D2	local pain most common complaint	na	no mother had serious adverse event four infants developed fever after maternal vaccination
Schwartz	single cohort	vaccinated lactating women	Pfizer Timing: post-delivery (n=61)	NA	self	na	y	all were positive for IgG, 31.7 S/Co	y	IgG detected in 60% of infant saliva, but none in the dried blood spot	y	all were positive for IgG, 6.3 S/Co positive correlation of IgG between maternal serum and breastmilk samples secretory IgA found in 15% of breast milk		na	na	na	na

Selma-Royo (Spain)	single cohort	vaccinated lactating women	Pfizer (n=30) Moderna (n=21) Astra Zeneca (n=24) Timing: post delivery	NA	none/ self-compared across vaccines	na		na		na	y	strong reactivity for IgG and IgA after vaccination , especially after D2 IgG levels higher than convalescent group IgA levels lower than convalescent group higher levels of IgG and IgA after first dose with mRNA vaccines vs AZ, no diff between Pfizer and Moderna except for higher IgA with Moderna		na	na	na	more adverse events in those vaccinated with AZ compared to mRNA vaccine 4 infants developed fever after maternal vaccination no serious adverse events
Valcarce	single cohort	lactating healthcare workers; no history of COVID,	Pfizer (n=14) Moderna (n=7) Timing: post-delivery (N=21)	NA	none/self	na		na		na	y	IgA significantly increased in milk (85% positivity) and correlated with maternal serum Same with IgG. Concentration of IgA higher than IgG		na	na	na	na

Appendix 3. Risk of Bias Assessment

STUDY ID	STUDY DESIGN	RANDOMIZATION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS	BLINDING OF INVESTIGATORS	BLINDING OF ASSESSORS	MISSING OUTCOMES/ FOLLOW UP	SELECTIVE REPORTING	AGE			COMORBIDITIES			EXPOSURE RISK			OVERALL RISK for CONTROL FOR CONFOUNDERS	OVERALL RISK OF BIAS
									A	B	C	A	B	C	A	B	C		
PREGNANT WOMEN REVIEW																			
Atyeo	comparative cohort	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	Y	U	Y	N	U	N	N	U	N	HIGH	SERIOUS
Atyeo2	comparative cohort	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	Y	Y	NA	Y	Y	NA	N	U	N	LOW	SERIOUS
Beharier	comparative cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	Y	N	N	Y	Y	NA	N	U	N	HIGH	SERIOUS
Bleicher	comparative cohort	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	Y	N	N	Y	Y	NA	Y	N	N	HIGH	SERIOUS
Butt	TNCC	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	Y	Y	Y	N	U	N	N	U	N	HIGH	SERIOUS
Collier	Comparative Cohort	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	Y	Y	NA	N	U	N	N	U	N	HIGH	SERIOUS
Dagan	Matched cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	Y	Y	Y	Y	Y	Y	Y	Y	Y	LOW	SERIOUS
Gray	comparative cohort	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	Y	N	N	Y	N	N	N	U	N	HIGH	SERIOUS
Kadali	cross sectional	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	N	U	N	N	U	N	N	U	N	HIGH	SERIOUS
Mithal	single cohort	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SERIOUS
Nir	comparative cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	Y	Y	NA	Y	Y	NA	N	U	N	LOW	SERIOUS
Peretz	comparative cohort	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	Y	N	N	Y	Y	NA	N	U	N	LOW	SERIOUS
Prabhu	single cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SERIOUS
Rotteinstrech	single cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SERIOUS
Rottenstreich2	comparative cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	Y	Y	NA	N	U	N	N	U	N	HIGH	SERIOUS
Shanes	comparative cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	Y	Y	NA	N	U	N	N	U	N	HIGH	SERIOUS
Shimabukuro	crossectional	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SERIOUS
Shook	comparative cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	Y	Y	NA	NA	NA	NA	NA	NA	NA	NA	SERIOUS
Theiler	comparative cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	Y	N	N	N	U	N	N	U	N	HIGH	SERIOUS
Trostle	crosssectional	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SERIOUS
Wainstock1	Case control	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	Y	U	Y	Y	U	Y	Y	U	Y	LOW	SERIOUS
Wainstock2	comparative cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	Y	N	Y	N	U	N	N	U	N	HIGH	SERIOUS
Zauche	cross sectional /	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SERIOUS
Zdanowski	single cohort	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SERIOUS
LACTATING WOMEN REVIEW																			
Atyeo	comparative cohort	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	Y	U	Y	N	U	N	N	U	N	HIGH	SERIOUS
Bertrand	Comparative cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	Y	N	N	N	U	N	N	U	N	HIGH	SERIOUS
Callil	Single cohort	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SERIOUS
Charepe	comparative cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	Y	Y	NA	Y	Y	NA	Y	Y	NA	LOW	SERIOUS
Collier	Comparative Cohort	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	Y	Y	NA	N	U	N	N	U	N	HIGH	SERIOUS
Esteve-Palau	Single cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SERIOUS
Fox	Single cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SERIOUS
Friedman	Single cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SERIOUS
Golan	Comparative cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	N	U	N	N	U	N	N	U	N	HIGH	SERIOUS
Gray	comparative cohort	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	Y	N	N	Y	N	N	N	U	N	HIGH	SERIOUS
Juncker	single cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SERIOUS
Low 1	comparative cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	N	U	N	N	U	N	N	U	N	HIGH	SERIOUS
Low 2	single cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SERIOUS
McLaurin-Jiang	crosssectional	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SERIOUS
Nir	comparative cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	Y	Y	NA	Y	Y	NA	N	U	N	LOW	SERIOUS
Perl	single cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SERIOUS
Schwartz	single cohort	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SERIOUS
Selma-Royo	single cohort	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SERIOUS
Valcarce	single cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SERIOUS

HIGH	UNCLEAR	LOW	NA

Y	Yes	N	No	U	Unclear	NA

Appendix 4. Summary of Findings Table of Efficacy and Safety Outcomes, Pregnant women

A. Efficacy outcomes

Efficacy Outcome	N Study Design	Quality Assessment					Summary of Findings			Certainty
		Risk of Bias	Incon-sistency	Indirect-ness	Impreci-sion	Overall Assess-ment	Vaccine	Control	Vaccine Efficacy (CI)	
1: COVID-19 infection / Breakthrough infection	4 OBS (2 TNCC 2 RC)	Serious (Observational, short ffup, uncontrolled confounders)	Not serious	Not serious	Not serious	Serious	VE COVID-19 infection: 96% (89-100) VE symptomatic COVID-19: 97% (91,100) VE hospitalization: 89% (43,100) OR COVID-19 infection: 4.5 (1.19-17.9) for unvaccinated Breakthrough infection during pregnancy: 0%			Low
2 : Maternal immunogenicity (humoral)	7 OBS	Serious (Observational, short ffup, uncontrolled confounders)	Not serious	Not serious	Not serious	Serious	Significant rise in IgA, IgG and NABs post-vaccination Higher antibody titers post vaccination versus previous infection Equivalent antibody titers between pregnant, nonpregnant and lactating vaccinees (with one study reporting lower titers in pregnant vs nonpregnant)			Low
3. Maternal immunogenicity (cellular)	1 OBS	Serious (Observational, short ffup, uncontrolled confounders)	Not serious	Not serious	Not serious	Serious	Similar T-cell response among pregnant and non-pregnant vaccinated women			
4. Neonatal immunogenicity	12 OBS	Serious (Observational, non-comparative)	Not serious	Not serious	Not serious	Serious	Evidence of placental transfer of maternal antibodies to fetus, titers correlated with maternal sera			Low

B. Safety outcomes

Safety Outcomes Outcome	N Study Design	Quality Assessment					Summary of Findings			Certainty
		Risk of Bias	Incon-sistency	Indirect-ness	Impreci-sion	Overall Assess-ment	Vaccine n/N (%)	Control n/N (%)	RR (95%CI)	
1: Maternal adverse reactions / adverse events	8 OBS	Serious (Observational, short ffup, uncontrolled confounders)	Serious (1 study with more local ARs in vaccinated pregnant vs nonpregnant)	Not serious	Not serious	Serious	Adverse reaction and event rates general similar to vaccinated non-pregnant women.			Low
2 : Pregnancy outcomes										
2a. PROM	0	Not reported	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed			na
2b. Intrauterine growth retardation	1 OBS	Serious (Observational)	Not assessed	Not serious	Not assessed	Serious	0.6%, not different from non-vaccinated group			Low
3. Delivery outcomes										
3a. Fetal Death in Utero/ Stillbirth	3 OBS	Serious (Observational, no control of confounders)	Not serious	Not serious	Not serious	Serious	0.1%; not different from published rates most studies reporting no stillbirths;			Low
3b. Preterm Delivery	3 OBS	Serious (Observational, no control of confounders)	Not serious	Not serious	Not serious	Serious	0-9.4%, no difference from non-vaccinated group or from published rates			Low
3c. Spontaneous abortion	5 OBS	Serious (Observational, no control of confounders)	Not serious	Not serious	Not serious	Serious	OR (vaccination in the previous 3 weeks) = 0.91, (95%CI 0.75, 1.10) OR (vaccination in the previous 5 weeks) = 0.81 (95%CI 0.69, 0.95) Risk for abortion from 6 to 19 weeks = 14.1% (95%CI 12.1 to 16.1%) No difference from published rates			Low
4. Neonatal outcomes										
4a. APGAR <7	1 OBS	Serious (Observational)	Not assessed	Not serious	Not assessed	Serious	No difference in incidence of APGAR<7 at 5 mins compared with unvaccinated			Low
4b. NICU admission	3	Serious	Not	Not	Serious	Serious	Reported rates : 1.5%, 4.5%, 15.5%			Low

	OBS	(Observational, non comparative)	serious	serious				
4c. Congenital anomaly	3 OBS	Serious (Observational, no control of confounders)	Not serious	Not serious	Not serious	Serious	Reported rates : 2.2%, 2.2%, 4.5% No difference from unvaccinated	Low

Appendix 5. Summary of Findings Table of Efficacy and Safety Outcomes, Lactating women

A. Efficacy outcomes

Efficacy Outcome	N Study Design	Quality Assessment					Summary of Findings			Certainty
		Risk of Bias	Incon-sistency	Indirect-ness	Impreci-sion	Overall Assess-ment	Vaccine n/N (%)	Control n/N (%)	Vaccine Efficacy (CI)	
1: COVID-19 infection / Breakthrough infection	0	Not reported	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed			na
2 : Maternal immunogenicity (humoral)	6 OBS	Serious (Observational, short ffup, uncontrolled confounders)	Not serious	Not serious	Not serious	Serious	IgG as dominant antibody in maternal sera with increasing levels over time; IgM and IgA detected at lower levels Similar antibody titers with vaccinated pregnant women after prime vaccine, antibodies increased more after booster dose versus pregnant women			Low
3. Maternal immunogenicity (cellular)	0	Not reported	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed			na
4. Breast milk antibody levels	13 OBS	Serious (Observational, short ffup, uncontrolled confounders)	Not serious	Not serious	Not serious	Serious	IgG as dominant antibody, positive correlation with maternal IgG serum levels and breastfeeding duration Varied IgA levels: 3 studies showed low levels, 1 study with no difference between vaccinated and infected, 2 studies with higher levels post vaccination and increasing trend			Low
5. Neonatal immunogenicity	2 OBS	Serious (Observational, short ffup, uncontrolled confounders)	Not serious	Not serious	Not serious	Serious	IgG detected in neonatal blood spot and saliva among newborns of vaccinated mothers			Low

B. Safety outcomes

Safety Outcomes Outcome	N Study Design	Quality Assessment					Summary of Findings			Certainty
		Risk of Bias	Incon-sistency	Indirect-ness	Impreci-sion	Overall Assess-ment	Vaccine n/N (%)	Control n/N (%)	RR (95%CI)	
1: Maternal adverse reactions / adverse events	5 OBS	Serious (Observational, short ffup, uncontrolled confounders)	Not serious	Not serious	Not serious	Serious	No serious adverse events reported Pain at injection site as most common side effect Symptoms more common after second dose of mRNA vaccines; higher incidence of fever and headache in those given ChAdOx1 versus mRNA vaccines			Low
2 : Breastmilk changes	4 OBS	Serious (Observational, short ffup, uncontrolled confounders)	Not serious	Not serious	Not serious	Serious	No adverse events in either lactating mothers or infants breastfed post vaccination Reduced milk supply in a few cases but resolved in 72 hours			Low