Evaluation of safety concerns for COVID-19 immunization of pregnant women: A systematic review of emerging evidence

Hare Krishna
All India Institute of Medical Sciences - Jodhpur
Rohini Motwani
AIIMS Bibinagar: All India Institute of Medical Sciences - Bibinagar
Chiman Kumari
PGIMER: Post Graduate Institute of Medical Education and Research
Chetan Sahni
Banaras Hindu University Institute of Medical Sciences
Monika Ananat
All India Institute of Medical Sciences - Patna
Abhishek Mishra
Houston Methodist Research Institute
Maheswari Kulandhasamy
MAMC: Maulana Azad Medical College
Kavita Rana
Dhiti Life Pvt. Ltd, New Delhi
Ashutosh Kumar (drashutoshkumar@aiimspatna.org)
All India Institute of Medical Sciences - Patna https://orcid.org/0000-0003-1589-9568

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Abstract

Objectives

There is an urgent need to review the status of COVID-19 vaccine immunization in pregnant women globally so that the adverse outcomes may be prevented. In this study we performed a systematic review of the available literature to evaluate the probable outcomes of COVID-19 vaccination in pregnant women.

Methods

An electronic search was conducted over the period of 3 months (June 15-August 15, 2021). The original studies evaluating safety concerns in pregnant women for COVID-19 vaccination were included. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 guidelines were used for the collection of the data and reporting of the findings. The inclusion and exclusion criteria for the studies were determined based on 'PICO principle' (Population, Intervention, Comparator, and Outcome, Study design. Risk of bias assessment was done using National Institute of Health (NIH) tool for systematic reviews.

Results

COVID-19 vaccination in pregnant women was not associated with increased adverse effects or complications to the mother as well as developing fetus or newborn compared to non-vaccinated pregnant women. Vaccinated pregnant women showed a robust immune response against COVID-19 infection.

Conclusions

COVID-19 vaccination during pregnancy causes no significant health risks for the mother or developing fetus or newborn.

Significance

This study makes a systematic review of the emerging evidence in global population to assess the safety of the COVID-19 immunization in the pregnant women. Based on the analysis of available data we conclude that COVID-19 vaccination during pregnancy causes no significant health risks for the mother or developing fetus or newborn. The findings of the study will inform public health policy decisions regarding COVID-19 immunization at global scale.

1. Introduction

The subsequent waves of COVID-19, caused by new variants of SARS-CoV-2, have kept raging across the world. The vaccination for the COVID-19 is being ramped up globally in an attempt to stabilize the ongoing pandemic. Increasing number of studies established high efficacy of current COVID-19 vaccines in protection against infection and disease severity. However, as most of the clinical trials for COVID-19 vaccines excluded pregnant women in their study there is not enough data about the vaccination safety and risks in this crucial population.

Teratogenic effect of many drugs as well as viral infections, which can cross the placental barrier to enter into fetal circulation, may influence the fetus development is a well-recognized (Fig. 1) (Schoenwolf et al., 2021). Particularly during the first trimester, the period of early embryogenesis, the risks of the teratogenicity are higher (Schoenwolf et al., 2021). Moreover, m-RNA and nano-particles based novel approaches in COVID-19 vaccines, has added to the apprehension of health policymakers, as their impacts on developing fetus are currently unknown. On the other hand, COVID-19 infection has some proven risks for pregnant women and their unborn babies. Pregnancy is an important risk factor for developing severe illness in COVID-19 infected women (Martinez-Portilla, 2021). Several researchers observed that hospitalization and maternal mortality in pregnant patients infected with COVID-19 were significantly higher in the comparison to women without COVID-19 (Jering et al., 2021; Lokken et al., 2021). Besides this pregnant women with COVID-19 have an increased risk of premature and/or low-birth weight infants, preeclampsia or eclampsia, postpartum haemorrhage, ICU admission, intrauterine/foetal distress, premature rupture of membranes, prolonged admission after birth, and complications requiring emergency caesarean delivery (Ahlberg et al., 2020; Akhtar et al., 2020; Gurol-Urganci et al., 2021; Handley et al., 2021; Hcini et al., 2021; Khalil et al., 2020; Lokken et al., 2021; Metz et al., 2021; Pineles et al., 2020; Stowe et al., 2021). The risk of neonatal adverse outcome, need for specialist neonatal care, and prolonged neonatal admission after birth were significantly higher in babies of mothers with SARS-CoV-2 infection (Gurol-Urganci et al., 2021). Intra-uterine fetal demises were more common in COVID-19 positive pregnant women in comparison to mother without COVID-19 (Hcini et al., 2021). Moreover, virus mediated inflammation and injury to placental tissue of infected mothers and vertical transmission of the COVID-19 infection from mother to fetus has been reported in multiple studies (both in utero, which is uncommon especially in third trimester, and peripartum(Baergen& Heller, 2020; Martinez-Portilla, 2021; Vivanti et al., 2020; Zhang & Zhang, 2021).

The emerging evidence does not indicate any significant harm to the pregnant women taking vaccination when compared to the unvaccinated, however, a clear view on this issue is lacking till date. In this article, we present a systematic review of the existing evidence from the human studies regarding safety concerns of COVID-19 vaccination in pregnancy.

2. Material And Methods

2.1 Objectives

To evaluate the probable outcome of COVID-19 vaccination in pregnant women for the development of evidence-based policy for the vaccination.

2.2 Information sources and search strategy

The online literature sources including PubMed/Medline (EBSCO & Ovid), EMBASE, Google Scholar, Science Direct, Scopus, Bio Medical and Web of Science (WoS) were searched using multiple combination of MeSH (Medical Subject Headings) and free keywords representing the components of the objective of the study such as ("COVID -19 VACCINE") OR ("COVID vaccine") OR ("SARS-COV-2 vaccine") AND ("Pregnancy") OR ("Pregnant women") OR ("Pregnancy outcome") OR ("Newborn"), ("COVID -19 vaccine"AND "Umbilical cord"), etc. Additionally, publication citations in original studies and review/commentary papers we searched for the original studies. Apart from these, technical reports and other papers from government agencies or scientific groups or committees addressing COVID-19 vaccination in pregnant women were searched. The studies published up to 15 August, 2021 were considered eligible for this study.

2.3 Protocol followed

A systematic review of the original studies about effect of COVID-19 vaccination on health of mother and fetus was performed following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Fig. S1). The inclusion and exclusion criteria for the inclusion of studies that met the objectives of this review were determined based on 'PICO principle' (Population, Intervention, Comparator, and Outcome, Study design) and are presented in Table S1.

2.4 Data selection, extraction, risk of bias assessment, and qualitative synthesis

Full articles reporting original clinical/epidemiological/case reports/ clinical trials/animal model studies were included in the study. A comprehensive literature search was performed to minimize the chances of publication bias. Assessments of the studies were performed in two steps. In first step, the titles and abstracts of citations were screened. The studies which did not meet the eligibility criteria were excluded at this step. Duplicates were also excluded. Studies that met the criteria at screening were included in second step and full text articles were assessed. Further the inclusion/exclusion eligibility criteria were applied to the full text articles and the studies only presenting relevant data were included for data extraction. No prioritization approach was adopted during search to prevent a selection bias. Citation details and abstracts of all retrieved studies were downloaded into Zotero bibliography manager for the record. The articles with only abstract, case reports, review and meta-analyses, and newsletters, and non-English language articles were excluded from the study. The original studies not providing effects in controls or having test groups with no statistical significance were also excluded from the study, however, no quantitative data analysis or further statistical testing were performed. Any study report currently available in preprint was peer reviewed by the authors before considering for inclusion. Risk of bias assessment for each included study was done independently by two authors using National Institute of Health (NIH) tool for systematic reviews and meta-analyses (Table S2). Two authors independently completed data collection while qualitative analysis was contributed and reviewed by all co-authors, and disagreements among the investigators were resolved by recheck for the errors (in the data collection and analysis process) and mutual discussions. Any study with odd results was discussed with all co-authors before its inclusion into the final analysis. The final inferences were made based on the qualitative synthesis from the collected data.

3. Results

Overall 2559 articles were identified using the relevant keywords and 7 articles from other sources. After exclusion of the duplicates, 1872 research articles were finalized for the screening, following which 1851 articles were excluded due to various reasons (contained no relevant data related to our study, or were perspective and commentary articles, etc.). Only 21 articles were found eligible for the final analysis based on the selection criteria (mentioned in the method section). Out of 21 studies, 19 studies were selected on the basis of availability of COVID-19 vaccine-related effect on mother and new-born outcome, antibody titers in mother and new-born related to human, and 2 studies were related to the effect of mRNA vaccination on implantation rates and embryological outcome during in-vitro fertilization. The findings of this review are being described below and key characteristics of the included studies have been provided in the tables (Tables 1-2).

3.1 Local and systemic reactogenicity in pregnant women

Pain (88.1-91.9%), soreness (57-88%), swelling (6.2- 11.9%), redness (3-5.4%), itching (1.5-5%), and rash (1-10.5%) at the injection site were the common local adverse reactions among vaccinated pregnant women after both vaccine doses, however, were more frequently reported after the second dose (Bookstein Peretz et al., 2021; Gray et al., 2021; Kadali et al., 2021; Shimabukuro et al., 2021)[Table 1 (k)]. Fatigue (29.6-71.5%), headache (18.1-55.4%), myalgia (11.6-54.1%),arthralgia (0.1-5.5%),nausea (6.7-29%), chills (4.1-47%), fever or felt feverish (4.2-52%) ,uterine contraction (1.2-8.9%), muscle spasm (3%) and paraesthesia (2.3-4.6%), axillary lymphedema (0.3-2.1%), stomach-ache (<0.1%) etc., were the common systemic adverse effects, which were more frequent after the second dose of vaccination (BooksteinPeretz et al., 2021; Collier et al., 2021; Goldshtein et al., 2021; Gray et al., 2021; Kadali et al., 2021; Shimabukuro et al., 2021)[Table 1 (k)]. About 0.5-1.5% of the participants after dose 1 and 8.0-9.0%of the participants after dose 2 of vaccination experienced temperature at or above 38°C(Bookstein Peretz et al., 2021; Shimabukuro et al., 2021)[Table 1 (k)]. Only 0.76% of pregnant women had a fever of 39°C and above, following 2nd dose of vaccination (Bookstein Peretz et al., 2021) [Table 1 (k)]. Overall the adverse local and systemic effects in pregnant women were similar to the non-pregnant women after vaccination. No serious adverse events were reported in all included studies, except in one case, the participant developed seizure attack, however the subject was a diagnosed case of a seizure disorder under treatment (Kadali et al., 2021)[Table1(k)].

3.2 Maternal and neonatal outcomes

The pregnancy outcomes following vaccination were reported as live birth (77.1-100%) (Beharier et al., 2021; Collier et al., 2021; Goldshtein et al., 2021; Kadali et al., 2021; Shimabukuro et al., 2021; Theiler et al., 2021)[Table 1 (c)], abortion (0.0-20.8%)(FDA, 2021a;Goldshtein et al., 2021; Head Zauche et al., 2021; Pfizer-BioNTech COVID-19 vaccine, 2021a; Regulatory Approval of Vaxzevria, 2021.; Shimabukuro et al., 2021)[Table 1 (d)], stillbirth (0.1-1.3%) (Goldshtein et

al., 2021; Shimabukuro et al., 2021)[Table 1(e)], premature rupture of membrane (PROM) (1.3-1.4%) (BooksteinPeretz et al., 2021; Shimabukuro et al., 2021) [Table 1 (f)], preterm birth (0.0-9.4%) (Beharier et al., 2021; BooksteinPeretz et al., 2021; Goldshtein et al., 2021;Gray et al., 2021; Kadali et al., 2021; Shimabukuro et al., 2021; Theiler et al., 2021)[Table 1 (g)], intrauterine growth retardation/ small for gestational age (IUGR/SGA) (0.5-7.9%) (Goldshtein et al., 2021; Shimabukuro et al., 2021; Theiler et al., 2021)[Table 1 (h)] congenital anomalies (0-2.2%)(Shimabukuro et al., 2021)[Table 1 (i)] and neonatal death (0-0.4%) (Bookstein Peretz et al., 2021; Shimabukuro et al., 2021)[Table 1 (j)].The mRNA COVID-19 vaccine during preconception or during pregnancy was not associated with an increased risk of spontaneous abortion compared to recognized pregnancies (Head Zauche et al., 2021). The incidences of pregnancy-related complications like a uterine contraction (1.2-8.9%) and vaginal bleeding (0.2-1.5%) were very low following vaccination (Bookstein Peretz et al., 2021; Shimabukuro et al., 2021) [Table 1 (k)]. The adverse outcome index (AOI) (the number of patients with one or more identified adverse events, divided by the total number of deliveries) was not affected by vaccination and was also insignificant (Theiler et al., 2021) [Table 1 (l)]. Further, the mode of delivery (caesarean section versus vaginal route) gestational age, thromboembolic events, and rates of gestational hypertensive disorders were similar in vaccinated and unvaccinated pregnant groups (Theiler et al., 2021) [Table 1 (l)]. Furthermore, preeclampsia (0.0-1.8%), postpartum haemorrhage (PPH) (10.5%), polyhydramnios (3.5%), oligohydramnios (1.8%), placental abruption (3.5%), NICU hospitalization (0.7-4.3%), need of supplemental oxygen/CPAP (7.7%), Transient tachypnea of the newborn (TTN) (7.7%) occurred following COVID-19 vaccination (Beharier et al., 2021; Bookstein Peretz et al., 2021; Gray et al., 2021; Theiler et al., 2021)[Table 1 (l)]. In overall, COVID-19 vaccination in pregnant women was not associated with any severe adverse effects or increased pregnancy or delivery related complications in comparison to unvaccinated pregnant women.

3.3 Maternal immunogenic response (antibody) & placental antibody transfer

Vaccination induced IgG, or IgM, or both antibodies were detected respectively in 71-100%, 30-56% and 16% of the pregnant mother, whereas 13% mother had neither IgG nor IgM (Mithal et al., 2021; Prabhu et al., 2021; Rottenstreich et al., 2021)[Table 2 (d)]. Vaccinated pregnant women showed a robust immunological response in comparison to COVID-19 infection(Shanes et al., 2021).IgG (subpopulation IgG1,IgG2, IgG3), IgM, IgA antibodies against spike protein (S1 and S2), receptor binding domain (RBD), pseudovirus neutralizing antibodies (NT50), FcR binding antibodies were found in the maternal serum following COVID-19 vaccination (Atyeo et al.,2021;Beharier et al., 2021; Collier et al., 2021; Gray et al., 2021; Rottenstreich et al., 2021)[Table 2 (d)]. After 4 weeks of 1st dose, IgG antibodies were detected in blood of all the pregnant women and cord of newborns with rare exceptions (Prabhu et al., 2021). The earliest detection of antibodies after first dose of vaccination occurred in 5 days in the mothers and after 16 days in the cord blood of the newborns. Maternal IgG level were progressively increased, starting 2 weeks after 1st dose as well as 1-2 weeks after 2nd dose ($p=0.05$ & $p=0.019$ respectively)(Prabhu et al., 2021) [Table 2 (i)]. IgG was detected in 89-99% and 44% of the tested cord blood samples of the newborns to the mothers who received two doses and single dose respectively, but none of them had detectable IgM (Prabhu et al., 2021)[Table 2(e)]. IgG, IgG3 antibodies against spike protein, viral RBD, pseudovirus neutralizing antibodies (NT50), FcR binding antibodies were found frequently in the cord blood samples following maternal vaccination [Table 2 (e)].

Maternal to cord antibody transfer was noted in multiple studies (Mithal et al., 2021; Rottenstreich et al., 2021; Zdanowski & Waśniewski, 2021)[Table 2 (h)]. Placental transfer ratio (cord: maternal) of antibodies correlated with number of weeks elapsed since maternal 2nd dose of vaccine (Mithal et al., 2021)[Table 2 (i)]. An increased latency from vaccination to delivery (weeks) was associated with an increased transfer ratio and increased infant IgG levels (Mithal et al., 2021). Second vaccine dose before delivery was significantly correlated with increased infant IgG levels (Mithal et al., 2021; Zdanowski & Waśniewski, 2021) [Table 1(i)]. SARS-CoV-2 anti-S and anti-RBD-specific IgG levels and IgG against all the analysed antigens except N antigens in maternal sera were positively correlated to their respective concentrations in the cord blood (Beharier et al., 2021; Rottenstreich et al., 2021; Zdanowski & Waśniewski, 2021). SARS-CoV-2 anti-S and anti-RBD-specific IgG titers in cord blood were directly correlated with the total duration of time since the first mRNA vaccine dose (Mithal et al., 2021; Rottenstreich et al., 2021; Zdanowski & Waśniewski, 2021)[Table 2 (i)]. Notably, in two studies the pregnant women had significantly lower SARS CoV-2 IgG levels and IgG subclass in maternal serum compared to the non-pregnant women (Atyeo et al., 2021; Bookstein Peretz et al., 2021).

3.4 Placental changes in vaccinated group

There were no increased incidences of decidualarteriopathy, fetal vascular malperfusion, chronic villitis, or histiocyticintervillositis in COVID-19 vaccinated group compared to unvaccinated control group. Incidence of high-grade chronic villitis was higher in the control group than in the vaccinated group (Shanes et al., 2021).

3.5 Effect of COVID-19 vaccination on In-vitro Fertilization (IVF)

The vaccinated individuals had similar implantation rates as the SARS-CoV-2 seropositive and seronegative pregnant women and the rates were consistent with pre-pandemic rates (Morris, 2021). Further, there were no differences in the vaccinated and control groups between the cycles in the length of ovarian stimulation (OS), total dose of gonadotropin used, peak estradiol and progesterone levels, number of oocytes and mature oocytes retrieved, and fertilization rate (Orvieto et al., 2021).

3.6 Vaccine effectiveness against COVID-19 infection

Vaccine effectiveness (VE) of the BNT162b2 mRNA COVID-19 vaccine against COVID-19 infection in pregnant women was noted to be 67% in 14–20 days, 71% in 21 – 27 days following the first dose, and96% in 7–56 days following the second dose of vaccination dose (Dagan et al., 2021). The estimated VE for symptomatic infection was 66% in days 14–20 following the first dose, 76% in days 21 – 17 following the first dose, and 97% in 7–56 days following the second dose.VE for COVID-19 related hospitalization was 89% in 7–56 days following the second dose (Dagan et al., 2021). 28 days after vaccination, the incidences of COVID-19 infection were noted 0.13% in vaccinated and 0.61% in unvaccinated pregnant women, respectively (Goldshtein et al., 2021). However, after 77 days post-vaccination, the incidences were significantly low (1.2-1.42%) in the vaccinated group in comparison to the unvaccinated (2.16-11.27%) (Dagan et al., 2021; Theiler et al., 2021)[Table 1 (i), Table 2 (l)].There was a statistically significant hazard reduction among vaccinated group during 11 to 28 days or more after vaccination (Goldshtein et al., 2021)[Table 1(l)].

4. Discussion

COVID 19 vaccination in pregnant women has come forth as a pertinent public health issue that required immediate resolution. Pregnancy is a condition of unique immunological and physiological tolerance that makes women more susceptible to viral infection (Rac et al., 2019). Despite the fact that pregnant women should be included in clinical studies, the rapid progress COVID-19 vaccinations and its unpredictability of fetal consequences reasoned to exclude pregnant women from the trials, As a result, currently, there is very little evidence available on the safety and efficacy of COVD-19 vaccines in pregnant women, However, several international agencies and scientific bodies have recently acknowledged the potential risks with keeping the pregnant women out of the vaccine trials (Chervenak et al., 2021). Of note, the previous experiences with the vaccination of pregnant women in other RNA -virus caused diseases have been largely uneventful. No prior use of mRNA based vaccines and lack of experience with corona virus vaccination draw scepticism for its administration during pregnancy. However, keeping the pregnant population unvaccinated has posed a serious public health risk as the emerging evidence indicated that non-vaccinated pregnant mothers not only have increased risk of developing severe COVID-19 but there is also a considerable risk to their in utero babies (Beharier et al., 2021; Goldshtein et al., 2021; Theiler et al., 2021).

Vaccines are generally advised for pregnant women when the possible benefit surpasses the potential risk by significant margin. Theoretically, the possible conceivable risk to the fetus comes from the live vaccines, however, all the licensed vaccines against SARS-CoV-2 are not live except one (Brillo et al., 2021).The first COVID-19 vaccines to enter clinical trials were Pfizer-BioNTech COVID-19 Vaccine (BNT162b2) and Moderna COVID-19 Vaccine (mRNA1273), both based on messenger RNA (mRNA).These mRNA vaccines have previously been studied for other viruses such as cytomegalovirus, influenza, and Zika viruses (Pardi et al., 2018).The first Emergency Use Authorization (EUA) for Pfizer-mRNA BioNTech's COVID-19 vaccine was issued by the U.S. Food and Drug Administration (FDA). This permitted the vaccine to be distributed nationally to people over the age of 16 years based on the safety and efficacy data from their worldwide trial [U.S. Food and Drug Administration]. In India, based on the recommendations from National Technical Advisory Group on Immunization (NTAGI), Ministry of Health and Family welfare (MoHFW) has approved voluntary vaccination of pregnant womenafter being informed about the risks and benefits (MoHFW, 2021).

Various pre-clinical as well as clinical studies showed no significant harms of COVID-19 vaccination in pregnancy (Bookstein Peretz et al., 2021; Bowman et al., 2021; FDA, 2021a; FDA, 2021b; Goldshtein et al., 2021; Gray et al., 2021; Kadali et al., 2021; Pfizer-BioNTech COVID-19 vaccine, 2021a; Pfizer-BioNTech COVID-19 vaccine, 2021b.; Shanes et al., 2021; Shimabukuro et al., 2021; Theiler et al., 2021), however any systematic assessment of the impact of the COVID-19 vaccination in pregnant women is currently limited. In this systematic review we have assessed the emerging evidence in humans on adverse impacts of COVID-19 vaccination on the health of mother and in utero or newborn babies. Only a few vaccinations are currently accessible and being given to pregnant and nursing women, all of which have been manufactured by various manufacturers, details of which are in Table-3.

Our results bring forth multiple observations which may have significant impact on the deciding health policies regarding vaccination of the pregnant women. COVID-19 vaccination in pregnant women was not associated with any severe adverse effects and nor increased pregnancy or delivery related complications compared to non-vaccinated pregnant women, with a rare exception, where a participant developed seizure attack, however the subject was a diagnosed case of a seizure disorder and anticonvulsant level in blood was borderline low (Kadali et al., 2021).Vaccinated pregnant women showed a robust immunological response against COVID-19 infection. IgG antibodies were detected in blood of the pregnant women and umbilical cord blood samples from newborns with rare exceptions (Mithal et al., 2021; Prabhu et al., 2021). A significantly lower levels of IgG antibodies following vaccination in the pregnant women in comparison to the non-pregnant noted in two studies (Atyeo et al., 2021; Bookstein Peretz et al., 2021) couldn't be related to any adverse effects, however, needs further investigation through randomized clinical trials. There were no increased incidences of placental injuries in COVID-19 vaccinated group compared with unvaccinated control group. Furthermore, in cases of IVF, the vaccinated women had similar implantation rates as the SARS-CoV-2 seropositive and seronegative pregnant women and the rates were consistent with pre-pandemic rates. The vaccines were found equally effective in protecting against the severe COVID-19 in pregnant women compared to non-pregnant.

Risk of the teratogenicity on the developing fetus is a well-established fact with providing drugs to the pregnant woman, however, the known mechanism of action for the COVID-19 vaccines currently in practice, including m-RNA vaccines (Figs. 2-3), don't warn for any potential risk [Figure 2]. Our review of the emerging evidence, which did not find a significant increase in risk in the vaccinated in comparison to the unvaccinated further confirms this (Tables 1-2).

Limitations and strengths

There are multiple limitations in this systematic review; first, the numbers of the original studies testing safety of the COVID-19 vaccines in pregnant women have been limited. Second, the sample sizes of most of the included studies were small. Third, the available studies did not precisely identify the safest period for the COVID-19 vaccination in pregnancy. Notably, most of the studies involved vaccination of the participants in the third trimester despite the fact that the first trimester of pregnancy is the most vulnerable period for the fetal injuries (Schoenwolf, Bleyl, 2021) Fourth, for some studies matching of the controls for the demographic factors and health conditions were not adequately informed. Fifth and lastly, for the few studies method of assessment was survey based and hence the cases were not examined clinically, which may have missed some essential data. All these factors may have possible influence on the interpretation of the results included in the study.

Although, currently, original studies are limited, there has been a consensus across the studies that the COVID-19 vaccines have a protective role in the mother as well as baby against COVID-19 infection and developing severe disease, and no significant health risks are caused to the developing fetus. The evidence is continually emerging and results of the larger scale clinical trials in the pregnant women may further validate the safety of the COVID-19 vaccines, however, the indications from the currently available data are encouraging for the full-fledged vaccination in the pregnant women.

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Declarations

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Tables

Table 1: Effect of COIV- 19 vaccine in pregnancy on maternal and neonatal outcomes.

References	Type of Study	Total Pregnant Participated in study (a) Gp1	Control (b) Gp2	Live birth (c)	Abortion (d)	Stillbirth (e)	PROM (f)	Preterm birth (g)	IUGR/SGA (h)	Congenital Anomalies (i)	Neonatal Death (j)	Local & systemic adverse event in pregnant N (%) vs control N (%) (k)	Other finding like preeclampsia, gestational hy PPH
Shimabukuro et al., 2021	Surveillance based Cohort study	35,691 pregnant in V-safe Surveillance system who received mRNA vaccine (16982 pregnant=1st dose, 12273= 2nd dose) 3958 vaccinated pregnant enrolled for pregnancy & neonatal outcome 827 completed pregnancy] Periconception=92 (2.3%) 1st trimester (<14 week) =1132(28.6%) 2nd trimester (≤14 to <28 week) =1714(43.3%) 3rd trimester (≥28 week) =1019(25.7%) Missing data=1 (<0.1%)	Non pregnant Vaccinated 1st dose=10,09,602 2nd dose=6,23631	712 (86.1%)	104/827 (12.6%)	1/725 (0.1%) #	NA	60/636 (9.4%) &	23/724 (3.2%) $	16/724 (2.2%)	0	Pregnant 1st dose N=16982 & 2nd dose N=12273 vs non-pregnant 1st dose N=10,09,602 & 2nd dose N=6,23,631 Injection-site pain: 14962 (88.1%) & 11274 (91.9%) vs 8,38788 (83%) & 5,48,922 (88%) Injection site swelling: 1057(6.2%) & 1462 (11.9%) vs 1,30,439 (13%) & 1,27,354 (20.4%) Injection-site redness: 508 (3%) & 660 (5.4%) vs NA Injection-side itching: 260 (1.5%) vs 302 (2.5%) vs NA Fatigue: 5022 (29.6%) & 8772 (71.5%) vs 3,23,121 (32%) & 4,42,846 (71%) Headache: 3078 (18.1%) & 6800 (55.4%) vs 253231 (25%) &382607 (61%) Myalgia: 1962 (11.6%) & 6638 (54.1%) vs 215795 (21%) & 392014 (62%) Chills: 696 (4.1%) & 4502 (36.7%) vs 9,6632 (9.5%) & 2,88,645 (46%) Fever or felt feverish: 709 (4.2%) & 4242 (34.6%) vs 97736 (9.6%) &283109 (45%) Measured temperature ≥ 38°C: 92 (0.5%) & 979 (8%) vs NA Measured temperature ≥ 39°C: 8 (<0.05%) & 67 (0.5%) vs 2226 (0.2%) &12,045 (1.9%)	COVID -19 inf vaccination- I) ≤14 days af first dose of vaccination in 10 pregnant (10/3958=0.3 II) >14 days a first dose of vaccination in 12 (12/3958=

												Nausea: 1130 (6.7%) & 3265(26.6%) vs 75252 (7.4%) & 1,49,956 (24%) Joint pain: 551 (3.2%) & 3,318 (25.6%) vs 85,592 (8.4%) & 2,25,852 (36%)	
Shimabukuro TT et al., 2021@	Surveillance based Cohort study	221 pregnant persons First (0–13 weeks) = 81 (49.7%) Second (14–27 weeks) 53 (32.5%) Third (28+ weeks) 29 (17.8%)	NA	171 (77.3%)	46 (20.8%)	3 (1.3%)	3 (1.3%)	2 0.9%)	NA	0 (0%)	1 (0.4%)	Fatigue 44 (20%) Headache 43 (20%) Chills 30 (13.5%) Pain in extremity 27 (12%) Nausea 25 (11.3%) Pain 21 (9.5%) Fever 18 (8.1%) Injection site pain 17 (7%) Dizziness 17 (7%) Injection site erythema 11 (4%)	Vaginal bleed cases, Fetal hydrops Each one case calcified place leakage of am shortened cer gestational di pre-eclampsia irregular/pain contractions
Gray et al., 2021	Cohort study	84 pregnant (13 deliverd during study) GA at 1st dose =23.2 weeks (Mean)	16 non-pregnant received vaccine	13	NA	NA	NA	1 (7.7%)	0	NA	NA	First dose vaccine & Second dose (pregnant vs non-pregnant) Injection-site soreness: 73 (88%) & 44 (57%) vs 12 (75%) & 12 (75%) Injection site reaction or rash: 1 (1%) &1 (1%) vs 0 (0%) & 0 (0%) Headache: 7 (8%) &25 (32%) vs 5 (31%) & 6 (38%) Muscle aches: 2 (2%) &37 (48%) vs 2 (12%) & 7 (44%) Fatigue: 12 (14%) & 41(53%) vs 6 (38%) & 9 (56%) Fever or chills: 1 (1%) & 25 (32%) vs 1 (6%) &8 (50%)	Preeclampsia Supplemental oxygen/CPAP-TTN-1 (7.7%) Mode of deliv Vaginal 10 (7 Caesarean 3 (
Kadali et al., 2021	Cross-sectional study	38 pregnant received vaccine	991 non-pregnant received vaccine	38	NA	NA	NA	NA	NA	NA	NA	Pregnant vs non-pregnant Sore arm or pain: 37 (97%) vs 894 (90%) Itching: 2 (5%) vs 98 (10%) Muscle spasm: 1 (3%) vs 103 (10%) Fatigue: 22 (58%) vs 643 (65%)	NA

												Headache: 19 (50%) vs 519 (52%) Chills: 18 (47%) vs 424 (63%) Myalgia: 13 (34%) vs 488 (49%) Nausea: 11 (29%) vs 211 (21%) Fever: 6 (16%) vs 279 (28%) Rash: 4 (10.5%) vs 67 (6.7%) Seizure: 1 (2.63%) vs 0 (0%) (p=0.0369), (history of seizure disorder & anticonvulsant level in blood was borderline low	
Goldshtein et al., 2021	Retrospective Study	7530 pregnant vaccinated (1387 reached at end of pregnancy)	7530 pregnant un vaccinated (1427 reached at end of pregnancy)	1386	128 (1.7%) in Gp1 vs 118 (1.6%) in Gp2	1 (<0.1%) in Gp1 vs 2 (< 0.1%) in Gp2	NA	77/1387 (6.6%) Gp1vs 85/1427 (6%) in Gp2	36 (0.5%) in Gp1 vs 38 (0.5%) In Gp2	NA		68 women vaccinated during pregnancy reported post-vaccinated adverse events Headache- 10 (0.1%) General weakness- 8 (0.1%) Stomachache- 5 (<0.1%) Dizziness- 4 (<0.1%) Rash -4 (<0.1%) Nonspecified pain – 6 (<0.1%)	Preeclampsia- in Gp1 vs 21 (Gp2 SARS-CoV-2 hospitalizatio in Gp1 vs 23 (0.3%) in G A statistically hazard reduct observed amo vaccinated gr 11 to 28 days post vaccinati In the initial 2 after vaccinati 46 infections observed in vaccinated an unvaccinated respectively.
BooksteinPeretz et al., 2021	Case- control Study	390 vaccinated pregnant included in study First dose vaccination 1st trimester=76 2nd trimester=193 3rd trimester=121	260 non-pregnant vaccinated	72 (57 had neonatal outcome data)	0	0	3 (1.6%)	0	3(5.3%)	NA	0	First dose & second dose (Pregnant vs non-pregnant) Local pain/swelling: 358 (91.8%) & 360 (92.4%) vs 250(96.2%) & 235 (90.4 %) Rash: 3 (0.8%) & 4 (1%) vs 2 (0.8%) &1 (0.4%) Fever>38°C : 6 (1.5%) & 35(9%) vs 1 (0.4%) & 26 (10%) Fever>39°C - 0 (0%) & 3 (0.76%) vs NA Severe fatigue: 100 (25.6%) & 220 (56.4%) vs 72 (27.7%) &154 (59.2%) Arthralgia: 4 (0.1%) & 16 (5.5%) vs	Preeclampsia- PPH-6 (10.5%) Polyhydramin Oligohydrami Placental abru (3.5%) Caesarean- 1(NICU for resp support- 2(3.5 Neonatal inva ventilation 2 (NICU hospital 2 (3.5%)

												10 (3.8%) & 56 (21.5%) Myalgia: 23 (5.9%) & 94 (24.1%) vs 50 (19.2%) &128 (49.2%) Paresthesia: 9 (2.3%) & 18 (4.6%) vs 4 (1.5%) & 3 (1.2%) Headache: 18 (4.6%) & 40 (10.25%) vs 45 (17.3%) & 127 (48.8%) Axillary lymphedema: 1 (0.3%) & 8(2.1%) vs 4 (1.5%) & 25 (9.6%) Contraction: 5 1.2%) & 26 (8.9%) vs NA Vaginal bleeding: 1 (0.2%) & 6 (1.5%) vs NA	
Theiler et al., 2021	Cohort	140 pregnant received vaccine GA at first vaccine dose (Median (IQR)) 32 (13.9-40.6) days	1650 unvaccinated uninfected pregnant 212 COVID 19 infection during pregnancy	142 (2 twins)		0		Gp1 vs Gp2 (<24 week to 36 & 6/7 week) 9.28 vs 8.5	11(7.9%) {<2500g} 3 (2.1 %) {,2500g}				Maternal & pr outcome (Vac Vs unvaccinat AOI- 7(5.0%) v (4.9%), p=0.9 Hypoxic, Ische Encephalopat (0.0%) vs 1 (0.1%), p-valu Uterine ruptu (0%) vs 1 (0%) Unplanned IC Admission- 1 ((0.1%), p= 0.195 Preeclampsia, 1 (0.7%) vs 23 p=1.00 Gestational Hypertension vs 225 (12.1% P=0.6038 NICU- 1 (0.7% 11(0.6%), p=0 5minute apga 3(2.1%) vs 38 0.7617 Mode of deliv Spontaneous 89(63.6%) vs (66.5%) Operative Vag (5%)vs 69 (3.7 Cesarean-44 (555 (29.8%) p=0.6517 Gestational ag

													37+- 127 (90.7 (91.5%) 32-36 6/7-10 (134 (7.2%) 24-31 6/7- 2 (1 (1.1%) <24- 1 (0.7%)\ p=0.7028 COVID 19 infe vaccinated gro significantly low 2*/140 (1. 210/1862 (11. [p=0.0004]
Collier et al., 2021	Cohort study	30 vaccinated pregnant (9 delivered during study) GA at 1st dose: <14 week =5 (17%) 14-28 week= 15 (50%) ≥28 week=10 (33%)	57 nonpregnant- (received vaccine) 22 infected unvaccinated pregnant	9								Pregnant vs Non-pregnant Fever after 1st dose; 0 (0%) vs 1 (2%) Fever after 2nd dose: 4 (14%) vs 27 (52%)	
Beharier et al., 2021	Cohort Study	86 vaccinated pregnant GA at first vaccine dose (Mean±SD) 34.5±7.5 weeks	62 unvaccinated noninfected 65 pregnant infected	86				4 (<37 week)					NICU -4 (4.3%
Head Zauche et al., 2021	Cohort study	2456 pregnant mRNA vaccine preconception or prior to 20 weeks' gestation	NA		Cumulative risk of SAB =14.1% (95% CI: 12.1, 16.1%) Compared to the recognized pregnancies, mRNA COVID-19 vaccine preconception or during pregnancy was not associated with an increased risk.								
Pfizer/BioNTech COVID-19 vaccine , 2021a	Vaccine Trial	12 accidental pregnancy out of 18,860 participants vaccinated	11 accidental pregnancy in placebo out of 18846 unvaccinated	NA	0 (0%)								
FDA., 2021a	Vaccine Trial	6 accidental pregnancy out of 15181 participants vaccinated	7 accidental pregnancy out of 15170 participants unvaccinated	NA	0 (0%)								
Regulatory approval of	Vaccine Trial	12 accidental pregnancy out of	9 accidental pregnancy out	NA	2 (17%)								

Vaxzevria., 2021		5807 Participant vaccinated	of 5829 Participant unvaccinated										

Gp- Group

PROM- Prerupture of membrane

IUGR- Intra uterine growth retardation

SGA- Small for gestational age

NA- Not available any data in article

The denominator consists of live born infants and stillbirth

&The denominator consists of only women vaccinated before 37 weeks of gestation

$ The denominator consists of 12 sets of twins

@ Adverse event finding on the VAERS (Vaccine Adverse Event Reporting System)

*- 2 Infections occurred prior to first dose of vaccine

GA-Gestational age

PPH- postpartum hemorrhage

NICU- Neonatal intensive care unit

TTN- Transient tachypnea of the newborn

AOI -Adverse Outcomes Index

SAB- Spontaneous abortion (pregnancy loss occurring from 6 to < 20 weeks' gestation

Table 2.Effect of COVID- 19 vaccine in pregnancy on maternal antibody response and antibody transfer to neonates.

References	Type of Study	Total Pregnants Participated in study (a)	Control (b)	Live birth (c)	Ab in mother (d)	Ab in umbilical Cord/Infants (e)	Ab in control (f)	Ab in milk
Mithal et al., 2021	Prospective Case Series	27 (22 pregnant -2 doses of mRNA vaccine) GA at first vaccine dose (Mean±SD) 33±2 weeks	0	28 (1 twin)	26 mother (96%)- IgG 15 mother (56%)- IgM	25 (89%) Infants IgG^ 0 infant- IgM		NA
Rottenstreich et al., 2021	Cohort Study	20 pregnant Vaccinated Median time lapsed 1st vaccine to delivery interval (Median 33(IQR 30-37 days) 2nd dose until delivery 11(IQR (9-15 days)	0	20	Anti-S IgG: 319 (IQR 211-1033) AU/mL Anti-RBD-Specific IgG: 11,150 (IQR 6154-17,575) AU/mL IgG in 20 (100%) IgM in 6 (30%)	Anti-S IgG (median : 193 (IQR 111-260) AU/mL Anti-RBD-specific IgG (median : 3494 (IQR 1817-6163) AU/Ml IgG in all, No IgM in any infants	NA	NA
Prabhuet al., 2021	Cohort Study	122 (67 -2 doses, 55-One dose of mRNA vaccine	0	122	87(71%)- only IgG 19 (16%)- both IgG +IgM 16- none £	Received 2 doses 65/67 (99%) of cord –IgG antibody Received one dose only 24/55 (44%) -IgG antibody	NA	NA

Shanes et al., 2021	Cohort Study	84 pregnant received vaccine 1st vaccine to delivery interval (Mean±SD) 45.96±24.3 days	116 not vaccinated	84	Vaccinated RBD IgG: 22.8±14.5 ,(P value<.001) RBD IgM: 4.1±13.2,(P value=.001) in n=52 vaccine group	NA	Vaccinated RBD IgG: 0.04±0.05 ,(P value<.001) RBD IgM: 0.19±0.12,(P value=.001) in n=116 control group	NA
Atyeo et al., 2021	Cohort Study	84 vaccinated pregnant	31 lactating, 16 non-pregnant (Vaccinated)	NA	IgG antibodies IgG3, FcR binding antibody	IgG antibodies IgG3, FcR binding antibody	IgG antibodies FcR binding antibody	IgG antibodies Boosting resultedin high FcR binding antibody IgA & IgM
Zdanowski et al., 2021	Retrospective Study	16 GA at 1st dose 31.75 week (29-36 week) GA at 2nd dose 35.13	0	16	Mean anti-S IgG antibody= 984.37 U/mL (±689.4)	Mean anti-S IgG antibody 1026.51 U/mL (±769.25)	NA	NA

		week (32-40 weeks)						
Grayet al., 2021	Cohort Study	84 pregnant (13 delivered during study) GA at 1st dose =23.2 weeks (Mean)	16 nonpregnant	13	IgM, IgA, IgG antibody response to S, RBD, S1 & S2 segment of S= significant rise from V0-V1, with further rise of Ig G from V1-V2. Spike titers rose more rapidly than RBD. IgG response induced robustly after both dose in comparison to IgA & IgM which induced robustly after 1st dose	Anti-S, anti-RBD, IgG, Neutralizing antibody titer low in comparison to mother Significant improvement of transfer of Anti- S specific 1Gg1 but not Anti-RBD into cord with time from V2.	Higher level of IgG after boost	IgG1 RBD increased significan from V0-V But, Anti-RBD IgA& IgM not significan increased either dos
BooksteinPeretz et al., 2021	Observational Case- control Study	390 vaccinated pregnant included in study who returned digital questionnaire (Out of 539 recruited pregnant)	260 non-pregnant vaccinated	72 (57 completed second questionnaire	IgG = 27.03±10.72 (N=96 pregnant tested for IgG 2weeks to 2 month foolowing 2nd dose)	NA	IgG= 34.35±10.25 (n=96 non-pregnant)	NA
Collier et al., 2021	Cohort Study	30 vaccinated pregnant (9 delivered during study) GA at 1st dose: <14 week =5 (17%) 14-28 week= 15 (50%) ≥28 week=10 (33%)	16 nonlactating 57 nonpregnant&nonlactating (received vaccine) 22 infected unvaccinated pregnant	9	RBD IgG antibodies titer in pregnant =27601AU Median pseudovirus Neutralizing antibodies titer (NT50)=910AU after 2nd dose RBD IgG antibodies titer in pregnant =14953AU Median pseudovirus Neutralizing antibodies titerNT50=1016AU at delivery	RBD IgG antibodies titer=19873 Neutralizing antibodies titerNT50=324AU at delivery	RBD IgG antibodies titer in vaccinated nonpregnant=37839AU In lactating=23497 AU Median NT50 in nonpregnant =901AU Lactating=783AU after 2nd dose	Breast mil RBD IgG= AU, NT50 =75AU an IgA bindi antibodies AU
Beharier et al., 2021	Cohort Study	86 vaccinated pregnant GA at first vaccine dose	62 unvaccinated noninfected 65 pregnant infected	86	After 1st dose – rapid IgG antibodies response to S1,S2,	IgG for S1,S2,AND RBD after 1stdose	In infected pregnant gradual rise in IgG response (anti-S1, -S2,	

		(Mean±SD) 34.5±7.5 weeks			RBD but not N antigens After 2nd dose further rise in IgG response.	trailed after after the maternal IgG showing a marked response already by day 15 Further increase after 2nd dose	-RBD, and -N) during the first 45 days after infection	
Daganet al., 2021	Cohort Study	10861 pregnant vaccinated	10861 not vaccinated					

GA- Gestational age

^ 3 infants negative including twins whose mother receive 1st dose of vaccine 3 weeks before delivery

£ Mother receive 1 dose of vaccine 4 weeks before delivery

S- Spike

RBD- Receptor binding domain

V0- At the time of 1st vaccine dose /baseline

V1- At the time of 2nd dose/prime profile

V2- 2-6 week's following 2nd dose / boost profile

ADCP - Antibody-dependent cellular phagocytosis

ADNP- Antibody-dependent neutrophil phagocytosis

NA- Not available data in study

AU- Arbitrary unit

VE- Vaccine effectiveness

Table 3. Globally available COVID-19 vaccines, and their known outcomes in pregnant women.

Vaccine name	Vaccine developed by	Vaccine characteristics	No. of doses	Efficacy Based on Randomized Clinical Trial	Clinical trials and pregnancy	References
mRNA BNT162b2	Pfizer-BioNTech	Encodes a P2 mutant spike protein (PS 2) and is formulated as an RNA-lipid nanoparticle (LNP) of nucleoside-modified mRNA (modRNA	2	95%	• Pregnant and lactating mothers, and those planning for pregnancy were excluded. • As of November 14, 2020, there had been 23 pregnant mothers accidentally exposed (12 vaccination and 11 placebo).	World Health Organization, 2021a
mRNA-1273	Moderna and the Vaccine Research Center at the National Institute of Allergy and Infectious Diseases (NIAID) in the USA.	LNP-encapsulated mRNA vaccine expressing the prefusion-stabilized spike glycoprotein	2	94.5%	• Pregnant and lactating mothers, and those for pregnancy were excluded. • As of December 2, 2020, there had been 13 pregnant mothers accidentally exposed (6 vaccination and 7 placebo).	World Health Organization, 2021b
ChAdOx1-S [recombinant] vaccines	Oxford AstraZeneca AZD1222-Vaxzevria; Serum Institute India (SII) Covishield; and SK Bioscience	Adenovirus-vectored vaccine	2	63.1%	• Pregnant, breastfeeding, and those attempting pregnancy excluded. No data on unintended vaccination in pregnancy available at this time.	World Health Organization, 2021c
Jansen Ad26.COV2.S.	Janssen Pharmaceuticals	Recombinant, replication-incompetent adenovirus serotype 26 (Ad26) vector encoding a full-length and stabilized SARS-CoV-2 spike protein.	1	66.9	• Pregnant, lactating mothers and those planning for pregnancy were excluded from the study. At this point of time, there were no statistics available regarding inadvertent vaccination in pregnancy.	World Health Organization, 2021d

Figures

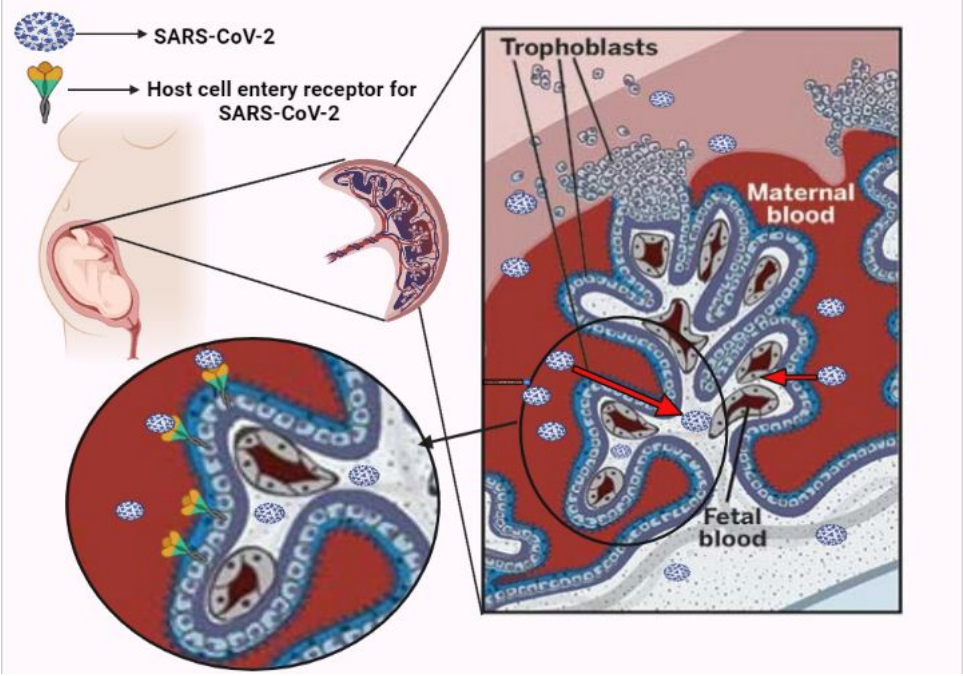

Figure 1

Schematic illustration of SARS CoV-2 infection of human placenta. The placenta uniquely contains maternal as well as fetal tissue components separated by an intricate septum known as 'placental barrier', which regulates maternal-fetal exchange of air, nutrients, and hormones. Multiple pathogens including some viruses circulating into the maternal blood are known to cross the tissue barrier and invade the fetal tissue. The SARS-CoV-2 entering into the blood vessels in the maternal component of the placenta (shown with larger arrow) can invade into the placental tissue—Trophoblasts , which is known to express viral host cell entry receptors, and further into the fetal tissue (shown with smaller arrow).

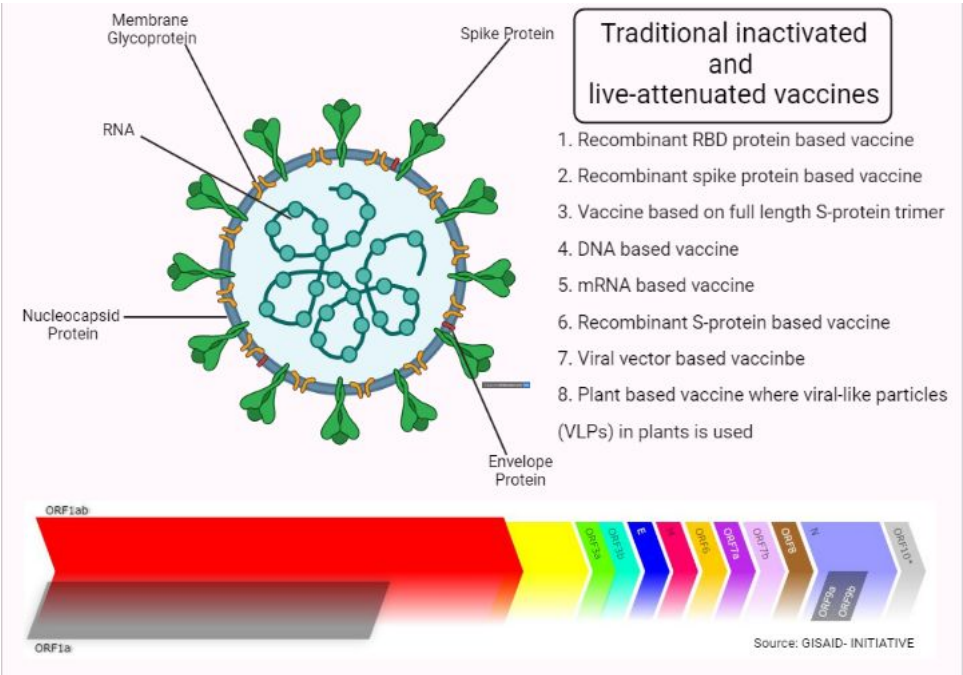

Figure 2

Schematic diagram of SARS-CoV-2 showing its structural proteins as target antigens for various vaccines. Most of the COVID-19 vaccines (1-8) are targeted to viral spike protein (S protein). The whole virion is used for the traditional inactivated vaccine, whereas various viral subunits are used for live attenuated vaccines.

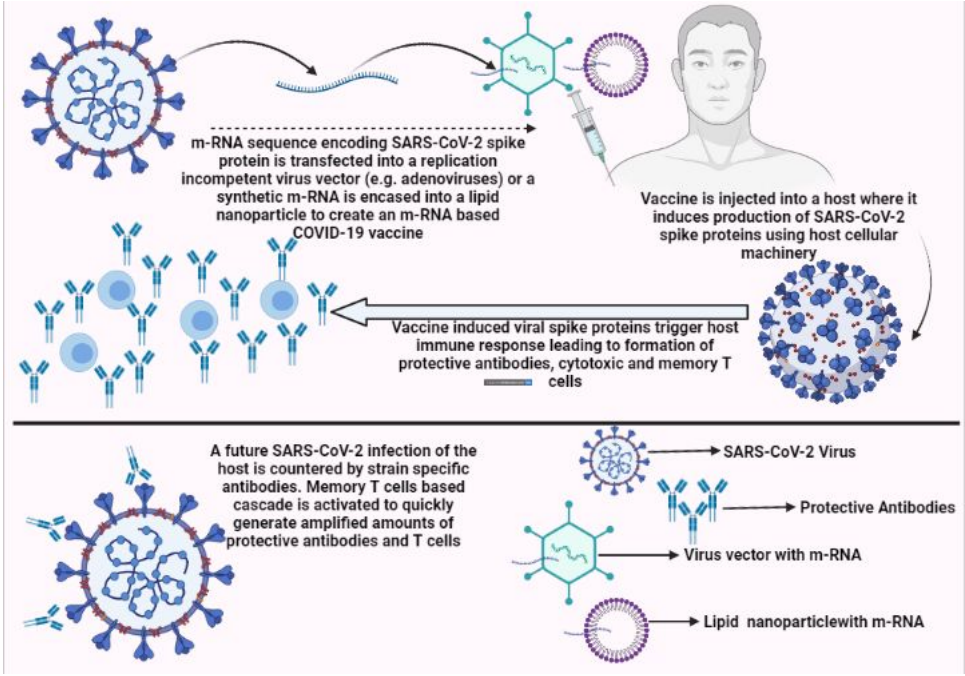

Figure 3

Schematic diagram showing mechanism of action of an m-RNA vaccine on the human body.

Supplementary Files

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- FigureS1.docx
- TableS1.docx
- TableS2.docx