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# Perspectives on administration of COVID-19 vaccine to pregnant and lactating women: a challenge for low- and middle-income countries

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Women who are in the pregnancy-puerperal cycle or are lactating have been deliberately excluded from participating in COVID-19 vaccine clinical trials that aimed to evaluate either the efficacy of the vaccines in inducing the formation of neutralizing antibodies or the investigational products' safety profile. The exclusion of pregnant and lactating women from such studies certainly and inequitably denies these women access to COVID-19 vaccines, since these products have become increasingly available to nonpregnant people and even to those who are pregnant and are in high-income settings. In this clinical opinion article, we discuss some aspects of the prolonged pandemic, the emergence of viral variants, the risks of severe complications of COVID-19 in pregnant women, and the disproportionate impact of the above on low- and middle-income countries. We argue that the decision to receive the COVID-19 vaccine should be a joint decision between the pregnant or lactating women and the healthcare providers, while considering the available data on vaccine efficacy, safety, the risks of SARS-CoV-2 infection in pregnant women, and the women's individual risks for infection and serious illness. The various types of vaccines that are already in use and their safety, effectiveness, and the potential risks and benefits of their administration to pregnant or lactating women are also reviewed.

**Key words:** breastfeeding, coronavirus disease, COVID-19, lactation, pregnancy, pregnancy complications, randomized trials, vaccine

## Introduction

Owing to the lack of specific treatments against COVID-19 and the low adherence to protective measures to prevent the spread of SARS-CoV-2, the pandemic continues to cause a large number of deaths worldwide. The SARS-CoV-2 is also mutating over time.[1] Owing to the failure of infection control measures to stop the spread of the virus,[2] vaccines have emerged as the best hope to control the pandemic, and this has been supported by the available evidence so far.[3–11]

Certain vulnerable groups have been identified as having a greater risk for developing severe COVID-19 and should be considered as a priority for vaccine administration. These include healthcare providers who work at the frontline, elderly people, and patients with heart and respiratory comorbidities, diabetes mellitus, obesity, neurologic diseases, and those who are immunosuppressed.[12] Physiological adaptations to the immune and cardiopulmonary systems imposed by the pregnancy, per se, predispose pregnant and postpartum women to an increased risk of developing serious complications from COVID-19.[13] In this clinical opinion article, we discuss the implications of excluding pregnant and lactating women from vaccine trials from a public health perspective, emphasizing its undesirable effects on low- and middle-income countries (LMIC) that are severely affected by the pandemic.

On the basis of nonmaleficence, women who are in the pregnancy-puerperal cycle or are lactating have been deliberately excluded from participating in COVID-19 vaccine clinical trials that aimed to evaluate either the efficacy of the vaccines in inducing the formation of neutralizing antibodies or the investigational products' safety profile.[14,15] The exclusion of pregnant and lactating women from randomized controlled trials certainly and inequitably denies these women access to COVID-19 vaccines, since these products became increasingly available to nonpregnant people and even to those during pregnancy in high-income settings. Although a few animal and human studies did assess pregnant individuals,[16–20] there is still a lack of robust evidence about the safety and effectiveness of the majority of the available vaccines in the pregnant population.[17]

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Secondary to these limitations, professional guidelines regarding vaccine administration to pregnant and lactating women are ambiguous, considering the maternal and perinatal risks of the disease and the theoretical risks of the vaccine.[21] Moreover, the lack of a clear policy to promote vaccination for these women may play an additional role in their limited access to these products in LMIC, where vaccine availability has been a major issue.

To determine whether vaccines should be administered to pregnant and lactating women, studies specifically targeting these groups are needed. Herein, we describe the prolonged pandemic, the emergence of viral variants, the higher risk of severe complications of COVID-19 in pregnant women, the disproportionate impact on LMIC, the risk of vertical transmission of SARS-CoV-2, and the perinatal prognosis of pregnancies complicated by COVID-19. Lastly, we briefly review the various types of vaccines already in use and their safety and effectiveness in the nonpregnant population. Given the recent approval and continued development of many different vaccines, more studies on this subject are warranted.

## General immunologic aspects of SARS-CoV-2 infection

Although the herd immunity effect, defined as a reduction in the spread of a disease secondary to large community-acquired immune protection caused by infection, was expected in some communities with high rates of SARS-CoV-2 infection early in the pandemic, it has not been consistently demonstrated yet. For example, during the first wave of the pandemic, in Manaus (capital of the state of Amazonas, Brazil), 75% of the population had serologically confirmed infection, whereas in São Paulo (capital of the state of São Paulo, Brazil), this rate was 25%.[22] However, during the second wave of the pandemic in Brazil, which is currently ongoing, the infection rates in Manaus are observed to be at least twice as high as in the first wave of the pandemic.[23] Therefore, even in locations where the infection rates were initially high, the current infection rates also remain high, meaning that no clear evidence of effective herd immunity has been observed.

In patients who have had SARS-CoV-2 infection, the duration of the production of neutralizing antibodies is variable; in some cases, it does not last for >90 days. This is mainly observed in asymptomatic individuals or in those with a mild form of the disease,[24] and it may become another factor contributing to the pandemic that is not under control after >1 year.

Being an RNA virus, SARS-CoV-2 can accumulate mutations over time during the pandemic.[25,26] Some of these mutations alter the pathophysiological characteristics of the virus, as demonstrated in the mutations identified in various parts of the world such as the United Kingdom, South Africa, and Brazil (David D. Ho, MD, unpublished material, 2021).[27,28] For some of the most widely studied mutations to date, the infection rate of the mutant virus is higher than that of the originally identified virus at the beginning of the pandemic. New mutant viruses have been shown to amplify the interface area of the receptor-binding domain of the angiotensin-converting enzyme 2 (ACE2) and the viral protein spike, thereby increasing the likelihood of infection.[29]

## SARS-CoV-2 infection in pregnant and lactating women

Cardiopulmonary and immune adaptations that occur during pregnancy alter the immune defenses against some forms of viral infection, thereby predisposing women to develop serious complications particularly in the case of respiratory viruses.[2,30,31]

Existing literature addressing the influence of SARS-CoV-2 infection on maternal outcomes was initially inconsistent. However, there currently seems to be a consensus that severe cases of COVID-19 are more common among pregnant women at a higher age strata and in those with comorbidities such as obesity, heart disease, asthma, and diabetes mellitus.[32−34] In addition, a higher rate of cesarean delivery is commonly reported for women with COVID-19 (odds ratio [OR], 3.0; 95% confidence interval [CI], 2.0−5.0), which is often indicated for severe complications related to this infection.[35]

Although some studies have not reported a worse prognosis among pregnant women than among nonpregnant women,[36,37] others have found the opposite results when considering the need for hospital admission,[38] admission to intensive care unit (ICU),[32,38−42] and evolving respiratory failure requiring invasive ventilation and extracorporeal membrane oxygenation (ECMO).[32,43] A study from the Centers for Disease Control and Prevention (CDC) including 23,434 pregnant women with symptomatic infection evaluated the severity parameters of COVID-19. The authors found increased risks of admission to ICU (adjusted risk ratio (aRR), 3.0; 95% CI, 2.6−3.4), mechanical ventilation (aRR, 2.9; 95% CI, 2.2−3.8), need for ECMO (aRR, 2.4; 95% CI, 1.5−4.0), and death (aRR, 1.7; 95% CI, 1.2−2.4) among pregnant women compared with nonpregnant women.[44] In a United States cohort, the COVID-19 case fatality rate in pregnant people was 13.6 times higher than in age-matched nonpregnant individuals with COVID-19.[38]

There are also many differences in COVID-19 pregnancy outcomes when considering the degree of economic development in certain countries, some of which are better equipped to deal with the pandemic and have more resources.[45] Brazil has the largest number of cases of maternal death resulting from infection by SARS-CoV-2.[46] Among all the causes of severe acute respiratory syndrome (SARS), SARS-CoV-2 infection is the most frequent during the third trimester and in the postpartum period in pregnant women, and it encompasses a worse disease prognosis in patients with concomitant diabetes mellitus, hypertension, and obesity.[34]

Information regarding pregnant women with COVID-19 shows a wide variation in the rates of perinatal complications compared with those in pregnant women without COVID-19, likely because of different sample sizes, differences in inclusion criteria and outcome

definitions, and possibly because of the variable impact of the pandemic on the different countries' health systems.[47] Even after considering these limitations, it appears that approximately 25% of pregnancies result in preterm births (OR, 3.0; 95% CI, 1.1−7.8), with an increased rate of neonatal ICU admission (odds ratio, 3.1; 95% CI, 2.0−4.7). Recent national reports,[48,49] multinational cohorts,[50] and systematic reviews[51] emphasized the increased incidence of preeclampsia, preterm birth, and stillbirth in pregnant women with SARS-CoV-2 infection, mainly for those with symptomatic and severe cases.[48,50] Preterm birth is the most important perinatal complication according to the majority of publications given its associated short- and long-term complications in the neonates.[32,48−50] According to the INTERCOVID cohort, the diagnosis of COVID-19 among pregnant women increased the severe neonatal morbidity index (RR, 2.7; 95% CI, 1.7−4.2) and the severe perinatal morbidity and mortality index (RR, 2.1; 95% CI, 1.7−2.8).[50] The association with increased low birthweight rates varied according to data in the literature from a OR of 9.0 (95% CI, 2.4−30.0)[35] to no difference from populational reports.[49] The World Association of Perinatal Medicine (WAPM) study of consecutive pregnant women with laboratory-confirmed COVID-19 from 25 different countries demonstrated rates of 2.3% spontaneous abortions; 2.3% fetal deaths (95% CI, 1.0%−4.8%); 2.0% neonatal deaths (95% CI, 0.9%−4.6%), and 4.2% perinatal mortality (95% CI, 2.3%−7.2%).[52,53] Chronic histiocytic intervillositis and syncytiotrophoblast necrosis were initially described in the placenta of patients with documented SARS-CoV-2 infection and could potentially be related to adverse pregnancy outcomes and transplacental fetal infection. However, the differences regarding placental pathology correlated with several underlying clinical obstetrical and fetal conditions were not observed between infected and noninfected women in recent publications.[54,55]

Studies have indicated that the rates of possible vertical transmission of SARS-CoV-2 are low.[20,56] Although the pooled rate of possible vertical transmission based on the case series, case-control studies, and the cohort studies was estimated to be 3.2%,[57] this figure falls to 0.9% when only the cohort studies are taken into consideration.[58] The potential reasons for the differences observed in these rates are different sample sizes, the time at which neonatal infection evaluations were carried out, and the differing criteria for the definition of vertical transmission among studies.[35] Although there are limited data on first and early second trimester maternal infection, no causality between SARS-CoV-2 and fetal malformations or clinical manifestations has been observed in infants, even in the rare cases when congenital infection is confirmed.[57] The absence of a typical neonatal clinically recognizable pattern emphasizes the importance of an almost exclusively oriented laboratory diagnosis.[59] However, the lack of universally accepted laboratory tests and the controversy regarding which perinatal biological samples should be required to substantiate the claim of vertical transmission have led to differences in the estimates of vertical transmission. Some authors consider only the positivity of a reverse transcriptase polymerase chain reaction (swab of the newborn's oropharynx, presence of the virus in the placenta, or presence of the virus in the amniotic fluid),[60] whereas others also consider immunoglobulin M (IgM) positivity in the newborn.[57,61,62] Although difficult to replicate in the majority of the settings, especially in LMIC, the best demonstration of a case of vertical transmission was described by Vivanti et al,[56] where reverse transcriptase polymerase chain reaction positivity was documented for antenatal and postnatal maternal (nasopharyngeal swab, vaginal swab, placenta, amniotic fluid, and blood) and neonatal (blood, nasopharyngeal, and rectal swabs) samples. Recognizing the limited evidence available, the World Health Organization has proposed the latest guidance for the definition and categorization of the timing of mother-to-child transmission of SARS-CoV-2 in an attempt to achieve standardized international consensus definitions.[63]

Although it is an uncommon event, the possibility of vertical transmission of SARS-CoV-2 makes it difficult to predict the future effects of the infection on the health of infected neonates. In addition, the pathophysiological mechanisms that increase the rates of prematurity, low birthweight, placental damage, and perinatal death are unknown. Because of these uncertainties for both the pregnant women and their children, the best option is prevention.

## Vaccines against SARS-CoV-2 infection

Vaccines against COVID-19 that are approved for use in humans or are in phase 3 trials and are available for clinical use can be classified into 3 different groups for didactic purposes based on the applied technology. The first group employs well-established strategies such as the use of inactivated viruses.[6] The second group includes technologically advanced vaccines that are mainly based on the induction of spike (S) protein synthesis using SARS-CoV-2 messenger RNA (mRNA) fragments. Lipid nanoparticles are used to carry these gene instructions to the ribosomes without entering the cell nucleus.[64] Protein S is responsible for the interaction of the virus with the ACE2 receptor of the host cell; when this antigen is exposed to the immune system, it triggers the immune response with the production of antibodies.[65] The third group of vaccines uses viral vectors to carry gene information to the cell nucleus; the vectors also express and control the production of protein S. Adenoviruses are the most widely used vectors. Their genetic material is removed so that they cannot replicate but are incorporated into double-stranded DNA sequences containing the protein coding information in the nucleus.[66]

The only antiviral vaccines that should not be used in pregnant women are those that use the attenuated live form of the disease vector, such as the vaccines against the measles and rubella

viruses. The use of such vaccines in pregnant women is authorized only in very special situations when the benefits clearly surpass the risks, such as when considering the use of yellow fever vaccine for patients who cannot avoid traveling to endemic areas.[67] Vaccines that are developed based on viral antigens that are inactivated by chemical or physical agents induce a less intense immune response than attenuated virus vaccines and can be used during pregnancy. The vaccines that are most frequently used in pregnant women and that are based on inactivated viruses are the vaccines for influenza (seasonal flu) and hepatitis A; these vaccines were approved for use during pregnancy several years ago. The vaccine against influenza is particularly important, and it has been expressly recommended for use in all women in the pregnancy-puerperal cycle.[68] The safety profile of these vaccines suggests that vaccines against SARS-CoV-2 infection employing inactivated viruses can be administered to pregnant and lactating women.[69,70] COVID-19 vaccines that use this technology are already being administered in several countries including China, India, and Brazil, among other LMIC.

The vaccine developed by Sinovac Biotech (CoronaVac, Sinopharm, Beijing, China) contains 600 standard units of inactivated SARS-CoV-2 virus antigen in each dose.[4] The recommended vaccination schedule is based on 2 doses administered 2 to 4 weeks apart.[3,71] This approach was reported to be 50.7% effective in preventing the spread of SARS-CoV-2 and from 83.7% to 100% effective in reducing moderate and severe disease, respectively.[4,72] There was a low rate of reported adverse effects, which mainly included pain at the administration site (77.1%). All serious adverse reactions were considered unrelated to vaccination.[72] In line with the US Food and Drug Administration (FDA) classification, the Brazilian version of this vaccine's information leaflet reports that animal reproduction studies have failed to demonstrate a risk to the fetus and that there are no adequate and well-controlled studies in pregnant women.[73]

Other vaccines using inactivated virus-based technology will complete phase 3 trials shortly. Data are available for the one currently being used in India. It is produced by Bharat Biotech/Indian Council of Medical Research (COVAXIN, Bharat Biotech, Hyderabad, Telangana, India; Indian Council of Medical Research, Ansari Nagar, New Delhi, India), and its vaccination schedule involves administering 2 intramuscular doses 4 weeks apart. The available phase 2 safety reports indicate that the product is safe, with a 10.3% rate of local and systemic adverse reactions without difference between study groups.[74] The first interim analysis of the phase 3 trial reported an effectiveness of 80.6% against polymerase-chain-reaction-confirmed symptomatic COVID-19.[75,76]

There are 2 mRNA vaccines that are currently being widely marketed. The vaccine produced by Pfizer/BioNTech (Comirnaty, BioNTech, Mainz, Germany; Pfizer, New York, NY) uses a vaccine schedule of 2 doses administered 3 weeks apart.[77] Each dose contains 30 $\mu$g of SARS-CoV-2 mRNA. The occurrence of mild adverse effects is higher in the vaccinated group than in the placebo group (27% and 12%, respectively), and the effects mainly involve local pain, fatigue, and headache; severe adverse effects are rare and are not different between the groups.[5] This vaccine has a high effectiveness rate of 95%.[5] However, a low temperature is required for its storage and transportation, as it must be stored frozen at −60°C to −90°C.[78]

The vaccine produced by Moderna (Moderna COVID-19 Vaccine, Moderna, Inc, Cambridge, MA) also uses technology based on the application of SARS-CoV-2 mRNA. As with previously described vaccines, preclinical rodent data were not conducted early enough to support the inclusion of pregnant women in the subsequent large-scale clinical trial. Hence, pregnant women were deliberately excluded from COVID-19 vaccination trials. These rodent data showed that the vaccine mRNA-1273, when administered at a dose of 100 $\mu$g before mating or during pregnancy, was not associated with adverse events.[16] The full vaccination course involves 2 doses given 4 weeks apart. Each dose contains 100 $\mu$g of COVID-19 mRNA. The occurrence of mild adverse effects is also high compared with the BioNTech vaccine, which mainly involve limited local reactions (84.2% vs 19.8% for Moderna and placebo groups) and grade 1 and 2 systemic (headache, fatigue, myalgia, and arthralgia) adverse events (79.4% vs 36.5% after the second dose); severe adverse effects are rare.[10] The reported effectiveness rate is high, reaching 94.1%.[10] This vaccine must be stored frozen at −25°C to −15°C.[78]

Among the vaccines that use viral vectors technology, the Oxford/AstraZeneca vaccine uses an adenovirus (AD) ChAdOx1 (acronym for Chimpanzee Adenovirus Oxford 1) from the chimpanzee as an antigen vector for the SARS-CoV-2 (Covishield, Oxford University, Oxford, United Kingdom; AstraZeneca, Södertälje, Sweden). Its effectiveness varies from 55.1% to 81.3% for second-dose administration intervals of <6 weeks or >12 weeks, respectively. Mild adverse effects such as local pain, headache, muscle pain, fever, and malaise are common, but similar to the placebo group, only 0.9% of the vaccinated individuals had serious adverse effects.[9] Recently, reports of the occurrence of rare central nervous system thrombosis and thrombocytopenia associated with positive antibodies to platelet factor 4, mainly in women under 30 years of age after ChAdOx1 vaccination, led some European countries to temporarily suspend its use or to recommend an alternative vaccine.[79−81]

The vaccine produced by the Gamaleya Research Institute (Sputnik V, Gamaleya Federal Research Center for Epidemiology and Microbiology, Moscow, Russia), which has a reported effectiveness of 91.6%, uses 2 ADs as vectors to carry gene instructions (double-stranded DNA) to the nucleus of the cell to produce S proteins. The complete vaccination schedule is 2 doses administered 3 weeks apart. The first dose uses AD26 as the vector, whereas the second uses AD5. This vaccine can

be stored in common refrigerators between 5°C and 8°C.[7] Adverse effects are mild (flu-like illness, injection site reactions, headache and asthenia) in 94% of cases, with more severe effects occurring only in 0.38% of cases.[7]

The vaccine produced by Janssen Pharmaceuticals (Adenovirus 26; Beerse, Belgium) has just completed phase 3 of evaluation. One of its advantages is that the vaccination schedule involves only 1 dose, with an effectiveness of around 66% against moderate to severe-critical COVID-19 and varying from 76.7% to 85.4% against severe-critical disease after 14 and 28 days of administration, respectively.[82] The storage temperature can vary between 2°C and 8°C using common refrigeration.[11] The most common adverse effects were local reaction (48.6%), headache (38.9%), fatigue (38.2%), myalgia (33.2%), and nausea (14.2%). Serious adverse events occurred in 0.4% of vaccine recipients, which was similar to the placebo group.[82] Similar to what happened with the adenovirus ChAdOx1 vaccine, reports of cerebral venous sinus thrombosis soon after administration led to a temporary interruption of Ad26.COV.2.S vaccination in the United States, suggesting that the rare occurrence of vaccine-induced immune thrombotic thrombocytopenia could have a relation to adenoviral vector vaccines, although there are structural differences between these products.[83,84]

## Vaccinating pregnant and lactating women

The promising results with vaccines against COVID-19 indicate that vaccination will be the main strategy for overcoming the pandemic.[2,85] However, there is still an ongoing debate regarding the use of vaccines in pregnant women, puerperal women, or lactating mothers,[86] which are populations at a high risk of developing serious disease.[44] Animal data are also limited, but mRNA-1273 vaccine administration to rodents before mating or during pregnancy was not associated with adverse outcomes.[16] Some COVID-19 mRNA vaccine trials had a few volunteers that became pregnant during the trial.[17] Recent studies of pregnant and lactating women vaccinated with mRNA vaccines showed similar humoral immunity compared with nonpregnant women and efficient maternal to neonatal transfer of antibodies against SARS-CoV-2,[18–20] but there is still a lack of robust evidence about safety and effectiveness from the majority of available vaccines in the pregnant population.[17] Pfizer/BioNTech are currently recruiting participants for a phase 2/3 trial to evaluate the safety, tolerability, and immunogenicity of their COVID-19 vaccine in adult pregnant women.

Given these results, some professional societies such as the American College of Obstetricians and Gynecologists (ACOG),[87] Society for Maternal-Fetal Medicine,[88] Royal College of Obstetricians and Gynaecologists (RCOG),[89] Brazilian Ministry of Health,[90] the International Foundation for Maternal, Periconceptional and Peri-Neonatal Medicine,[86] and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development[17] pointed out that pregnant and lactating women should be included in clinical trials to assess the efficacy and safety profile of the vaccines. They also recommended that, in the meanwhile, vaccines against COVID-19 should not be denied to pregnant or lactating women particularly if they are healthcare providers or have comorbidities. The statement by the International Federation of Gynecology and Obstetrics (FIGO)[91] is slightly clearer and considers that there are no risks—actual or theoretical—that would outweigh the potential benefits of vaccinating pregnant women. Therefore, FIGO supports offering COVID-19 vaccination to all suitable pregnant and lactating women. The vaccination program of the Israeli Ministry of Health is also very assertive in stating that COVID-19 vaccine should be administered to pregnant and lactating women.[92]

For lactating women who were also excluded from the clinical trials of COVID-19 vaccines, there are still no data on the excretion of these vaccines into the breast milk and no formal contraindications. SARS-CoV-2 RNA is rarely found in breast milk, and specific IgG and IgA antibodies are frequently found in high concentrations; this could help with the prevention or attenuation of neonatal infection.[93] Several countries (including the United Kingdom, Italy, and Brazil) and professional societies (such as FIGO and ACOG) have provided vaccination guidance for lactating women taking into account the regional differences regarding indication priorities and distribution issues.[86–92,94,95] In general, there is no contraindication for the vaccination of this population, and the interruption of breastfeeding is not indicated for women receiving the vaccine.[86–92,94,95]

These guidelines for vaccinating pregnant women and lactating mothers must be considered with precautionary measures while considering the ethical implications of denying access to resources such as the COVID-19 vaccine that can save lives.[96] Despite the noninclusion of pregnant and lactating women in randomized trials, a recent publication reported the preliminary findings of a registry that collected the safety information for mRNA COVID-19 vaccination in 35,691 pregnant women in the United States. The main results observed are that there are no obvious safety concerns among pregnant women who received mRNA vaccines mainly in the third gestational trimester.[97] Unfortunately, there are no such studies with inactivated and AD vector vaccines in pregnant and lactating women, but previous experience with inactivated vaccines for other pathogens probably attests the safety of this type of vaccine. For the AD vector vaccines, owing to the possibility of an idiosyncratic increase in the occurrence of serious central nervous system thrombotic events in young women, the RCOG recommends that pregnant women should be properly counseled and their choice of vaccine should be respected.[98,89] The Brazilian Ministry of Health has temporarily suspended the use of the Oxford/AstraZeneca vaccine in pregnant and lactating women after a serious adverse event postvaccination that culminated in maternal death by suspected thrombotic thrombocytopenic syndrome but has continued to

recommend vaccination with the other 2 available products (Sinovac Biotech's CoronaVac and Pfizer/BioNTech Comirnaty).[99] Therefore, the decision to receive the COVID-19 vaccine should be a joint decision between the pregnant, puerperal, and lactating women and the healthcare providers while considering the available data on vaccine efficacy, safety, the risks of SARS-CoV-2 infection in pregnant women, and the woman's individual risk for infection and serious illness.[43,100] At this moment, it seems reasonable to prioritize the vaccination of pregnant and lactating women using mRNA vaccines followed by inactivated viruses vaccines, according to the local availability. Additional information from clinical trials on vaccinated pregnant women will be critical for updating these guidelines.

## The disproportionate impact for low- and middle-income countries

In LMIC, the intrinsic economic, educational, and social deprivation exacerbate the severity of COVID-19 among pregnant women, which can be demonstrated by the following: (1) the increased challenges in accessing healthcare facilities because of COVID-19 restrictions, individual and governmental financial constraints; (2) the high rates of vaccination hesitancy by women of reproductive age; (3) the high number of deaths among pregnant and lactating women; (4) the occurrence and rapid spread of the mutant forms of SARS-CoV-2; (5) the slow implementation of the COVID-19 vaccination program across LMIC; (6) these countries' intrinsic difficulties in organizing the adequate storage and distribution of vaccines and supplies, and (7) the failure to prioritize pregnant women as a group at a higher risk of the most serious forms of COVID-19 in these settings. All these factors can be observed in varying degrees of intensity in the LMIC and deserve special attention.

Although the WHO classifies maternal antenatal, delivery, and postnatal care health services as essential to be continued during the COVID-19 pandemic, the access to care seems to be more profoundly affected in the LMIC. In Nigeria, a country that accounts for 25% of global maternal mortality, 43.5% of pregnant women reported at least 1 challenge in accessing the healthcare facilities, with close to one-third of women not being able to access these essential services at all because of the COVID-19 lockdown or transport restrictions.[101] In Ethiopia, maternal health service access was not achieved by 35.2% of the pregnant women, mainly the illiterate, the economically dependent, the mothers who had to travel >30 minutes to reach the health facility, and those who did not practice COVID-19 prevention measures.[102] In a district in India, there was an overall decrease of 2.3% in the number of institutional deliveries, a decrease of 22.9% in antenatal care, and a decrease of 20% in immunization services.[103] The distinct requirements for storage, transportation, and administration schemes among the different vaccines may also be a challenge in low-resource settings. Although a 1-dose regime (Janssen vaccine) could simplify the process, 2-dose schemes with different time intervals between doses and the mRNA vaccine requirement for a −70°C cold chain storage and transportation pose additional difficulties to many nonindustrialized tropical climate countries.[104] In addition, vaccination hesitancy has been amplified globally by circulating rumors regarding the association of COVID-19 vaccination with subfertility, pregnancy, and breastfeeding concerns in what might have a deeper impact in settings less prepared to promote concerted, multidisciplinary, and multistakeholder public health interventions.[105] These reinforce the necessity of policies in the LMIC to empower pregnant women, create awareness on COVID-19 preventive measures, and to facilitate access not only to maternal healthcare utilization but also to vaccination sites.[104] Recently, artificial intelligence and machine learning are being explored as tools to diminish health inequalities and to decrease the burden on the health systems in the LMIC. Deep-learning systems could also be utilized for studying viral components that could be utilized as antigens, accelerating traditional vaccine development and availability.[106]

Data from a recent meta-analysis on the global changes in antenatal and maternity care provision during the COVID-19 pandemic highlighted the clear changes in healthcare usage and provision and in the perinatal outcomes.[107] There was a marked reduction in antenatal care contacts, antenatal screening for infection and fetal anomaly, companionship in labor, and the postpartum length of hospital stay in most settings; there was also an obviously disproportionate increase in remote or virtual care provision between the high-income countries and the LMIC. Although, in high-income countries, antenatal care has incorporated a hybrid model to keep the previous number of contacts, in the LMIC, there was a dismal reduction in antenatal care attendance. All these changes may pose additional risks to pregnant people and their offspring and might be plausibly linked to the significant increase in maternal-fetal morbidity and mortality, COVID-19 related or not, in low-resource countries as a result of a fall in pregnancy care attendance during this period.[107]

Comparing the rates of COVID-19-related maternal death observed in LMIC with those observed in high-income settings, it is clear that they are objectively higher in the former countries[108] such as Brazil,[46] México,[109,110] and some Asian countries.[111] Because most of these data are derived from case series and reports, reliable maternal death rates are difficult to report. However, a mortality rate of 12.7% has already been reported for the Brazilian obstetrical population compared with 0.8% from the WAPM study, which was mainly composed of European countries.[46,108] In México, 31% of maternal mortality was because of respiratory causes in 2020, compared with 5% from 2011 to 2019. COVID-19 was the leading cause (202/934 deaths, 21.6%).[110] The Brazilian Obstetric Observatory on COVID-19 (Brazilian Ministry of Health) updates on a weekly basis the number of deaths of pregnant

and postpartum women because of COVID-19. Although, in 2020, there were 456 COVID-19–reported maternal deaths (an average of 10 deaths per week), from January 2021 to August 18, 2021 there were 1336 deaths (an average of 42 maternal deaths per week). Of note, 32% of these women did not have access to intensive care facilities and were not intubated, denoting real difficulties in accessing advanced life support resources in this country.[112]

The high rates of maternal mortality in these countries need to be faced without subterfuge, with a view to adopting measures such as vaccine prioritization, which can compensate the lack of infrastructure and proper care for these women. Fortunately, the Brazilian and Mexican governments recently launched a universal vaccination program for pregnant women.[99,110] In Israel, for instance, a retrospective cohort of pregnant women vaccinated with BNT162b2 mRNA compared with no vaccination reported an adjusted hazard ratio of 0.22 (95% CI, 0.11–0.43).[113] It is imperative to replicate the findings of this study with prospective design studies in the LMIC, where the benefits could be majored owing to all the previously discussed restraints.

## Concluding remarks

Lack of data on the efficacy and evaluation of the immune response of vaccines against SARS-CoV-2 does not justify a passive attitude toward the request of pregnant, puerperal, and lactating women to be vaccinated. Especially in the LMIC, where there is widespread transmission of SARS-CoV-2 and a lack of vaccine supply, it is important to recognize that women in the pregnancy-puerperal cycle are at an increased risk of severe COVID-19, and their offspring are at increased risk of the deleterious impact of preterm birth. This makes a strong case for primary prevention. Therefore, vaccination should be offered to all women in the pregnancy-puerperal cycle. For pregnant, puerperal, and lactating healthcare providers or those with risk comorbidities, a consensus will likely be reached that this group should be a priority for vaccination.[15,90,91] Notably, regardless of vaccination, pregnant women must maintain antenatal care and must be emphatically guided regarding the measures to reduce SARS-CoV-2 transmission, which include vigorous hand hygiene, social distancing, and wearing a mask.[114]

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