





## REVIEW

# A reasoned approach towards administering COVID-19 vaccines to pregnant women

Angsumita Pramanick<sup>1,2</sup>  | Abhiram Kanneganti<sup>1</sup> | Jing Lin Jeslyn Wong<sup>1,2</sup> | Sarah Weiling Li<sup>1,2</sup> | Pooja Sharma Dimri<sup>1</sup> | Aniza Puteri Mahyuddin<sup>2</sup>  | Sailesh Kumar<sup>3,4</sup> | Sebastian Enrique Illanes<sup>5</sup>  | Jerry Kok Yen Chan<sup>6,7</sup> | Lin Lin Su<sup>1,2</sup> | Arijit Biswas<sup>1,2</sup> | Paul Anantharajah Tambyah<sup>8</sup> | Ruby Yun-Ju Huang<sup>9</sup> | Citra Nurfarah Zaini Mattar<sup>1,2</sup> | Mahesh Choolani<sup>1,2</sup> 

<sup>1</sup>Department of Obstetrics and Gynaecology, National University Hospital Singapore, Singapore

<sup>2</sup>Department of Obstetrics and Gynaecology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

<sup>3</sup>Mater Research Institute-University of Queensland, South Brisbane, Queensland, Australia

<sup>4</sup>Faculty of Medicine, The University of Queensland, Herston, Queensland, Australia

<sup>5</sup>Department of Obstetrics & Gynaecology, Faculty of Medicine, Universidad de los Andes, Santiago, Chile

<sup>6</sup>Department of Reproductive Medicine, KK Women's and Children's Hospital, Singapore

<sup>7</sup>Academic Clinical Program in Obstetrics and Gynaecology, Duke-NUS Medical School, Singapore

<sup>8</sup>Infectious Diseases Translational Research Programme, Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

<sup>9</sup>School of Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan

**Correspondence**

Mahesh Choolani, Department of Obstetrics and Gynaecology, NUHS Tower Block, Level 12, 1E Kent Ridge Road, Singapore 119228. Email: [obgmac@nus.edu.sg](mailto:obgmac@nus.edu.sg)

**Abstract**

There are over 50 SARS-CoV-2 candidate vaccines undergoing Phase II and III clinical trials. Several vaccines have been approved by regulatory authorities and rolled out for use in different countries. Due to concerns of potential teratogenicity or adverse effect on maternal physiology, pregnancy has been a specific exclusion criterion for most vaccine trials with only two trials not excluding pregnant women. Thus, other than limited animal studies, gradually emerging development and reproductive toxicity data, and observational data from vaccine registries, there is a paucity of reliable information to guide recommendations for the safe vaccination of pregnant women. Pregnancy is a risk factor for severe COVID-19, especially in women with comorbidities, resulting in increased rates of preterm birth and maternal morbidity. We discuss the major SARS-CoV-2 vaccines, their mechanisms of action, efficacy, safety profile and possible benefits to the maternal-fetal dyad to create a rational approach towards maternal vaccination while anticipating and mitigating vaccine-related complications. Pregnant women with high exposure risks or co-morbidities predisposing to severe COVID-19 infection should be prioritised for vaccination. Those with risk factors for adverse effects should be counselled accordingly. It is essential to support patient autonomy by shared decision-making involving a risk-benefit discussion with the pregnant woman.

**Key points****What is already known about this topic?**

- COVID-19 infection in pregnancy leads to an increase in adverse maternal outcomes.
- Owing to paucity of data regarding SARS-CoV-2 vaccine use in pregnancy there is uncertainty regarding safety of use and subsequent pregnancy outcomes.

Angsumita Pramanick and Abhiram Kanneganti are co-first authors.

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**What does this study add?**

- Provides an overview of the available SARS-CoV-2 vaccines, their mechanisms of action and feasibility of use in pregnancy.
- Summarises recommendations regarding vaccination of pregnant or lactating women.

**1 | INTRODUCTION**

On 8th December, 2020, a 90-year-old woman in the United Kingdom was the first clinical recipient of a SARS-CoV-2 vaccine.<sup>1</sup> At the time of writing this article, almost 1.5 billion doses of SARS-CoV-2 vaccine have been administered. As much as globalisation has contributed to the rapid spread of COVID-19, with almost 130 million infected and three million lives lost, it has also promoted a high degree of international cooperation and collaboration in therapeutics and vaccine development. Emergency-use authorisation (EUA) and federal level investments in the United States of America (USA), European Union (EU), China and India have expedited development of the SARS-CoV-2 vaccine and implementation of global vaccination programs.<sup>2</sup>

**2 | PATHOPHYSIOLOGY AND IMMUNOLOGY OF SARS-COV-2 IN PREGNANCY**

SARS-CoV-2, like other human coronaviruses, consists of a single-stranded positive sense RNA genome encased in a helical nucleocapsid, with an outer envelope of four structural proteins: envelope (E), spike (S), membrane (M) and nucleocapsid (N) proteins. The S1 subunit of the S protein contains the receptor-binding domain (RBD) responsible for binding to host cell angiotensin converting enzyme-2 (ACE2), after being primed by the serine protease TMPRSS. High levels of neutralising antibody response against RBD-located epitopes<sup>6,7</sup> have been observed in convalescent individuals, correlating with CD4+ T cell response.<sup>8</sup> Convalescent plasma has, thus, been used for treatment<sup>9</sup> with variable results. Additionally, earlier work on SARS-CoV demonstrated the suitability of the spike protein as a target for vaccine development.<sup>10</sup> Like other vaccines, it is postulated that SARS-CoV-2 vaccine needs to elicit both antibody-mediated and T cell-mediated immunity for effective protection.<sup>5,10</sup>

The second trimester of pregnancy is characterised by an anti-inflammatory, T<sub>H</sub>2-biased microenvironment with increased immunoglobulin synthesis and decreased cell-mediated response to infection. This switches to a pro-inflammatory T<sub>H</sub>1-type response in the third trimester.<sup>11</sup> While the relationship between these immunological shifts in pregnancy and SARS-CoV-2 remains unclear, it may potentially exaggerate the 'cytokine storm' due to the strong T<sub>H</sub>1-polarised response to virus-linked programmed lytic cell death of infected cells that characterises severe SARS-CoV-2 infection.<sup>5</sup> This may explain the increased rates of intensive care admission, mechanical ventilation, and death among pregnant women with symptomatic COVID-19 infection,<sup>12,13</sup> especially during the third trimester. Pro-inflammatory

cytokines IL-1 $\beta$ , IL-2, IL-6, TNF and IFN $\gamma$  are released by cell-mediated pathways and the Toll-like receptors activation<sup>14,15</sup> at the maternal-fetal interface. These disrupt the protective anti-inflammatory milieu maintained at the maternal-fetal interface by decidual natural killer cells and T<sub>reg</sub> cells<sup>11,16,17</sup> and may contribute to the observed increased stillbirth and preterm delivery rates.<sup>18-21</sup>

Vertical transmission of SARS-CoV-2 has been extensively discussed.<sup>22-25</sup> While large observational studies report that 2.6%–5% of infants born to mothers with SARS-CoV-2 test positive,<sup>19,26,27</sup> only a few case reports<sup>28-31</sup> have provided evidence of congenital infection through isolating viral particles in fetal tissue not exposed to maternal fluids or tissue.<sup>32</sup> Both the ACE-2 receptor and TMPRSS2 serine protease are required for infection but placental expression of these is highly variable with few placental cells consistently co-expressing both throughout pregnancy.<sup>33-37</sup> Thus, it is biologically not surprising that vertical transmission rates are low.

Finally, SARS-CoV-2 IgG has been identified in offspring of serology positive mothers<sup>38,39</sup> and, together with IgM and IgA, has been found in breastmilk of mothers in active or convalescent phase of SARS-CoV-2 infection<sup>40-43</sup> with proof of specificity against the RBD.<sup>43,44</sup> However, the efficacy and duration of this protection remains to be assessed by longitudinal cohort studies.

**3 | COVID-19 VACCINES**

Vaccination in pregnancy has dual-fold benefit, protecting the mother through the induction of cell-mediated and humoral immunity, and passive protection of the offspring via transplacental transfer of maternal IgG. Recommendations regarding vaccines in pregnancy are summarised in Table 1. Most of the information regarding safety of inactivated vaccines in pregnancy comes from observational studies and historical data.<sup>45</sup> While live attenuated vaccines (LAV) are generally more immunogenic than inactivated vaccines,<sup>46</sup> they retain replication potential, may be trafficked transplacentally and are therefore relatively contraindicated in pregnancy. Reassuringly though, observational studies of women inadvertently vaccinated during early pregnancy with rubella, plio, yellow-fever and dengue LAV have not demonstrated an increased incidence of malformations, prematurity, stillbirth, neonatal death or miscarriage.<sup>47-50</sup> Smallpox<sup>51</sup> and anthrax<sup>52</sup> LAVs, however, have been associated with a small increase in malformations.

At the time of writing this paper, 50 SARS-CoV-2 vaccines, utilising both familiar and novel mechanisms, are either in Phase 2 or 3 clinical trials<sup>53,54</sup> (Table 2) or in clinical use. While it normally takes about 3 years for vaccines to complete Phase 3 trials, in the face of a

TABLE 1 Various vaccines and recommendations for use in pregnancy

Type	Examples	Recommendation for use in pregnancy
Inactivated	Inactivated influenza	Recommended in pregnancy.
	Inactivated polio	
	Hepatitis A	Use if high-risk of exposure and benefits outweigh risks of vaccination.
	Rabies <sup>a</sup>	
Peptide/toxoid	Diphtheria	Recommended in pregnancy.
	Tetanus	
	Acellular pertussis	
	Haemophilus influenza B	<ul style="list-style-type: none"> <li>• Generally safe.</li> <li>• Use if high-risk of exposure and benefits outweigh risks of vaccination.</li> </ul>
	Hepatitis B	
	Pneumococcal	
	Meningococcal	
	Typhoid vi capsular polysaccharide	
Live attenuated	Mumps, measles and rubella	<ul style="list-style-type: none"> <li>• Avoid in pregnancy.</li> <li>• Risks of complications in event of inadvertent vaccination is low.</li> </ul>
	Rotavirus	
	Varicella zoster	
	Smallpox <sup>a</sup>	
	Anthrax	
	Influenza	
	Oral polio	
	Live typhoid	
	Yellow fever	Consider if travel to endemic regions is unavoidable.
	Nucleic acid vaccines (DNA plasmid, mRNA)	Zika, HIV, SARS-CoV-1
SARS-CoV-2		<ul style="list-style-type: none"> <li>• Approved for emergency use in some countries.</li> <li>• Correlate with local guidelines.</li> </ul>
Viral vector	SARS-CoV-2	Under investigation.
	Ebola rVSV-ZEBOV	

<sup>a</sup>Should be given post-exposure.

pandemic, the USA's Food and Drug Administration (FDA) grants EUA following evaluation of Phase 3 safety data for at least 3000 vaccine recipients followed up for 2 months.<sup>55</sup> Table 3 summarises the characteristics of the five most widely used vaccines that have been approved in at least two or more countries.

The use of DNA- or RNA-based technology has contributed to the speed of vaccine production by being both quick to design and easy to manufacture.<sup>56,57</sup> Moderna and Pfizer-BioNTech mRNA-based vaccines were the first two COVID-19 vaccines to attain FDA EUA for administration in the USA and represent the first ever mRNA-based vaccines provisionally approved for clinical use. These novel vaccines with efficacies of almost 95% in Phase 3 trials<sup>58,59</sup> and above 85% in real-world cohort studies<sup>60-62</sup> and work by injecting mRNAs nucleosides coding for S Protein peptides, encased in transfection reagents such as lipid nanoparticles, that induce host

production of spike proteins peptides using the native cellular translation machinery. These spike proteins are expressed on the cellular surface, triggering the activation of cell-mediated and humoral immune systems and the creation of B memory cells which produce SARS-CoV-2-spike protein specific antibodies. The vaccine mRNA does not enter the nucleus or change host DNA,<sup>63</sup> are replication-deficient and have short lifespan characteristics, thus the likelihood of transplacental transfer of mRNA vaccine active compounds is low.<sup>57,64,65</sup>

Pfizer-BioNTech's BNT162b2's Phase 3 clinical trial data reports side-effects such as local injection-site reactions (66%–88%), and mild to moderate systemic events including fever, fatigue, headache, and musculoskeletal pain (less than 60%). Two deaths were reported in the intervention arm but were deemed unrelated.<sup>58</sup> The CDC has determined that anaphylaxis with the first dose of BNT162b2 and

TABLE 2 SARS-CoV-2 vaccines which have been approved for use or are in Phase 2 or 3 Trials (Updated 15th May 2021)

Phase 2	Phase 3
<i>Comirnaty</i> or <i>Tozinameran</i> (BNT162b2) - Pfizer & BioNTech (USA & Germany) – mRNA based# Δ	
AG0302-COVID19 - AnGes, Osaka University & Takara Bio (Japan)	
SCB-2019 + AS03 or CpG 1018 - Clover Biopharmaceuticals, GSK and Dynavax (PRC, UK and USA)	
GRAd-COV2 - ReiThera & Lazzaro Spallanzani National Institute for Infectious Diseases (Italy) – Simian adenovirus, non-replicating*	
ARCoV – Suzhou Abogen Biosciences, Walvax Biotechnology, Academy of Military Medical Science (PRC) – mRNA based	<i>Sputnik V</i> - Gamaleya Research Institute (Russia) – Adenovirus, non-replicating#
GLS-5310 - GeneOne Life Science (S. Korea) – DNA based§	<i>Ad26.COV2.S</i> - Beth Israel Deaconess Medical Center and Johnson & Johnson (USA) – Adenovirus, non-replicating#
ARCT-021 - Arcturus – Duke-NUS (Singapore & USA)	AZD1222 - University of Oxford and AstraZeneca (UK and Sweden) – Adenovirus, non-replicating# Δ
HGC019 - Gennova Biopharmaceuticals & HDT Bio (India & USA)	<i>ZyCoV-D</i> - ZyDus Cadila (India) – DNA Based†§
DS-5670 - Daiichi-Sankyo and University of Tokyo (Japan) – mRNA Based	<i>mRNA-1273</i> - Moderna (USA) – mRNA based#
MRT5500 – Sanofi and Translate Bio (France and USA) – mRNA Based	<i>CvCoV</i> - CureVac (Germany)
COVID-eVax – Takis Biotech and Rottapharm Biotech (Italy) – DNA Based	ZF2001 - Anhui Zhifei Longcom and Chinese Academy of Medical Sciences (PRC) † #
<i>GX-19</i> - Genexine (S. Korea) – DNA Based	<i>EpiVacCorona</i> - Vector Institute (Russia) #
<i>INO-4800</i> - Inovio (USA) – DNA Based§	<i>NVX-CoV2373</i> - Novavax (USA)
<i>rVSV-SARS-CoV-2-S</i> - Israel Institute for Biological Research (Israel) - vesicular stomatitis virus, replicating*	<i>Abdala</i> - Center for Genetic Engineering and Biotechnology of Cuba (Cuba)†
<i>MVC-COV1901</i> - Medigen & Dynavax (Taiwan & USA)	<i>SOBERANA 2</i> - Instituto Finlay De Vacunas (Cuba)*
<i>ABCov2</i> – Bavarian Nordic (EU) Δ	<i>CoVLP</i> - Medicago and GSK (Canada and UK)
<i>VBI-2902a</i> – VBI Vaccines (USA) – Virus-like protein	<i>BECOV2</i> - Baylor College of Medicine, Texas Children's Hospital, Dynavax & Biological E (USA & India)
<i>GBP510</i> - University of Washington, SK Bioscience, GSK (USA, S. Korea and UK) Δ	<i>VLA2001</i> – Valneva and Dynavax (France and USA)
<i>EuCorVac-19</i> - EuBiologics (S. Korea)	Shenzhen Kangtai Biological Products (PRC)
Shionogi, National Institute of Infectious Disease & Kyushu University (Japan) Δ	<i>BBIBP-CorV</i> - Sinopharm (PRC)#
<i>RBD SARS-CoV-2 HBsAg VLP vaccine</i> – SpyBiotech, Accelagen Ply & Serum Institute of India (UK, Australia & India)	<i>QazCovid-in</i> - Research Institute for Biological Safety Problems (Kazakhstan)
Zhongyianke Biotech, Liaoning Maokangyuan Biotech and Academy of Military Medical Sciences (PRC)	Sinopharm and Wuhan Institute of Biological Products (PRC) #
<i>RBD SF9</i> – West China Hospital and Sichuan University (PRC)	<i>CoronaVac</i> - Sinovac Biotech (PRC)#
<i>UB-612</i> - Vaxxinity (USA)	<i>Convidecia</i> - CanSino Biologics, Institute of Medical Biology at the Chinese Academy of Medical Sciences (PRC)* #
<i>VAT00002</i> - Sanofi and GSK (France & UK)	<i>Covaxin BBV152</i> - Indian Council of Medical Research, National Institute of Virology and Bharat Biotech (India) #
<i>Nanocovax</i> - Nanogen Biopharmaceutical (Vietnam)	
<i>CoviVac</i> - Chumakov Center (Russia)	
Shenzhen Kangtai Biological Products (PRC)	
<i>ERUCOV-VAC</i> - Erciyes University (Turkey)	

Name of Vaccine in *Italics* (where available) - Companies, Agencies or Collaborators in **Bold** – Country of origin of collaborating bodies (Brackets) – Subtype of Vaccine

- \*Single dose preparation
- †Three dose preparation
- ‡Intranasal
- § Dermal
- ¶ Oral
- # Approval in two or more countries
- Δ Includes pregnant women

Sources: COVID-19 – Landscape of Novel Coronavirus Candidate Vaccine Development Worldwide, Last updated 22<sup>nd</sup> Dec 2020; World Health Organisation <https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines>

RNA or DNA Vaccine
Viral Vector
Live attenuated
Inactivated, protein or virus-like proteins

Moderna's mRNA-1273 is uncommon at 11.1<sup>66,67</sup> and 2.5<sup>68</sup> cases per million doses, respectively. While this rate is higher than the seasonal influenza vaccine (1.3 cases per million doses),<sup>69</sup> it is similar to penicillin (1.9–27.2 per million).<sup>70</sup>

Developmental and reproductive toxicity (DART) studies for the mRNA-1273 in pregnant and lactating female Sprague Dawley rats did not demonstrate adverse effects on the female reproductive system or fetal development following administration of the therapeutic dose.<sup>71</sup> DART animal data for BNT162b2 vaccine have not

been published although preliminary reports do not reveal any safety concerns.<sup>65</sup> A review of 35,691 pregnant vaccine-recipients who submitted data to the CDC's 'v-safe' smartphone-based post COVID-19 vaccination health checker reported more frequent injection-site pain but less frequent systemic side-effects compared to non-pregnant women. The v-safe pregnancy registry with 3958 pregnant women reported similar miscarriage, stillbirth, congenital anomaly, intrauterine growth restriction and other antenatal complications compared to background rates,<sup>72</sup> however robust long

TABLE 3 SARS-CoV-2 vaccines approved for use in two or more countries (updated 15th May 2021)

Vaccine candidate (Manufacturer - Name)	Type	No. of doses	Storage temperature (°C)	Vaccine efficacy against symptomatic, laboratory-confirmed COVID-19 in Phase III trials (%)	Significant adverse effects	DART studies & pregnancy data
<b>BioNTech-Pfizer - BNT162b2 or Tozinameran/Comirnaty</b>	mRNA vaccine	2	-70	95	<ul style="list-style-type: none"> <li>Injection-site pain ~80% versus 10%–15% (placebo)</li> <li>Temperature <math>\geq 38^{\circ}\text{C}</math> 11%–16% versus &lt;1% (placebo)</li> <li>Fatigue 59%, headache 52%</li> <li>Severe systemic events &lt;2%</li> <li>Anaphylaxis 11.1 per million doses</li> </ul>	<ul style="list-style-type: none"> <li>DART in progress. Unpublished reports cite no adverse effects to female reproduction or fetal/postnatal development.</li> <li>Prospective cohort studies - vaccine-induced titres similar to non-pregnant population</li> <li>Neutralising antibodies seen in umbilical cord blood and breast milk, higher after 2nd dose</li> <li>No increase in adverse pregnancy outcomes in post-vaccination registry review</li> <li>Reduced efficacy against B.1.1.17 and B.1.351 variants</li> </ul>
<b>Moderna - mRNA-1273</b>	mRNA vaccine	2	2–8 up to 30 days –20 for long-term storage	94.1	<ul style="list-style-type: none"> <li>Severe injection-site reaction 7% versus 0.5% (placebo)</li> <li>Severe systemic side effects e.g. fever, myalgia, fatigue, nausea, vomiting, arthralgia, chills:</li> <li>Temperature <math>\geq 38^{\circ}\text{C}</math> 15.5% versus 0.3% (placebo)</li> <li>Anaphylaxis 2.5 per million doses</li> </ul>	<ul style="list-style-type: none"> <li>DART - No adverse effects on female reproduction or fetal/postnatal development</li> <li>Prospective cohort studies -vaccine-induced titres similar to non pregnant population</li> <li>Neutralising antibodies seen in umbilical cord blood and breast milk, higher after 2nd dose</li> <li>No increase in adverse pregnancy outcomes in post-vaccination registry review</li> </ul>
<b>AstraZeneca &amp; University of Oxford - AZD1222/Vaxzevria</b>	ChAdOx1 non-replicating chimpanzee adenoviral vector	2	2–8	70.4	<ul style="list-style-type: none"> <li>No difference in serious adverse effects.</li> <li>Pyrexia &lt;0.1%</li> <li>1 case of transverse myelitis (&lt;0.1%)</li> <li>Risk of TTS 10.9:1,000,000 doses</li> </ul>	<ul style="list-style-type: none"> <li>DART in progress</li> </ul>
<b>Johnson &amp; Johnson - Janssen - Ad26.COV2.S</b>	Ad26 non-replicating human adenoviral vector	1	2–8 up to 3 months –4 for long-term storage	65.5–66.3 <sup>a</sup>	<ul style="list-style-type: none"> <li>In cohort age 18–55 years old<sup>b</sup></li> <li>Local adverse events: 64%–78% versus 9% (placebo)</li> <li>Grade 3 systemic adverse events: 9%–20% versus 0% (placebo)</li> <li>Temperature 39°–40°C: 5%–9%</li> <li>Risk of TTS 2:1,000,000 vaccines amongst women age &lt;50</li> </ul>	<ul style="list-style-type: none"> <li>DART - No adverse effects on female reproduction or fetal/postnatal development</li> <li>8 inadvertently pregnant women (3 in vaccine group) 1 spontaneous abortion and 1 ectopic pregnancy in vaccine group. Pregnancy outcomes unknown.</li> </ul>

TABLE 3 (Continued)

Vaccine candidate (Manufacturer - Name)	Type	No. of doses	Storage temperature (°C)	Vaccine efficacy against symptomatic, laboratory-confirmed COVID-19 in Phase III trials (%)	Significant adverse effects	DART studies & pregnancy data
Gamaleya research Institute - Sputnik V	Ad5 and Ad26 non-replicating human adenoviral vector	2	2-8	91.6	<ul style="list-style-type: none"> <li>Flu-like illness: 15.2% versus 8.8% (placebo)</li> <li>Serious adverse events: 0.3% versus 0.4% (placebo)</li> <li>Local reactions: 5.4% versus 1.2% (placebo)</li> <li>Pyrexia: 0.5% versus 0.3% (placebo)</li> </ul>	<ul style="list-style-type: none"> <li>No data</li> </ul>
Sinopharm - BBIBP-CorV	Inactivated SARS-CoV-2 (vero cells)	2	2-8	79-86 <sup>a</sup>	Injection site reactions 35% <sup>b</sup>	<ul style="list-style-type: none"> <li>No data</li> </ul>
Sinovac - CoronaVac	Inactivated SARS-CoV-2	2	2-8	50-91.25 <sup>a</sup>	Injection site reactions 27.5% <sup>b</sup>	<ul style="list-style-type: none"> <li>No data</li> </ul>

Abbreviations: DART, Developmental and Reproductive Toxicity studies; TTS, Thrombosis with thrombocytopenia syndrome.

<sup>a</sup>Self-reported from interim analysis published in press, but not in a peer-reviewed journal.

<sup>b</sup>Based on phase 1/2 studies.

term data spanning the entire gestational length of pregnancy and beyond is required.

Two prospective cohort studies<sup>73,74</sup> of mRNA-1273 or BNT162b2 vaccine recipients comparing non-pregnant and pregnant or lactating women did not reveal serious adverse effects. Comparable vaccine-induced neutralising antibody titres, functional antibody responses and cell-mediated immune responses were seen, and these were higher than in the infected and unvaccinated. Neutralising IgG antibodies titres were present in the umbilical cord and breastmilk but were lower compared to maternal sera.<sup>73,74</sup> Breastmilk IgG, but not IgA, was boosted by a second vaccine dose.<sup>73</sup>

University of Oxford and AstraZeneca's AZD1222 is a double-dose replication-deficient chimpanzee adenoviral vector vaccine.<sup>75</sup> Interim analysis reports an overall vaccine efficacy of 70.4%.<sup>76</sup> This vaccine is comparatively more affordable than mRNA vaccines<sup>75</sup> and does not require ultra-low temperature storage.<sup>77</sup> The AZD1222 vaccine trial is one of the few which did not exclude pregnant women.<sup>78</sup> Johnson & Johnson-Janssen Pharmaceutical's Ad26.COVS is a single-dose non-replicating human adenoviral vector vaccine that has been recently approved by the FDA and European Union with interim efficacy reported at 65.5%–66.3%.<sup>79</sup> DART studies for Ad26.COVS vaccine in pregnant and lactating female rabbits did not demonstrate adverse effects on the female reproductive system or fetal development. While in Phase 3 trials, 8 participants had inadvertent pregnancies during vaccination but no adverse effects were reported except for one spontaneous miscarriage and one ectopic pregnancy in the study arm.<sup>80</sup>

Vaccine-induced thrombosis with thrombocytopenia syndrome (TTS) is autoimmune-mediated and guidelines have been formulated for its effective management.<sup>81</sup> Reports of TTS have emerged<sup>82,83</sup> in association with AZD1222<sup>84,85</sup> and Ad26.COVS<sup>86</sup> with a higher predisposition for the latter amongst women less than 50-years-age (7 per million vaccine doses in women less than 50-years-age vs. 0.9 for older women and none amongst males for Ad26.COVS).<sup>86</sup> A maternal death due to stroke at 23-weeks-gestation in an AZD1222 recipient in Brazil attracted further attention<sup>87</sup> and several countries have started restricting their usage in younger persons with varying upper age limits.<sup>88</sup> Regulatory bodies, currently, maintain that there remains an overall positive benefit-risk profile with absolute rates remaining very low<sup>89,90</sup> when seen in the context of COVID-19's mortality rate of 116 deaths per million infections. Further investigation and long-term monitoring for these events are required.<sup>91</sup> mRNA vaccines have not been implicated in TTS<sup>86,92</sup> although a pre-print has reported a higher incidence of cerebral venous sinus thrombosis (CVST), the hallmark of TTS, in individuals vaccinated with the Pfizer and Moderna vaccines. This incidence is higher than that following influenza infection but much lower than following natural COVID-19 infection.<sup>93</sup> While CVST is rare, it has been associated with pregnancy and larger observational studies are required to ascertain the modification of CVST risk in pregnant vaccines.

Russia's Gamaleya Research Institute's Sputnik V vaccine utilises Ad5 and Ad26 adenoviruses and has obtained early approval within



Russia, Hungary, Belarus and Argentina<sup>53</sup> with Phase 3 trials reporting 91.6% efficacy and no significant increase in serious adverse effects, the finalised clinical trial results are awaited. A potential limitation of viral vector vaccines is the possibility of pre-existing or vaccine-induced anti-vector immunity, which could reduce the efficacy of the starting or booster vaccines, respectively.<sup>94</sup>

The Peoples Republic of China (PRC) has developed two inactivated vaccines: Sinovac's CoronaVac<sup>95</sup> and Sinopharm's BBIBP-CorV.<sup>96</sup> The latter has received EUA within the PRC, Indonesia, Bahrain, and United Arab Emirates. Unpublished Phase 3 interim analysis show vaccine efficacies of 50%–91.3%<sup>97,98</sup> and 79%–86%<sup>99,100</sup>, respectively. Favourable safety profiles in Phase 1 and 2 trials have been published, with febrile symptoms reported in <5% of subjects.<sup>95,96,101</sup>

Novavax is a recombinant Spike protein peptide vaccine<sup>102</sup> that is undergoing Phase 3 trials and is likely to receive FDA EUA. Virus-like particles have been used in human papillomavirus vaccines, which involves particles mimicking viral structures that can present antigenic proteins to antigen-presenting cells.

SARS-CoV-2 variants of concern (VOC) B.1.1.7, B.1.351, P.1, B.1.427, B.1.429, B.1.617 with S protein mutations have emerged from England, South Africa, Brazil and India. These VOCs have slightly higher transmissibility,<sup>85</sup> increased disease severity<sup>85</sup> along with concerns of reduced vaccine efficacy<sup>103</sup> and immune escape.<sup>104</sup> The B.1.617 variant, in particular, is thought to be responsible for India's second wave.<sup>105</sup> Analysis of B.1.351's neutralization activity titres for AZD1222 and BNT162b2 show reductions of 9-fold and 7.6-fold, respectively.<sup>85</sup> One cohort study amongst pregnant and lactating BNT162b2 and mRNA-1273 vaccine recipients showed reduced neutralising antibody titres against B.1.1.17 and B.1.351 but preserved T-cell response.<sup>74</sup> Amongst vaccinated healthcare workers, BNT162b2 has shown efficacy against B.1.1.17.<sup>62</sup> Real world data corroborates that the currently licensed vaccines are effective against the major VOCs.<sup>106</sup> The role of additional booster doses and pre-clinical candidate variant-specific boosters are being evaluated.<sup>107</sup>

Figure 1 illustrates the mechanism of action of various types of SARS-CoV-2 vaccines.

As of 15th May 2021, of the 50 candidate vaccines in Phase 2 or 3 trials, 40.0% (20) are protein or virus-like protein vaccines, 28.0% (14) are DNA or RNA-based, 10.0% (5) are viral vector vaccines, 22.0% (11) are live attenuated. Of these, 42.0% (21) are undergoing Phase 3 clinical trials and 12 have been approved in at least 2 countries (Table 2). Almost all the trials exclude pregnancy except for AZD1222<sup>78</sup> and BNT162b2.<sup>108</sup>

As vaccination campaigns progress, the herculean tasks of large-scale manufacture, cold-chain transportation, and equitable distribution of vaccines requires prioritisation of high-risk and vulnerable groups such as the elderly and healthcare workers.<sup>75,109–111</sup> The WHO's Strategic Advisory of Experts (SAGE) recommends a three-staged prioritisation process depending on each country's vaccine availability. Where vaccine availability exists for 1%–10% of a

population, the highest Stage 1 targets healthcare workers and seniors.<sup>112</sup> Uniquely, pregnant healthcare workers who care for a largely unvaccinated pregnant population may find themselves at a higher risk of exposure. While there has been conflicting evidence on whether COVID-19 in pregnancy is associated with adverse effects<sup>113–116</sup> larger studies demonstrate a higher risk of death, intensive care unit admission, invasive ventilation and extracorporeal membrane oxygenation<sup>117</sup> as well as increased preterm delivery and stillbirth rates.<sup>18,19</sup> Despite this, pregnant women have been placed in the lowest prioritisation Stage 3. With over 130 million births per year globally, increases in maternal mortality will have significant societal impacts. Awaiting long-term vaccine safety and efficacy data may lead to pregnant women and their offspring bearing a disproportionate burden of disease. It is thus critical, to address the issue of vaccination of pregnant women.

Currently, a clear global consensus on vaccination of pregnant women against COVID-19 is yet to be formulated (Table 4). The American College of Obstetrics and Gynecology (ACOG) and the Society for Maternal Fetal Medicine (SMFM)<sup>65,120</sup> endorse the inclusion of pregnant and lactating women in vaccination campaigns. The UK's Joint Committee of Vaccination and Immunisation (JCVI)<sup>75</sup> and Royal College of Obstetricians and Gynaecologists<sup>121</sup> opine that pregnant women should be offered vaccination based on their age and clinical risks and preferable vaccines would be Pfizer-BioNTech's BNT162b2 or Moderna's mRNA-1273. Those at risk of SARS-CoV-2 exposure (healthcare or social workers, residential carers, drivers, cleaners) or COVID-19 complications with infection (diabetes, solid organ transplant, immunosuppression, chronic respiratory, heart, or kidney disease, BMI > 40) should be offered vaccination.<sup>75</sup> Royal Australian and New Zealand College of Obstetricians and Gynecologists (RANZCOG)<sup>122</sup> recommend risk based discussion of vaccination with women who are susceptible to complicated COVID-19 infection. Additionally, RANZCOG recommends that pregnant women with high SARS-CoV-2 exposure risk should have their duties adjusted to reduce exposure or, if this is not possible, consider vaccination. The European Medicines Agency states that BNT162b2<sup>123,124</sup> and mRNA-1273<sup>125</sup> can be considered on a case-by-case basis after close consultation on the risks and benefits but more studies are needed. The Society of Obstetricians and Gynaecologists of Canada<sup>126</sup> additionally recommends against counselling for termination of pregnancy in the event of inadvertent pregnancy during a vaccination series and to discuss the pros and cons of continuing or delaying of subsequent dose(s) depending on the woman's vulnerability factors. Determining the local rate of community transmission and individualised exposure risk would facilitate a risk-benefit based discussion tailoring the recommendations to the individual.<sup>119</sup>

While emerging data from observational studies<sup>73</sup> and post-vaccination surveillance data<sup>72</sup> suggest minimal harm with vaccinating pregnant or lactating women, there is still insufficient data to be certain about the safety of COVID-19 vaccines in this population until longer-term studies can be conducted. Current guidelines

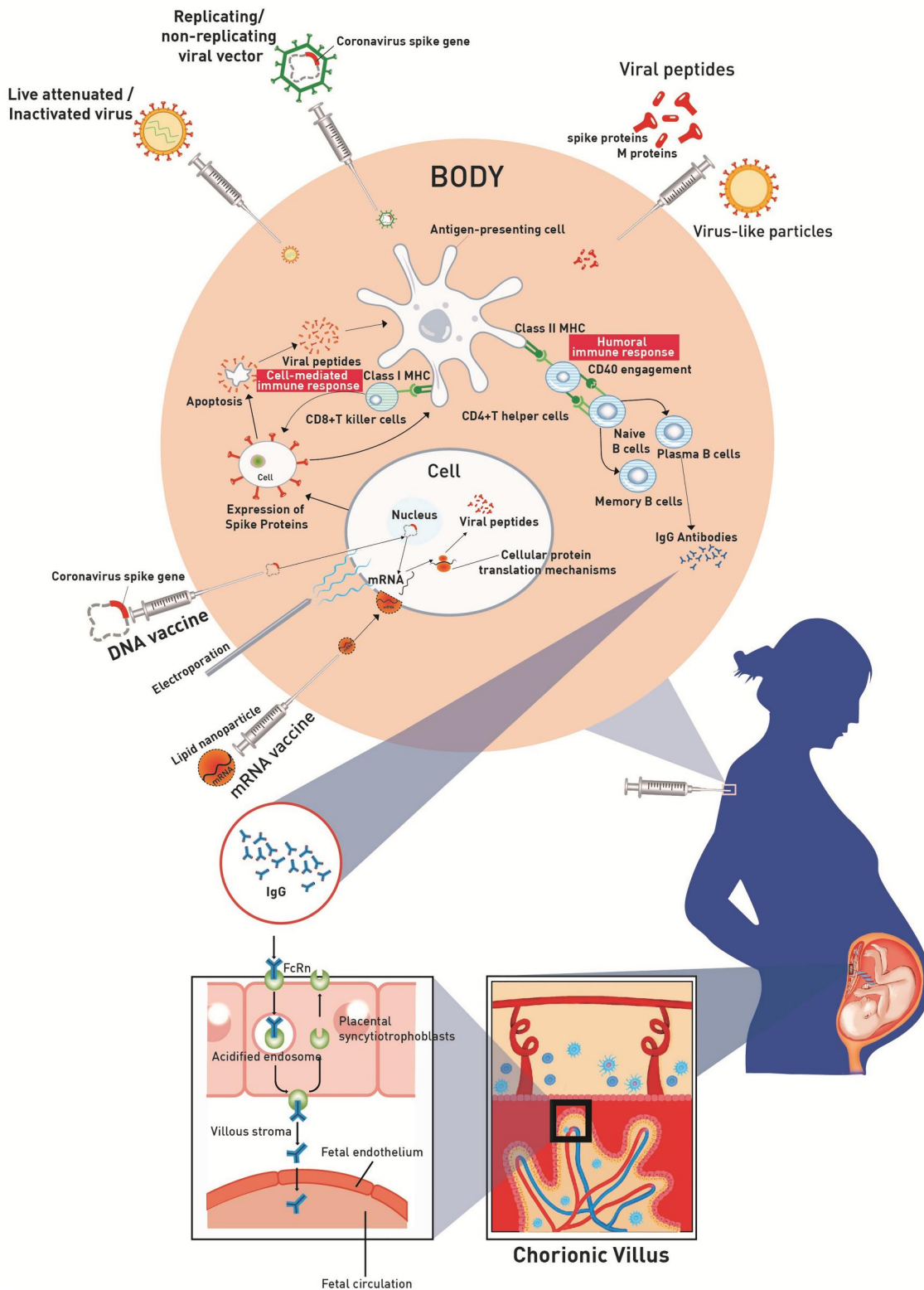


FIGURE 1 Mechanism of action of various types of SARS-CoV-2 vaccines [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

recommend risk-based vaccination of breastfeeding women and those vaccinated can continue breastfeeding.<sup>86,98</sup> Women planning pregnancy can be vaccinated and there is no evidence that vaccines affect fertility.

While endorsement of universal vaccination in pregnancy is not feasible at present, these organisations recognise that pregnancy or lactation is not an absolute contraindication for vaccination, and individualisation of risk and informed decision making is crucial.



TABLE 4 Recommendations by international professional and regulatory bodies regarding SARS-CoV-2 vaccination in pregnancy (updated 15th May 2021)

Country/region	Professional or regulatory body	Key recommendations
United States of America	American College of Obstetricians and Gynecologists	<ul style="list-style-type: none"> <li>• Pregnant women should have access to COVID-19 vaccines.</li> <li>• Vaccine should be offered to lactating women similar to non-lactating individuals.</li> <li>• Permissive recommendation based on appropriate risk/benefit discussion and shared clinical decision making between clinicians and pregnant patients.</li> <li>• Defer influenza &amp; Tdap vaccines for 14 days after COVID-19 vaccination.</li> <li>• Claims linking COVID-19 vaccines to infertility have been scientifically disproven.</li> <li>• Risk of thrombosis and thrombocytopenia with Janssen vaccine should be discussed.</li> </ul>
	Food and Drug Administration	<ul style="list-style-type: none"> <li>• Vaccine sponsors should conduct developmental &amp; reproductive toxicity studies.</li> <li>• Encourages inclusion of pregnant &amp; women of childbearing age in studies.</li> <li>• Recommends maintenance of pregnancy exposure registry and follow up data.</li> </ul>
	Centre for Disease Control and Prevention	<ul style="list-style-type: none"> <li>• Pregnant or lactating women can receive COVID-19 vaccination.</li> <li>• Women should be allowed to make an informed decision, providing current knowledge of COVID-19 vaccines with pregnancy and risk of disease.</li> <li>• Pregnant women receiving vaccine should consider participating in the v-safe pregnancy registry.</li> <li>• No evidence of COVID-19 vaccines causing fertility issues.</li> <li>• COVID-19 vaccines can be co-administered with or within 14 days of other vaccines.</li> </ul>
	American Society for Reproductive Medicine	Patients who are undergoing fertility treatment, are pregnant or breastfeeding should be encouraged to receive vaccination, based on eligibility criteria
Europe	European Society of Human Reproduction & Embryology	<ul style="list-style-type: none"> <li>• Women with co-morbidities putting them at higher risk of complicated COVID-19 should be encouraged for vaccination before conception.</li> <li>• Consider postponing assisted reproduction treatment for a few days after vaccination to allow immune response to settle or up to 2 months to allow antibody development.</li> </ul>
	European Medicines Agency	Vaccinating pregnant women with BNT162b2 or mRNA-1273 can be considered on a case-by-case basis and after close consultation with a healthcare professional while considering the benefits and risks.
United Kingdom	Joint Commission on Vaccination & Immunisation	<ul style="list-style-type: none"> <li>• Pregnant women should be offered COVID-19 vaccine based on their age and clinical risk, followed by a joint decision after discussing benefits and risks.</li> <li>• Available data does not indicate safety concerns or harm in pregnancy.</li> <li>• Pfizer-BioNTech's BNT162b2 or Moderna mRNA-1273 is preferable for pregnant women.</li> <li>• Vaccination should be offered to pregnant women at high risk of <ul style="list-style-type: none"> <li>◦ Complicated COVID-19: solid organ transplant recipients, severe respiratory conditions (e.g., cystic fibrosis or severe asthma), homozygous sickle cell disease, significant congenital or acquired heart disease, on immunosuppression or on dialysis, BMI &gt;40, gestational diabetes.</li> <li>◦ SARS-CoV-2 infection: frontline health/social workers &amp; residential home carers.</li> </ul> </li> <li>• Breastfeeding can continue during the course of vaccination.</li> </ul>
	Royal College of Obstetricians & Gynaecologists	

TABLE 4 (Continued)

Country/region	Professional or regulatory body	Key recommendations
		<ul style="list-style-type: none"> <li>• Women planning for pregnancy can be vaccinated.</li> <li>• No evidence of vaccines affecting fertility.</li> <li>• Recommends maintenance of pregnancy exposure registry and follow up data.</li> </ul>
Canada	Society of Obstetricians & Gynaecologists of Canada National Advisory Committee on Vaccination	<ul style="list-style-type: none"> <li>• Vaccination should be offered to eligible pregnant or breastfeeding individuals in the absence of contraindications, with informed consent following discussion regarding the absence of evidence.</li> <li>• Individuals who get pregnant during vaccine series should not be counselled for termination of pregnancy. Decision to complete or delay second dose should be individualised and discussed.</li> <li>• A 28 days interval is recommended between completion of COVID-19 vaccine and other vaccines; 14 days interval between other vaccine and starting COVID-19 vaccine. These can be individualised depending on indications.</li> </ul>
Australia & New Zealand	Royal Australian and New Zealand College of Obstetrics & Gynaecology Australian Technical Advisory Group on Immunisation (ATAGI)	<ul style="list-style-type: none"> <li>• Discuss vaccination with pregnant women who are vulnerable to complicated COVID-19.</li> <li>• There is insufficient evidence to recommend routine vaccination in pregnancy.</li> <li>• Pregnant workers with increased exposure risk should be allotted lower risk duties or be offered vaccination.</li> <li>• Pregnancy need not be delayed following vaccination.</li> <li>• Pfizer BioNTech vaccine if preferred for those less than 50 years of age.</li> </ul>
Global	World Health Organisation <sup>118</sup>  International Federation of Obstetrics and Gynecology <sup>119</sup>	<ul style="list-style-type: none"> <li>• Pregnant women with comorbidities or high risk of exposure may be offered vaccination.</li> <li>• Lactating woman can be offered vaccination if they are part of a vaccine recommended group.</li> <li>• In the absence of risks outweighing benefits, pregnant and lactating women should be offered vaccination.</li> <li>• Healthcare workers should support women in making an informed decision.</li> </ul>

## 4 | ETHICAL CONSIDERATIONS

In the absence of conclusive evidence of harm, there are reasonable ethical arguments to support vaccinating pregnant women (Table 5). Following the debacle surrounding thalidomide and diethylstilbestrol, various research-related legislations and guidelines protect pregnant women and their fetuses from unintended harm.<sup>127</sup> This unfortunately, has also led to pregnant women being frequently excluded from trials to avoid exposure to 'greater than minimal harm'.<sup>128,129</sup> This exclusion may be a result of anticipated socio-cultural complications if the vaccination program reports adverse pregnancy outcomes which could potentially jeopardise the entire program. However, during a pandemic, the balance between 'benefit' and 'minimal harm' might vary significantly when compared to a non-pandemic situation.<sup>130</sup> For example, during the West African Ebola pandemic of 2013–2016, pregnant women faced a case fatality rate of 89%–93%.<sup>131</sup> While inclusion of pregnant women in drug and vaccine trials under such circumstances could have been justified, they were excluded despite the World Health Organisation Ethics Review Committee<sup>132</sup> recommending protocol amendments when there were no objective reasons to exclude pregnancy. A review of

927 SARS-CoV-2 clinical trials found that only 3 (1.7%) were pregnancy-specific and 52% excluded pregnancy.<sup>133</sup> Towards the goal of harmonising safety data collection in clinical trials, the Global Alignment of Immunization Safety Assessment in Pregnancy (GAIA project) has formulated guidance on data collection and reporting in vaccine trials involving pregnant women allowing applicability in diverse settings.<sup>134</sup>

With no precedent for mRNA vaccines and accelerated vaccine-development programs lacking long-term Phase 3 safety data, it is right for investigators, funding bodies and the public to be concerned about the risk of harm in pregnancy. However, as with any new drug category, the potential for teratogenicity must be balanced against the potential for significant benefit, especially given that COVID-19 has significantly higher morbidity during pregnancy.<sup>19,117</sup> To address non-maleficence, the pharmacokinetics of mRNA vaccines (i.e., short-lived and having very local effect), DART studies,<sup>65,71</sup> cohort studies<sup>73,74</sup> and post-vaccination registry reviews<sup>72</sup> do not suggest significant risk of harm while demonstrating comparable levels of vaccine efficacy. Additionally, cohort studies suggest that vaccinating pregnant women may benefit the offspring through the passive transfer of antibodies. The safety of adenoviral vector

TABLE 5 Ethical principles guiding SARS-CoV-2 vaccination in pregnancy

Ethical principle	Application
Justice	Pregnant women, just as any other human subject, should have the right to be included in research trials and participate in vaccination campaigns where there are no compelling scientific or ethical reasons to exclude them.
Non-maleficence	The risks of mRNA vaccine in pregnancy are unknown with little precedent amongst the non-pregnant population. As with any new drug class, the potential for teratogenicity should be balanced with the untapped potential for benefit to the mother, fetus and neonate. Limited animal Developmental and reproductive toxicity studies and observations in Phase 3 participants with inadvertent pregnancy suggest no harm.
Beneficence	COVID-19 in pregnancy has a greater risk of severe complications and there exists a potential to reduce morbidity and mortality amongst pregnant women by including them in vaccination. There is also a possibility of passive immunisation of the fetus and neonates through transplacental IgG transfer or through breastfeeding.
Autonomy	Adult pregnant women regularly exercise autonomy by providing informed consent for clinical decision-making. Similarly, they have the capacity to weigh the risks and benefits of vaccination and provide informed consent.

vaccines in pregnant women, however, remains an unanswered concern given the predisposition of young women for TTS and reports of cerebral venous thrombosis. More data from prospective cohort studies and passive registries are needed.

The classification of pregnant women as vulnerable individuals has been challenged by various bodies arguing that pregnant women routinely exercise autonomy in complex clinical decisions to protect both their own and fetuses' interests.<sup>135,136</sup> It is unreasonable to expect a pregnant woman not to have capacity to weigh the risks and benefits of vaccination even in the face of limited evidence and provide informed consent for or against vaccination.

## 5 | RECOMMENDATIONS

A personalised risk-benefit analysis-based discussion is required for each pregnant woman to balance the paucity of pregnancy specific and long term data with the risks of non-vaccination and potentially severe SARS-CoV-2 infection,<sup>137</sup> with an aim of supporting her decision regardless of whether she is in favour of, or against Covid 19 vaccination.

Pregnant women with risk factors (advanced maternal age, obesity, diabetes, hypertension, solid organ transplant, immunosuppression, sickle cell disease, chronic lung, kidney or heart disease<sup>27,117,138-140</sup>) or high exposure risks (healthcare workers, drivers, cleaners or residential home carers)<sup>121,122,126,141</sup> may be prioritised for early vaccination. Healthcare workers are within the highest WHO SAGE Stage 1 vaccine priority<sup>112</sup> and women comprise about 70% of that workforce,<sup>142</sup> a large proportion being of reproductive age. Other high risk groups, are those who are socially disadvantaged, including African American and Hispanic women in USA,<sup>65,143</sup> as they have higher rates of COVID-19 infection<sup>144</sup> and death.<sup>117</sup> These groups could also be considered for preconception vaccination. Studies determining vaccine acceptability and factors influencing decisions in pregnant women are required.<sup>145</sup>

As concerns surface regarding vaccine-related anaphylaxis<sup>66,146</sup> clinicians need to be cognizant that severe anaphylaxis in pregnancy poses additional risks of preterm labour, fetal hypoxic brain injury or intrauterine fetal death.<sup>147-153</sup> The CDC reports an anaphylaxis rate of 11.1<sup>67</sup> (Pfizer-BioNTech's BNT162b2) and 2.5<sup>68</sup> (Moderna's mRNA's-1273) cases per million doses after the first dose, compared to 1.3 cases per million following inactivated influenza vaccine.<sup>69</sup> Majority of the cases occurred within 30 min of vaccination, mostly in women, and/or in persons with history of allergies. Reasons for female predisposition are unclear and has also been seen with the 2009H1N1 influenza vaccine.<sup>68,154</sup> While a history of allergy to the mRNA vaccine, polyethylene glycol or polysorbate are strict contraindications to vaccination,<sup>146,155</sup> drug or food allergies and previous anaphylaxis should be declared for closer post-vaccination anaphylaxis monitoring. Despite low absolute risks of TTS in adenoviral-vector vaccines, women of reproductive age or those pregnant or breastfeeding should be allowed the autonomy to select alternate vaccines<sup>156</sup> pending more conclusive data.

Maternal vaccination should be done in units with capacity for emergency obstetric resuscitation and management.<sup>121</sup> Equipment and medication for managing anaphylaxis should be within easy access with at least three doses of epinephrine on hand, preferably in prefilled syringes or autoinjectors.<sup>146</sup> Currently, post-vaccination observation of 30 min is recommended.<sup>118,146</sup> Additionally, all healthcare workers at vaccination centres, first-responders, frontline medical services such as emergency departments and primary care providers should be educated on early recognition and management of anaphylaxis in pregnancy,<sup>152,153,157</sup> which may present atypically with delayed features of shock, preterm labour, low back pain and uterine cramps. Additionally, they should be proficient in the principles of maternal resuscitation.<sup>158</sup>

A personalised vaccine card stating pregnancy status, vaccine name, dosage and schedule should be provided along with patient information leaflets outlining expected symptoms and red flags requiring urgent medical review. As a cautionary measure, a two-

week gap is recommended between COVID-19 and influenza or pertussis vaccination. However, with availability of more safety data, currently COVID-19 vaccines may be co-administered along with other vaccines.<sup>119</sup>

As Phase 3 mRNA vaccines trials<sup>58,59</sup> report a 15% rate of moderate to severe fever ( $38.5 \geq ^\circ\text{C}$ ) after the second dose and potential complications of pyrexia in the first trimester include oral clefts, neural tube or congenital heart defects in the fetus<sup>159</sup> adequate and appropriate anti-pyrexial treatment is advisable.

Currently, women with positive SARS-CoV-2 IgG serology should still be offered vaccination, as although naturally acquired antibodies and T-cell responses appear to be protective,<sup>160</sup> the nature and duration of protection from reinfection is presently unknown. Similar to other coronavirus infections, SARS-Cov-2 neutralising antibody titres demonstrate a decline, especially in individuals with less severe infection.<sup>161</sup> As circulating antibody titres may not indicate B-memory cell efficacy and cell-mediated  $T_H1$  response, it is unclear if this reduction in titres is associated with increased re-infection risk<sup>7,8,40,162-164</sup> although convalescent individuals demonstrate strong CD4+ & CD8+ T cell memory responses against S<sup>40</sup> and N<sup>165</sup>

proteins. Additionally, there have been concerns of antibody-dependent enhancement due to the waning of neutralising antibodies,<sup>166</sup> although clinical evidence from vaccine trials, treatment with passive antibodies and infections in patients with previous human coronavirus infections have not conclusively demonstrated this.<sup>10,167</sup> Furthermore, Phase 1 studies for Moderna's mRNA-1273 vaccine<sup>168</sup> suggest superior vaccine-mediated immunity when compared to natural infection,<sup>169-171</sup> though this requires validation through the larger Phases 3 and 4 cohorts.

Caution is necessary and more vaccine safety data in pregnancy is vital. Safety surveillance systems should be maintained by public health bodies, professional medical organisations or healthcare facilities at a local, regional or national level with attention to pregnant women<sup>172,173</sup> such as the UK Obstetric Surveillance System (UKOSS)/UK Teratology Information Service (UKTIS) and the CDC's 'v-safe' COVID-19 Vaccine Pregnancy Registry.<sup>66</sup> Maternity services may take the lead in registering pregnant women under their jurisdiction either by administering these vaccines or coordinating notification of vaccination.<sup>121</sup> While awaiting results from prospective trials,<sup>108</sup> recommendations on vaccinating pregnant women should

### Box 1. Proposed recommendations regarding vaccination of pregnant women

Vaccination in pregnant women should be individualised based on risks and intended benefits. Informed consent should be obtained. Relevant information and frequently asked questions regarding maternal vaccination should be posted on easily accessible media (websites, posters at vaccination sites, clinics and maternity units, patient information leaflets).

Priority for pre-conception or antenatal vaccination could be given to women who are at high risk for

- COVID-19 exposure: Healthcare workers, social workers, residential home carers.
- Complicated COVID-19: Advanced maternal age or co-morbidities such as obesity, diabetes, solid organ transplant, sickle cell disease and chronic cardiac, lung, or kidney diseases.

Priority for pre-conception or antenatal vaccination could be given to women who are at high risk for

Women with positive SARS-CoV-2 IgG serology could still be offered vaccination as the degree and duration of immunity conferred by previous infection is unknown and vaccine-mediated immunity is superior to naturally acquired immunity.

Maternal vaccination should be performed in facilities with access to services competent in managing anaphylaxis and maternal resuscitation. Healthcare workers at vaccination centres, first responders and frontline health services should be educated on recognition of anaphylaxis in pregnancy and the principles of maternal resuscitation.

The following should be made available in all centres conducting maternal vaccination.

- Medical equipment, emergency medications, personnel competent in managing anaphylaxis and resuscitation in pregnancy.
- Clear written guidelines.
- Facility for post vaccination observation.
- Post-vaccination leaflet, tailored to pregnancy detailing common side effects, red flag symptoms for adverse effects and anaphylaxis, emergency contact information.

Anti-pyretic management should be pre-emptively provided, especially with mRNA vaccines.

Passive registries should be maintained to observe pregnancy outcomes of women who undergo vaccination. Data should be analysed to formulate regular updates to guide future vaccination strategies in pregnancy.

be constantly reviewed based on accumulated observational evidence. Interim reports should be regularly released indicating vaccine-related adverse effects and efficacy, and rates of miscarriages, terminations of pregnancy, fetal anomalies, preterm births and perinatal mortality.<sup>174</sup>

Contemporaneously updated guidelines and frequently asked questions featured in clinic posters, patient information leaflets, public health websites and maternity forums could serve as an adjunct to professional counselling prior to informed consent. Improved patient education through easily understood and reliable information would complement pre-vaccination counselling and alleviate burdens on busy healthcare services.

These recommendations have been summarized in [Box 1](#).

## 6 | CONCLUSION

COVID-19 in pregnancy is associated with higher rates of pregnancy-related complications. With a likely future of intermittent outbreaks, exclusion of pregnant women from vaccination may lead to a disproportionately higher burden being borne by this vulnerable cohort and their offspring. This must be balanced against the risks related to vaccination. Given the rapidity of new information emerging, it is vital that healthcare providers keep abreast of recent developments and guidelines.

While it was initially postulated that 'herd immunity' for SARS-CoV-2 could be achieved by attaining at least 70% population immunity,<sup>175</sup> logistical challenges in vaccine distribution,<sup>176</sup> the economic desire to open borders and the emergence of VOCs which may reduce vaccine-efficacy makes passive protection of pregnant women through herd immunity a long term objective which may take years. While we await high vaccination rates, similar to that of measles, rubella and polio, periodic outbreaks may continue due to importation from low vaccination areas or vaccine non-response, albeit with lower severity.<sup>62,177-179</sup> Mask wearing, hand hygiene and social distancing will remain important methods for pregnant women who remain unvaccinated either due to medical reasons, personal preference or exclusion from vaccination policies.

Informed consent and patient autonomy should be the cornerstones for decision-making regarding vaccination. Individualised discussion covering each woman's specific risks and possible benefits of vaccination should be conducted. Women at high priority for vaccination include those at high exposure risk or who have comorbidities that place them at high risk for severe COVID-19.

Pregnant women are a significant part of the spectrum of every population. We hope that future clinical trials will consider including pregnant women, whenever pre-clinical studies show no objective reason to exclude them.

## ACKNOWLEDGEMENTS

We would like to acknowledge Mr Mohesh K Mohan for his assistance in the illustration, Ms Cecille Laureano Asibal for her administrative support.

## CONFLICT OF INTEREST

The authors have no conflicts of interest in connection with this article.

## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

## ORCID

Angsumita Pramanick  <https://orcid.org/0000-0002-1544-4945>

Aniza Puteri Mahyuddin  <https://orcid.org/0000-0001-8570-8427>

Sebastian Enrique Illanes  <https://orcid.org/0000-0001-5433-9315>

Mahesh Choolani  <https://orcid.org/0000-0001-8336-0973>

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**How to cite this article:** Pramanick A, Kanneganti A, Wong JLJ, et al. A reasoned approach towards administering COVID-19 vaccines to pregnant women. *Prenatal Diagnosis.* 2021;41(8):1018-1035. <https://doi.org/10.1002/pd.5985>