INTRODUCTION

The COVID-19 pandemic has waned in countries with high vaccination coverage (UK, Israel and the US) while resurging or continuing to surge in countries with low vaccine coverage. The ongoing second wave of the pandemic is thought to be due to variants of concern (VOC) such as B.1.1.7 (UK), B.1.351 (South African) and most recently the B.1617 (Indian) variants, which have been found in preliminary studies to be potentially more transmissible, therefore resulting in more rapid community spread.1-3 Asian countries such as Taiwan, Thailand, South Korea, Japan and Singapore, which have had successful containment thus far, are now facing a resurgence of cases from these variants of concern.

A community serology sampling study conducted between September and October 2020 in Singapore found that only four out of 1600 subjects had a positive serology test, which translated into a community prevalence rate of 0.25 per cent.4 However, more recently with the evolution of VOCs, we have witnessed a resurgence of community-transmitted cases locally. Aside from maintenance of good hygiene and social distancing, the most effective strategy in our fight against COVID-19 is vaccination, as it reduces the risk of transmission as well as the risk of severe COVID-19 infection and death. This is especially so for those at higher risk of complications from COVID-19 infection, such as those of 60 years and above, or those with underlying comorbidities such as hypertension, diabetes or heart disease. Pregnant women also form a high-risk group as they have been found to be at increased risk for severe illness from COVID-19 infection compared to non-pregnant people.5

This guideline thus aims to provide guidance for medical practitioners caring for women in the reproductive age group who are either planning for pregnancy, currently pregnant or breast-feeding. It will provide guidance on the applicability and safety of COVID-19 vaccination in this group of women in the context of an ongoing COVID-19 pandemic, so as to aid appropriate counselling and management. The presented guideline is based on the latest evidence and will be updated further if new evidence becomes available.

RISK OF COVID-19 INFECTION IN PREGNANCY AND RATIONALE FOR VACCINATION

Although the overall absolute risks for severe COVID-19-associated complications among women are low, pregnant women have been found to be at significantly higher risk for severe COVID-19-associated outcomes compared with non-pregnant women. This may be due to the physiological changes in pregnancy such as increased heart rate and oxygen consumption, decreased lung capacity, a shift away from cell-mediated immunity and increased risk for venous thromboembolism.6,7

In terms of maternal outcomes, a recent meta-analysis including 192 studies demonstrated that compared with non-pregnant women of reproductive age, pregnant and recently pregnant women had an increased risk of critical illness requiring intensive care unit admission (OR 2.13, 1.53 to 2.95), invasive ventilation (OR 2.59, 2.28 to 2.94) and need for extra corporeal membrane
oxygenation (OR 2.02, 1.22 to 3.34) with a mortality of 0.02%. Risk factors for more severe COVID-19 infection in pregnancy included increased maternal age, obesity, pre-existing maternal comorbidity, chronic hypertension, pre-existing diabetes and pre-eclampsia.

In terms of adverse pregnancy and perinatal outcomes, COVID-19 infection in pregnancy has been found to be associated with an increased risk for preterm birth (OR 1.82, 1.38 to 2.39) and stillbirth (OR 2.11, 1.14 to 3.90). The odds of admission to the neonatal intensive care unit (OR 4.89, 1.87 to 12.8) were also higher in babies born to mothers with COVID-19 versus those without COVID-19.

The above outcomes were demonstrated during the second wave of COVID-19 infection in the United Kingdom, where the numbers of pregnant and peripartum women with severe COVID-19 disease increased, with more of these women requiring admission to intensive care and consideration for ECMO.

The risk of adverse outcomes is dependent on patient and societal factors such as access to quality healthcare. Given the recent increase in community cases and circulating variants of concern, coupled with the increasing data available on the safety of existing vaccines, the risk-benefit equation for vaccinating pregnant women has shifted in Singapore. Therefore, it is reasonable to offer pregnant women vaccination for protection against an infection which could confer risks to both mother and fetus.

Apart from the above benefits of maternal protection against severe disease, COVID-19 mRNA vaccines generate humoral immunity in both pregnant and breastfeeding women, similar to non-pregnant people. This allows for transplacental transfer of maternal IgG to the fetus antenatally. IgG, IgA and IgM antibodies have also been detected in breastmilk following vaccination. Vaccination can thus allow for passive transfer of antibodies to the fetus and neonate, although the nature and extent of protection for the neonate remains to be ascertained.

**SAFETY AND EFFICACY OF COVID-19 VACCINATION IN PREGNANCY**

Currently, the large clinical trials demonstrating the safety and effectiveness of COVID-19 vaccines did not include pregnant women.

In terms of efficacy, although there is no strong evidence demonstrating that efficacy of vaccines in pregnancy, there is no evidence or scientific rationale either to suggest a difference in efficacy of vaccines administered during pregnancy compared to outside of pregnancy.

As for the safety of COVID-19 vaccines on pregnancy outcomes, a recent study based on real world data from the US have demonstrated the initial safety of mRNA COVID-19 vaccines in pregnant mothers. In this study, among 3958 participants enrolled in the V-safe pregnancy registry, 827 had a completed pregnancy, of which 115 (13.9%) resulted in a pregnancy loss and 712 (86.1%) resulted in a live birth (mostly among participants with vaccination in the third trimester). Adverse neonatal outcomes included preterm birth (in 9.4%) and small size for...
gestational age (in 3.2%), and no neonatal deaths were reported. The calculated proportions of adverse pregnancy and neonatal outcomes in persons vaccinated against COVID-19 who had a completed pregnancy were similar to incidences reported in studies involving pregnant women that were conducted before the Covid-19 pandemic, although not directly comparable. The authors concluded that preliminary findings did not show obvious safety signals among pregnant mothers who received mRNA COVID-19 vaccines, but recognised that more longitudinal follow-up, including the follow-up of large numbers of women vaccinated earlier in pregnancy, was necessary to inform maternal, pregnancy, and infant outcomes.

There have been some concerns regarding vaccine-induced thrombosis with thrombocytopenia syndrome (TTS) reported in association with the adenovirus vector vaccines AZD-1222 (ChAdOx1 nCoV-10; AstraZeneca) and Ad26.COV2.S (Janssen[Johnson & Johnson]), with a higher predisposition in women less than 50 years of age (7 per million vaccine doses in women less than 50 years of age versus 0.9 for older women and none amongst males for Ad26.COV2.S). However, the risk for death and serious outcomes of COVID-19, including thrombosis, outweigh the risk for TTS possibly associated with vaccination. Therefore, regulatory bodies currently opine that the benefits of prevention of infection by vaccination outweighs the risks. In any case, the above 2 vaccines have not yet been approved for use in Singapore.

There have been reports of cerebral venous sinus thrombosis (CVST) in people who received an mRNA vaccine (Pfizer and Moderna) which may cause concern. However, the incidence of CVST in the matched cohort of people vaccinated with the mRNA vaccine is compatible with the lowest estimate of the baseline rate of CVST in the USA (0.53 per million people in any 2-week interval). Furthermore, the overall risk of developing CVST is eight to ten times higher following COVID-19 infection as compared to the risk associated with receiving a COVID-19 vaccine. Pregnancy itself confers a higher risk for CVST even outside of the context of COVID-19 infection because of the increased thrombogenicity in pregnancy. Although the exact impact of CVST risk in pregnant women vaccinated with the mRNA vaccines remains to be ascertained, it is plausible that the benefits through prevention of COVID-19 infection and its accompanying thrombogenic risk through vaccination may outweigh its risks.

The Centers for Disease Control and Prevention (CDC) and ACIP, in collaboration with the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics, have now issued guidance indicating that Covid-19 vaccines should not be withheld from pregnant persons. The Royal College of Obstetricians and Gynaecologists in the UK now also support that COVID-19 vaccines should be offered to pregnant women at the same time as the rest of the population, based on their age and clinical risk group.

Currently, the large clinical trials demonstrating the safety of COVID-19 vaccines did not include breast-feeding women. As such, there is limited evidence available on the safety of COVID-19 vaccines in lactating women, the effects of vaccination on the breastfed baby and also its effects on milk production or excretion. However, there has been no known risk identified in the
administration of COVID-19 vaccines to breastfeeding mothers, and there is also no plausible scientific mechanism by which any vaccine component could pass to the baby through breast milk. Breastfeeding mothers can thus receive a COVID-19 vaccine. In addition, studies have also demonstrated that breastfeeding mothers who have received an mRNA COVID-19 vaccine have antibodies in their breastmilk which could potentially be protective for the baby, although the nature and extent of protection for the neonate remains to be ascertained.\textsuperscript{13}

**SAFETY OF COVID-19 VACCINATION IN WOMEN PLANNING TO CONCEIVE**

There is no evidence to suggest that COVID-19 vaccines will affect fertility, nor is there any biologically plausible mechanism by which current vaccines would cause any impact on women's fertility. Women who are planning to conceive thus do not need to avoid pregnancy after vaccination.

**RISK STRATIFICATION IN PREGNANT WOMEN**

Pregnant women are at higher risk for severe COVID-19 outcomes compared to non-pregnant women. However, some pregnant mothers are at higher risk than others based on certain risk factors such as:

- Those with pre-existing comorbidities such as chronic hypertension, pre-existing diabetes, renal disease, chronic respiratory disease and heart disease;
- Those with personal risk factors such as obesity, immunosuppression, older age groups (\(\geq 45\) years old);
- Those with pregnancy-associated risk factors such as pre-eclampsia and gestational diabetes;
- Those at a higher risk of acquiring COVID-19 infection based on occupational exposure e.g. frontline workers, healthcare workers;
- Those in the 3\textsuperscript{rd} trimester of pregnancy who are at higher risk for severe COVID-19 disease.
RECOMMENDATIONS ON COVID-19 VACCINATION ON PREGNANT WOMEN, BREASTFEEDING WOMEN AND WOMEN PLANNING TO CONCEIVE

1. All pregnant and lactating women should be provided information and offered COVID-19 vaccination. [Level 4, Grade D]

2. The discussion and offer of vaccination should be based on individual risk factors. [Level 2++, Grade D]

3. Women should receive individualised risk-based pre-vaccination counselling and information regarding benefits of vaccination, possible risks including anaphylaxis, a growing body of evidence of safety in pregnancy and lactation but paucity of long-term robust data. [GPP]

4. Women should be supported in their choice regarding vaccination. [GPP]

5. Pregnant women should be offered vaccination at the same time as the rest of the population, based on their age and clinical risk group, if no contraindications exist. As COVID-19 is associated with more severe complications in the later part of pregnancy, some women may choose to delay their vaccine until after the first 12 weeks which is the most crucial period for fetal development. [Level 3, GPP]

6. Breastfeeding women should be offered vaccination in the absence of other contradictions. [GPP]

7. Breastfeeding can be continued throughout the duration of the vaccine course. [Level 3, GPP]

8. Women planning a pregnancy do not need to delay pregnancy after vaccination as there is no evidence that vaccination impairs fertility. [GPP]

9. Preconception vaccination of reproductive age women should be encouraged. [Level 3, Grade D]

10. Non pregnant reproductive age women assessed to be at higher risk of severe COVID-19 infection should be prioritised for vaccination prior to conception. [Level 2++, Grade D]

11. Women who conceive after the first dose of vaccine may opt to continue with the second dose or defer to a later date as there is little evidence to support delaying or completing vaccination in first trimester of pregnancy. [GPP]

12. The choice of vaccine administered is largely based on local availability. Currently, mRNA Vaccines (Pfizer-BioNTech’s BNT162b2 and Moderna’s mRNA-1273) are preferable to adenovirus vector vaccines for pregnant women and women younger than 50 years of age. [Level 3, Grade D]
13. Irrespective of vaccination status pregnant women should continue to follow safe practices of social distancing, hand washing and mask use. [Level 2++, Grade D]

14. Pregnant women with occupational risk of exposure could have their work-related risk adjusted by deployment to areas of lower exposure risk. [GPP]

RECOMMENDATIONS ON SURVEILLANCE POST COVID-19 VACCINATION

1. Women who opt for vaccination should be encouraged to consent for collection of follow up data regarding pregnancy outcomes. [GPP]

2. A nationwide vaccination-in-pregnancy registry should be established to facilitate uniform collection of data and review of outcomes amongst pregnant women. [GPP]

3. The collected data should be constantly reviewed to base further guidelines on accumulated evidence. [GPP]

RECOMMENDATIONS ON VACCINATION PROTOCOLS AND MANAGEMENT OF SIDE EFFECTS FOR PREGNANT AND BREASTFEEDING WOMEN

1. Vaccination of pregnant women should be done after informed discussion and joint decision with a healthcare professional. [GPP]

2. Vaccination should be performed in a facility with capacity for management of anaphylaxis and emergency resuscitation. [Level 2+, Grade D]

3. Staff involved in vaccination should be trained in recognition and management of anaphylactic reactions. [GPP]

4. Vaccination card recording the details of the vaccination, pregnancy or breastfeeding status and emergency contact numbers should be given to the patient. [GPP]

5. Pyrexia can be managed by using regular paracetamol, in the absence of paracetamol allergy. [Level 2++, Grade B]

6. Patient information leaflet outlining expected symptoms, management and frequently asked questions should be provided. [GPP]

7. A 14-day interval is recommended between the administration of the COVID-19 vaccine and other vaccines in pregnancy such as the influenza or Tdap vaccine. [GPP]
RECOMMENDATIONS ON THE TYPE OF COVID-19 VACCINE ADMINISTERED IN PREGNANCY

1. The choice of vaccine administered is largely based on local availability of vaccines, which are currently the mRNA vaccines Pfizer BioNTech-BNT162b2 and Moderna-mRNA-1273 in Singapore. [GPP]

2. Currently, mRNA vaccines (Pfizer-BioNTech’s BNT162b2 and Moderna’s mRNA-1273) are preferable to adenovirus vector vaccines for pregnant women and women younger than 50 years of age because of available real world safety data on the mRNA vaccines which have not raised any safety concerns. [Level 3, Grade D]

3. Adenovirus vector vaccines (AstraZeneca and Janssen/ Johnson & Johnson) have been associated with vaccine-induced thrombosis with thrombocytopenia syndrome with a higher predisposition amongst women less than 50 years of age. These vaccines have not been approved by Health Sciences Authority (HSA) for use in Singapore [Level 3, Grade D]

4. The data on the use of inactivated SARS-CoV-2 vaccine in pregnancy is currently awaited. [GPP]
## Levels of Evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Type of Evidence</th>
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<tbody>
<tr>
<td>1**</td>
<td>High quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias</td>
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<tr>
<td>1−</td>
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<tr>
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<tr>
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<tr>
<td>3</td>
<td>Non-analytic studies, e.g. case reports, case series</td>
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<td>4</td>
<td>Expert opinion</td>
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## Grades of Recommendation

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<tr>
<td>A</td>
<td>At least one meta-analysis, systematic review of RCTs, or RCT rated as 1++ and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results</td>
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<tr>
<td>B</td>
<td>A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+</td>
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<td>C</td>
<td>A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++</td>
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<td>D</td>
<td>Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+</td>
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<td>GPP</td>
<td>Recommended best practice based on the clinical experience of the guideline development group</td>
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# ACKNOWLEDGEMENT

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