CLINICAL GUIDELINES ON COVID-19 VACCINATION IN MALAYSIA

Ministry of Health, Malaysia
3rd Edition

Executive Summary

The number of COVID-19 vaccines available in Malaysia has increased to five i.e *Cominarty*® (Pfizer-BioNTech), *CoronaVac*® (Sinovac), *ChAdOx1-S* (Oxford-AstraZeneca), *Ad26.COV2-S®[Recombinant]* (Janssen) and *Convidecia™* (CanSinoBio). In general, all the vaccines have shown to be effective and fairly safe with a few important but rare side effects to be aware of.

1. **Allergy concern.** The suspected allergenic ingredients have not changed for any of the vaccines, which is either polyethylene glycol (PEG) or polysorbate 80. *Cominarty*® (Pfizer-BioNTech) has PEG while *ChAdOx1-S* (Oxford-AstraZeneca), *Ad26.COV2-S®[Recombinant]* (Janssen) and *Convidecia™* (CanSino) have polysorbate-80. *CoronaVac*® (Sinovac) has neither PEG nor polysorbate-80. With the many different COVID-19 vaccines in our stable, we are provided with an alternative should one develop an allergic reaction to the other. New flow charts have been added as a quick reference guide for people on the ground. To date, Malaysia's incidence of anaphylaxis following vaccination is quite similar with developed countries. Nonetheless, the importance of reporting cannot be overemphasized.

2. **Vaccine induced Immune thrombocytopenic thrombosis.** Extremely rare cases of thrombosis occurring with thrombocytopenia have been observed following vaccination with *ChAdOx1-S* (Oxford-AstraZeneca) and *Ad26.COV2-S [Recombinant]* (Janssen). This includes some severe cases with thrombosis in different or unusual locations and excessive clotting or bleeding throughout the body. Some cases were life-threatening or had a fatal outcome. Majority of cases occurred within the first 3 weeks following vaccination, though some have also been reported after this period. It seems to be more common in the younger age groups (<60 years old) though it has also been reported in people above 60 years. For people in the younger age groups, the benefits of vaccination outweigh the potential risks during a time of moderate to severe transmission of COVID-19.

3. **Vaccine induced myocarditis/pericarditis.** Extremely rare cases of myocarditis and pericarditis have been observed following vaccination with *Cominarty*® (Pfizer-BioNTech) especially in those below the age of 30. This has been found to be more common in males and in the first week after the second vaccination dose. Most cases have fully recovered. For people under the ages of 30, the benefits of vaccination outweigh the potential risks during a time of moderate to severe transmission of COVID-19.

4. **Pregnant mothers are vulnerable and should be offered the benefits of vaccination.** The implications of COVID-19 infection among pregnant mothers are significant, especially in the late second and third trimester where the need for ICU admission, mechanical ventilation, premature delivery, stillbirth, embolism and maternal deaths have increased. As safety and benefits of vaccination among pregnant and breastfeeding mothers continues to evolve, current evidence suggests that mRNA-based vaccines are safe to be used in pregnancy. Hence, pregnant mothers should be prioritised towards having the mRNA COVID-19 vaccine while safety of other types of vaccines continues to be evaluated. There is no need for cessation of breastfeeding among vaccinated mothers.

Foreword from the Director General of Health Malaysia

Vaccination coverage has been selected as one of the Threshold Indicator for the National Recovery Plan of COVID-19 pandemic in Malaysia. Until the end of June 2021, the National COVID-19 Immunisation Programme has successfully immunised about 17.7 % population with Dose 1 and 7.1% has completed both doses. Supply of vaccine, access to vaccination centre and speed of vaccination are crucial in achieving at least 70% vaccination coverage in our country to attain herd immunity, However, efficacy of vaccine and safety aspect of vaccinee should also be given prime importance during vaccination.

The main objectives of this Guidelines are:

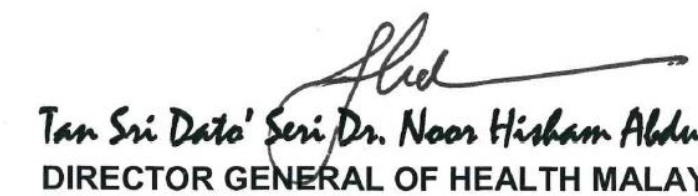
1) To provide pertinent information on COVID-19 vaccines.
2) To explain contraindications and precautions of each vaccine.
3) To guide the healthcare provider in making decision to vaccinate individuals especially those who are at risk of receiving vaccination.
4) To describe various process involves. Namely pre-vaccination assessment, vaccination and post-vaccination.
5) To share frequently asked questions related to – vaccine safety, vaccine eligibility and medical conditions.
6) To provide information on specific clinical condition in relation to immunisation.

As we are entering the third and fourth phase of the vaccination programme, new type of vaccines are used in our country. Hence, this 3rd Edition of Clinical Guidelines On COVID-19 Vaccination in Malaysia has also added pertinent information such as:

1) More recent vaccines - Oxford Astra-Zeneca, Janssen and CanSinoBio vaccine.
2) Recent issues related to vaccination such as - vaccine-induced immune thrombocytopenia, myocarditis and systemic capillary leaking syndrome.
3) Recent update on vaccination for pregnant and lactating mothers.
4) Adverse Events of Special Interest (AESI).

I would like to congratulate the clinicians from various disciplines, the researchers, COVID-19 Immunisation Task Force of Medical Development Division MoH, Public Health Programme of MoH, the university hospitals, all the contributors and organisations for their commitment and hard work in producing this comprehensive updated guidelines.

"Lindung Diri Lindung Semua". Thank you.



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Acknowledgement

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Table of Contents

List of Abbreviations

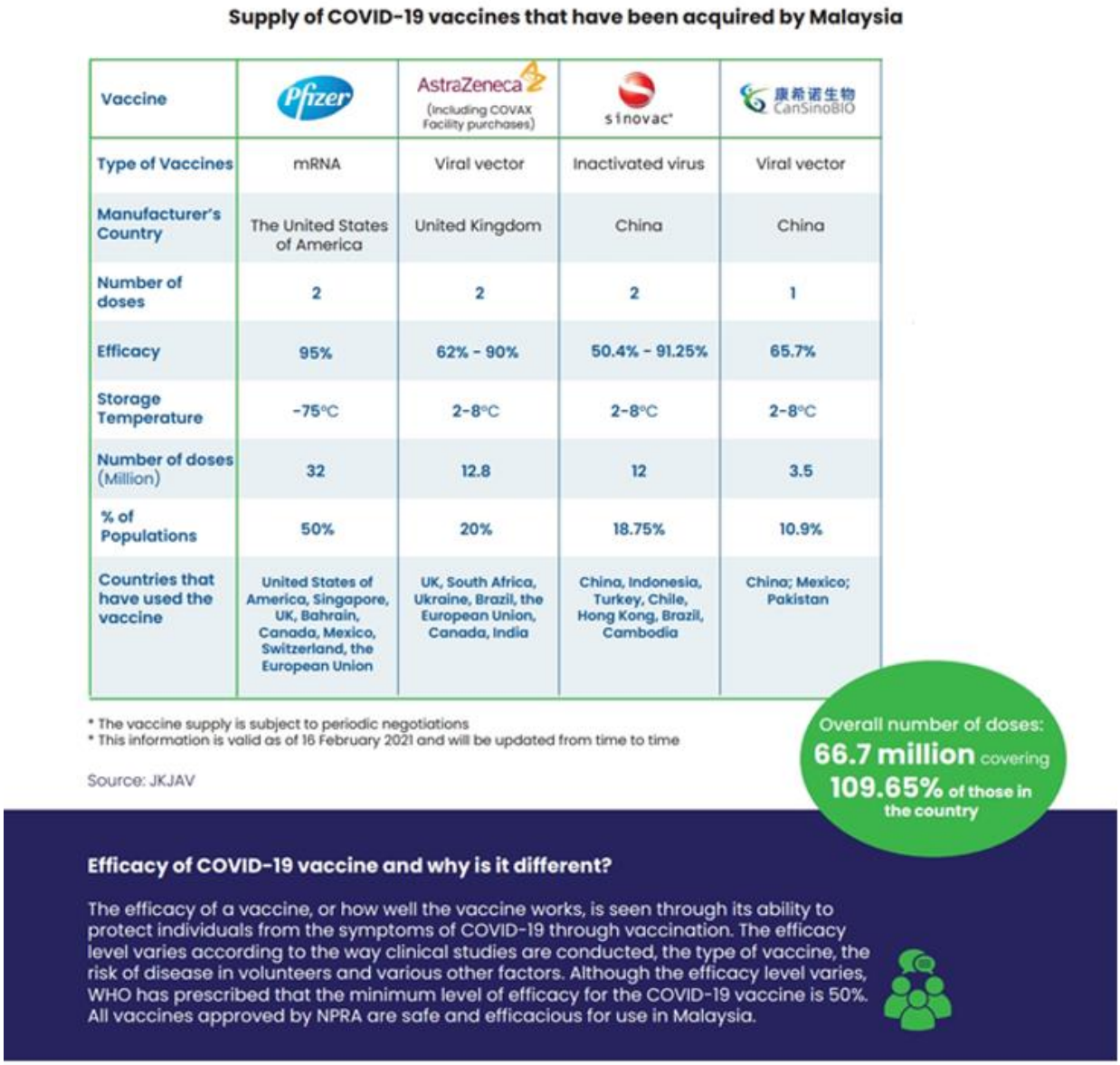
ABC	:	airway, breathing, circulation
ACEI	:	angiotensin converting enzyme inhibitor
ADEM	:	acute disseminated encephalomyelitis
ADR	:	adverse drug reaction
AEFI	:	adverse event following immunization
ANC	:	absolute neutrophil count
anti-TNF	:	antitumor necrosis factor therapy
ART	:	antiretroviral therapy
BMI	:	body mass index
BPD	:	bronchopulmonary dysplasia
CN VII palsy	:	cranial nerve VII palsy
COPD	:	chronic obstructive pulmonary disease
COVID-19	:	coronovirus disease 2019
CSU/A	:	chronic spontaneous urticaria/angioedema
DM	:	diabetes mellitus
DOAC	:	Direct Oral Anticoagulant
DRESS	:	drug reaction with eosinophilia and systemic symptoms
EES	:	erythromycin ethyl succinate
F	:	female
GBFDE	:	Generalized Bullous Fixed Drug Eruption
GBS	:	Guillain Barré Syndrome
HAART	:	Highly Active Antiretroviral Therapy
HIV	:	Human Immunodeficiency Virus
ICU	:	intensive care unit
IgE	:	Immunoglobulin E
IHD	:	ischaemic heart disease
IM	:	intramuscular
INR	:	International Normalised Ratio
IRIS	:	Immune Reconstitution Inflammatory Syndrome
ISRR	:	Immunization Stress Related Response
ITP		Immune Thrombocytopenic Purpura
IV	:	intravenous
LMA	:	laryngeal mask airway
LMWH	:	Low Molecular Weight Heparin
M	:	male
MDI	:	metered-dose inhaler
MMF	:	mycophenolate mofetil
MPE	:	maculopapular eruption
MS		Multiple sclerosis
NPRA	:	national pharmaceutical regulatory agency
NSAIDs	:	non-steroidal anti-inflammatory drugs
OIs	:	opportunistic infections
PEF	:	peak expiratory flow
PEG	:	polyethylene glycol
PhIS	:	pharmacy information system
PLHIV	:	people living with HIV

PVA	:	pre-vaccination assessment
RA	:	rheumatoid arthritis
SBP	:	systolic blood pressure
SCARs	:	severe cutaneous adverse drug reactions
SCLS		Systemic Capillary Leakage Syndrome
SJS	:	Stevens-Johnson Syndrome
SLE	:	Systemic Lupus Erythematosus
SOB	:	shortness of breath
TEN	:	Toxic Epidermal Necrolysis
TIA	:	transient ischaemic attack
TM		Transverse myelitis
TTS		Thrombosis with Thrombocytopenic Syndrome
VITT		Vaccine Induced Immune Thrombocytopenia and Thrombosis

1. COVID-19 Vaccine

1.1 Types of vaccine available in Malaysia

Malaysia has secured 66.7 million doses of COVID-19 vaccine through the COVAX Facility and direct purchase from five vaccine manufacturers. Malaysia will receive the supply of vaccines in stages and subject to approval from the Drug Control Authority (DCA) and the National Pharmaceutical Regulatory Agency (NPRA).



Supply of COVID-19 vaccines that have been acquired by Malaysia

Vaccine	Pfizer	AstraZeneca (including COVAX Facility purchases)	sinovac	康希诺生物 CanSinoBIO
Type of Vaccines	mRNA	Viral vector	Inactivated virus	Viral vector
Manufacturer's Country	The United States of America	United Kingdom	China	China
Number of doses	2	2	2	1
Efficacy	95%	62% - 90%	50.4% - 91.25%	65.7%
Storage Temperature	-75°C	2-8°C	2-8°C	2-8°C
Number of doses (Million)	32	12.8	12	3.5
% of Populations	50%	20%	18.75%	10.9%
Countries that have used the vaccine	United States of America, Singapore, UK, Bahrain, Canada, Mexico, Switzerland, the European Union	UK, South Africa, Ukraine, Brazil, the European Union, Canada, India	China, Indonesia, Turkey, Chile, Hong Kong, Brazil, Cambodia	China; Mexico; Pakistan

* The vaccine supply is subject to periodic negotiations
* This information is valid as of 16 February 2021 and will be updated from time to time

Source: JKJAV

Overall number of doses: **66.7 million** covering **109.65%** of those in the country

Efficacy of COVID-19 vaccine and why is it different?

The efficacy of a vaccine, or how well the vaccine works, is seen through its ability to protect individuals from the symptoms of COVID-19 through vaccination. The efficacy level varies according to the way clinical studies are conducted, the type of vaccine, the risk of disease in volunteers and various other factors. Although the efficacy level varies, WHO has prescribed that the minimum level of efficacy for the COVID-19 vaccine is 50%. All vaccines approved by NPRA are safe and efficacious for use in Malaysia.

Source: Jawatankuasa Khas Jaminan Akses Bekalan Vaksin COVID-19 (JKJAV)

What are the types of vaccines?

Types of vaccines	mRNA	Viral vector	Inactivated virus
Primary content and how it reacts 	mRNA sequence which enters the individual cell to produce the specific virus protein	Contains modified (vector) virus to transport the antigen genetic code. The human cell will produce the targeted protein	Virus that have been killed using high heat, chemical or radiation
Function 	Uses the mRNA molecule to stimulate the immunity in order to recognise the targeted virus protein	A safe viral vector is used to deliver the genetic material of the targeted virus and stimulating the human immune response	Virus that has been killed and used to stimulate the human immune response
Advantages 	• Simple and quick to produce • Does not require living component and synthetically produced. • Triggers an adaptive immune response	• Proven technology • Triggers an adaptive reaction for a more effective immune response	• Proven technology • Suitable for those who have a weak immune system • Easy to produce
Challenges 	• Some mRNA vaccines require extremely cold storage conditions • Used as a vaccine for the first time in medical history	• Complex manufacturing process • Important to ensure the virus vector is safe to be used	• High manufacturing cost
Example	None	Ebola, Vaccines for livestock	Polio, Japanese Encephalitis & Rabies
Vaccine candidate	• Moderna • Pfizer/BioNTech	• AstraZeneca • CanSino Biologics • Johnson & Johnson • Sputnik V	• Sinovac

Source: Analysis & Compilation: The Academy of Sciences Malaysia

1.1.1. Pfizer-BioNTech (*Comirnaty*®)

	Description
Type of vaccine	mRNA
Constituents	• Polyethyleneglycol/macrogol(PEG) as part of ALC-0159. • ALC-0315=(4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), • ALC-0159=2-[(polyethyleneglycol)-2000]-N,N-ditetradecylacetamide • 1,2-Distearoyl-sn-glycero-3-phosphocholine • Cholesterol • Potassium chloride • Potassium dihydrogen phosphate • Sodium chloride • Disodium hydrogen phosphate dihydrate • Sucrose • Water for injection This vaccine contains potassium, less than 1mmol (39mg) per dose, i.e. essentially 'potassium free'. This vaccine contains less than 1mmol sodium (23mg) per dose, i.e. essentially 'sodium free'.
Presentation	The vaccine is a white to off-white frozen dispersion. It is contained in a multi-dose clear glass vial.
Number of doses in each vial	6 doses If more than six 0.3ml doses can be safely and accurately withdrawn from a diluted vial, they can be used as valid doses
Dilution	Yes with 0.9% Sodium Chloride (supplied separately) *For detailed instructions of use, please refer to package insert*
Latex	No The vial has a rubber (bromobutyl) stopper, aluminium seal and a flip-off plastic cap. *Bromobutyl is a synthetic rubber*
Preservatives	No
Dosage	0.3ml
Number of doses required	2
Interval between doses	The recommended interval between doses is 21days
Storage	• **Unopened** vial: Store in a freezer at -90°C to -60°C. • Once **removed** from the freezer, the unopened vaccine can be stored for up to 31 days (1 month) at 2°C to 8°C, and up to 2 hours at temperatures up to 30°C, prior to use • Once **diluted**, vaccine is stable for 6 hours at 2°C to 30°C

<table>
<tr><td>Contraindications</td><td colspan="2">History of anaphylaxis to injectable medicines of multiple different drug classes, or substances possibly containing PEG, idiopathic anaphylaxis
Person with a previous history of severe allergic reactions to the vaccine (e.g. anaphylaxis, SCARs) after a previous dose or to any ingredient of the Pfizer-BioNTech COVID-19 Vaccine
Allergic reaction of any severity within 72 hours after a previous dose or any known (diagnosed) allergy to any ingredient of the Pfizer-BioNTech COVID-19 Vaccine
Acute febrile illness</td></tr>
<tr><td rowspan="5">Possible events (by frequency)</td><td>Very Common (≥1/10)</td><td>Local:
Injection site swelling and erythema

General:
arthralgia, fatigue, fever, headache, myalgia</td></tr>
<tr><td>Common (≥ 1/100 to <1/10)</td><td>Local: injection site pain, erythema

General: nausea</td></tr>
<tr><td>Uncommon
(≥ 1/1,000 to <1/100)</td><td>Local: injection site pruritus

General: insomnia, lymphadenopathy, malaise, extremity pain</td></tr>
<tr><td>Rare
(≥ 1/10,000 to <1/1,000)</td><td>Local: -

General: acute peripheral facial paralysis / Bell’s Palsy</td></tr>
<tr><td>Very Rare</td><td>Anaphylaxis
Myocariditis / pericarditis</td></tr>
</table>

1.1.2. Sinovac *(CoronaVac®)*

	Description
Type of vaccine	Inactivated (Vero Cell)
Constituents	• Aluminium hydroxide • Disodium hydrogen phosphate • Monosodium dihydrogen phosphate • Sodium chloride • Sodium hydroxide • Water for injection
Presentation	Milky-white (opalescent) suspension. Stratified precipitate may form (dispersed by shaking)
Number of doses in each vial	1 dose
Dilution	Not applicable
Latex	No
Preservatives	No
Dosage	0.5ml
Number of doses required	2
Interval between doses	2 – 4 weeks
Storage	Store between +2ºC to +8ºC and protect from light. Do not freeze. Use immediately.
Contraindications	• Person who are hypersensitive or known to be allergic to any components (active ingredients or excipients or any material used in process) of the vaccine or similar vaccines • Person with a previous history of severe allergic reactions to the vaccine (e.g. anaphylaxis, SCARs) after a previous dose or to any ingredient of the vaccine • Allergic reaction of any severity within 72 hours after a previous dose or any known (diagnosed) allergy to any ingredient of the *CoronaVac®* (Sinovac) Vaccine • Person with severe neurological conditions (e.g. transverse myelitis, Guillain-Barre syndrome, demyelinating diseases) • Individuals with uncontrolled severe chronic diseases
Precautions	• Person with acute diseases, acute exacerbation of chronic diseases, severe chronic diseases, allergies and fever

Possible events (by frequency)	Very Common (≥1/10)	Local: injection site pain General: fatigue, headache
	Common (≥ 1/100 to <1/10)	Local: injection site erythema, injection site urticaria, injection site swelling, injection site itchiness, redness, hardening General: muscle pain, nausea, diarrhea, joint pain, cough, shivering, itchiness, loss of appetite, runny nose, sore throat, stuffy nose, stomachache
	Uncommon (≥ 1/1,000 to <1/100)	Local: injection site burning sensation General: vomiting, hypersensitivity, abnormal skin and mucous membrane condition, fever, trembling, flushing, swelling, dizziness, drowsiness
	Rare (≥ 1/10,000 to <1/1,000)	Local: - General: muscle cramp, swelling of eyelids, nose bleeds, bloating, constipation, diminished sense of smell, pink eye, hot flashes, hiccups, eye redness

1.1.3. Oxford-AstraZeneca *(ChAdOx1-S®[recombinant])*

	Description
Type of vaccine	Adenovirus vector
Constituents	One dose (0.5 mL) contains $5x10^{10}$ viral particles of recombinant, replication-deficient chimpanzee adenovirus vector encoding the SARS-CoV-2 Spike (S) glycoprotein. The product contains genetically modified organisms. Excipients: ● L-Histidine ● L-Histidine hydrochloride monohydrate ● Magnesium chloride hexahydrate ● Polysorbate 80 (E 433) ● Ethanol ● Sucrose ● Sodium chloride ● Disodium edetate (dihydrate) ● Water for injections This vaccine contains less than 1mmol sodium (23mg) per dose, i.e. essentially 'sodium free'.
Presentation	Slightly brown, clear to slightly opaque solution Discard if particulate matter or differences in the described appearance are observed Do not shake the vial.
Number of doses in each vial	10 doses
Administration	Intramuscular
Dilution	Not applicable
Latex	No The vial has a rubber (bromobutyl) stopper, aluminium seal and a flip-off plastic cap. *Bromobutyl is a synthetic rubber*
Preservatives	No
Dosage	0.5ml
Number of doses required	2
Interval between doses	6 – 12 weeks

Storage	**Unopened** vial: Store in a refrigerator (2 to 8°C). Do not freeze. Keep vials in outer carton to protect from light. **After first dose withdrawal**: Use the vial as soon as practically possible and within 6 hours (stored at 2°C to 25°C). Discard any unused vaccine.
Contraindications	● History of anaphylaxis to previous non COVID-19 vaccines, injectable medicines of multiple different drug classes, or substances possibly containing polysorbate or polyethylene glycol (PEG), idiopathic anaphylaxis ● Person with a previous history of severe allergic reactions to the vaccine (e.g. anaphylaxis, SCARs) after a previous dose or to any ingredient of the AstraZeneca COVID-19 vaccine ● Allergic reaction of any severity within 72 hours after a previous dose or any known (diagnosed) allergy to any ingredient of the AstraZeneca COVID-19 vaccine
Precautions	● Acute illness/infection ● Pregnancy ● Patients with a history of Cerebral Venous Sinus Thrombosis or splanchnic vein thrombosis. ● Patients with underlying antiphospholipid syndrome ● Patients with a history of heparin-induced thrombocytopenia and thrombosis (HITT or HIT type 2). ● Patients who have experienced major venous and/or arterial thrombosis occurring with thrombocytopenia following vaccination with any COVID-19 vaccine should not receive a second dose of COVID-19 vaccine AstraZeneca

Possible events (by frequency)	Very Common(≥1/10)	Local: injection site tenderness, injection site pain, injection site warmth, injection site pruritus, injection site bruising[a] General: headache, nausea, myalgia, arthralgia, fatigue, malaise, pyrexia[b], chills
	Common (≥ 1/100 to<1/10)	Local: injection site swelling, injection site erythema, injection site induration General: vomiting, diarrhoea, influenza-like illness
	Uncommon (≥ 1/1,000 to <1/100)	Local: rash, pruritus General: lymphadenopathy, decreased appetite, dizziness, abdominal pain, hyperhidrosis
	Rare (≥ 1/10,000 to<1/1,000)	Local: - General: -
	Very rare (<1/10,000)	Thrombosis in combination with thrombocytopenia *Very rare events of neuroinflammatory disorders have been reported following vaccination with COVID-19 Vaccine AstraZeneca. A causal relationship has not been established.*
	Not known (cannot be estimated from available data)	Anaphylaxis, Hypersensitivity

[a] injection site bruising includes injection site haematoma (uncommon, unsolicited adverse reaction)
[b] pyrexia includes feverishness (very common) and fever ≥38°C (common)

1.1.4. Janssen (*Ad26.COV2-S*®[Recombinant])

	Description
Type of vaccine	Adenovirus vector
Constituents	Each 0.5 mL dose contains not less than 2.5 x 10^{10} virus particles of Ad26.COV2-S or not less than 8.92 $\log_{10}$infectious units (Inf.U) Excipients: • Citric acid monohydrate (0.14 mg) • Trisodium citrate dihydrate (2.02 mg) • Ethanol (2.04 mg) • 2-hydroxypropyl-β-cyclodextrin (HBCD) (25.50 mg) • Polysorbate-80 (0.16 mg) • Sodium chloride (2.19 mg) • Hydrochloric acid • Sodium hydroxide • Water for injections This vaccine contains less than 1mmol sodium (23mg) per dose, i.e. essentially 'sodium free' It contains 2 mg of alcohol (ethanol) per 0.5 mL dose. The small amount of alcohol in this medicinal product will not have any noticeable effects.
Presentation	Colorless to slightly yellow, clear to very opalescent suspension. Do not administer if vaccine is discolored or contains particulate matter.
Number of doses in each vial	5 (Discard any remaining vaccine in the vial after 5 doses have been extracted)
Administration	Intramuscular
Dilution	Not applicable
Latex	No The vial stoppers are not made with natural rubber latex (chlorobutyl with fluoropolymer coated surface).
Preservatives	No
Dosage	0.5 mL
Number of doses required	1
Interval between doses	Not applicable

<table>
<tr><td>Storage</td><td colspan="2">Unopened vial:
2 years (stored at -25°C to -15°C)
Once thawed at 2°C to 8°C, to store for 3 months (not exceeding printed expiry date). New expiry date to be updated on the outer carton. Do not re-freeze.
Thawing time: a carton of 10 vials (approx. 12 hours), a single vial (approx. 2 hours)
After first puncture of vaccine vial (opened vial):
6 hours at 2° to 8°C
Discard the vial if vaccine is not used within these times.</td></tr>
<tr><td>Contraindications</td><td colspan="2">History of anaphylaxis to previous non COVID-19 vaccines, injectable medicines of multiple different drug classes, or substances possibly containing polysorbate or PEG, idiopathic anaphylaxis
Person with a previous history of severe allergic reactions to the vaccine (e.g. anaphylaxis, SCARs) after a previous dose or to any ingredient of the Janssen COVID-19 Vaccine
Allergic reaction of any severity within 72 hours after a previous dose or any known (diagnosed) allergy to any ingredient of the Janssen COVID-19 Vaccine</td></tr>
<tr><td>Precautions</td><td colspan="2">Thrombosis with thrombocytopenia
Patients with underlying antiphospholipid syndrome
Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the Janssen COVID-19 Vaccine.</td></tr>
<tr><td rowspan="5">Possible events (by frequency)</td><td>Very Common (≥1/10)</td><td>Local: injection site pain

General: headache, nausea, myalgia, fatigue</td></tr>
<tr><td>Common (≥ 1/100 to <1/10)</td><td>Local: injection site erythema, injection site swelling

General: cough, arthralgia, pyrexia, chills</td></tr>
<tr><td>Uncommon (≥ 1/1,000 to <1/100)</td><td>Local: rash

General: tremor, sneezing, oropharyngeal pain, hyperhidrosis, muscular weakness, pain in extremity, back pain, asthenia, malaise</td></tr>
<tr><td>Rare (≥ 1/10,000 to < 1/1,000)</td><td>Local: -
General: hypersensitivity[a], urticaria</td></tr>
<tr><td>Very Rare (< 1/10 000)</td><td>Thrombosis in combination with thrombocytopenia*</td></tr>
</table>

	Not known (cannot be estimated from the available data)	Anaphylaxis[b]

[a] *Hypersensitivity refers to allergic reactions of the skin and subcutaneous tissue.*
[b] *Cases received from an ongoing open-label study in South Africa.*
** Severe and very rare cases of thrombosis in combination with thrombocytopenia have been reported post-marketing. These included venous thrombosis such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis.*

1.1.5. CanSinoBio (*Convidecia*®)

	Description
Type of vaccine	Adenovirus vector
Constituents	Each 0.5mL contains ≥ 4×10^{10} viral particles of replication-defective recombinant human type 5 Adenovirus expressing S protein of SARS-CoV-2. **Excipients:** • mannitol • sucrose • sodium chloride • magnesium chloride • polysorbate 80 • glycerin • N-(2-Hydroxyethyl) piperazine-N'-(2-ethanesulfonic acid) (HEPES) • water for injection (as solvent)
Presentation	Colorless or slightly white liquid injection
Number of doses in each vial	1
Dilution	No dilution required
Latex	No information available
Preservatives	No
Dosage	0.5mL
Number of doses required	1
Interval between doses	Not applicable
Storage	6 months (when store at 2°C – 8°C)

Contraindications	• History of anaphylaxis to previous non COVID-19 vaccines, injectable medicines of multiple different drug classes, or substances possibly containing polysorbate or PEG, idiopathic anaphylaxis • Person with a previous history of severe allergic reactions to the vaccine (e.g. anaphylaxis, SCARs) after a previous dose or to any ingredient of the *Convidecia*® (CanSinoBio) • Allergic reaction of any severity within 72 hours after a previous dose or any known (diagnosed) allergy to any ingredient of the *Convidecia*® (CanSinoBio) • People with uncontrolled epilepsy and other progressive neurological diseases, and the history of Guillain-Barré syndrome. • Pregnant and lactating women.
Precautions	• People suffering from acute diseases, acute-outbreak period of chronic diseases, severe chronic diseases, allergies and fever • Diabetic patients and those with history of convulsions, epilepsy, encephalopathy or mental illness or family history. • Those with a history of asthma. • Patients with thrombocytopenia or any coagulation dysfunction (intramuscular injection of this vaccine may cause bleeding) • Safety and efficacy data for people with impaired immune function (such as malignant tumors, nephrotic syndrome) is limited should be vaccinated based on individualized considerations. • Those who have been injected with immune globulin should vaccinate at an interval of more than 1 month to avoid decreasing the immune effect. • No evidence of the efficacy of Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector) for people with SARS-CoV-2 infection history at this point • People with positive HIV infection

Possible events (by frequency)	Very Common (≥1/10)	Local: injection site pain General: fever, headache, fatigue, myalgia, drowsiness, nausea, diarrhoea
	Common (≥ 1/100 to <1/10)	Local: injection site swelling, itch, redness, induration General: joint pain, cough, oropharyngeal pain, vomiting, loss of appetite, dizziness, mucosal disease, pruritus; breathing, acute bronchospasm, itching (non-vaccination site), acute allergic reaction, skin and mucosa abnormalities
	Uncommon (≥ 1/1,000 to <1/100)	Local: injection site rash, bleeding, cellulitis General: -

2. Vaccine Priority Groups

Priority groups - Underlying medical conditions that increase the risk of severe illness from COVID-19 (*adapted from Green Book, Public Health England, Chapter 14a, Covid-19*) **Conditions listed here are in no order of priority**		
1	**Immunocompromised due to disease or treatment**	Bone marrow or stem cell transplant recipients
		Solid organ transplant recipients
		Haematological malignancies
		People with cancers undergoing active chemotherapy, immunotherapy, radiotherapy or other targeted therapy that result in immunosuppression
		Genetic disorders affecting the immune system
		Autoimmune diseases like SLE, RA and psoriasis who require long term immunosuppressive treatment
		Those who are receiving systemic steroids for > 1 month at a daily dose equivalent to prednisolone 20mg or more (for adults)
		Individuals who are receiving immunosuppressive or immunomodulating biological therapy such as anti-TNF, rituximab
2	**HIV infection**	Those with CD4 count $\leq$350cells/mm^2 or with additional underlying conditions that increase the risk of severe illness from COVID-19 are to be considered as priority groups for vaccination
3	**Asplenia or dysfunction of the spleen**	Those who have undergone splenectomy and those with conditions that may lead to splenic dysfunction, such as thalassemia major and coeliac syndrome
4	**Chronic heart disease and vascular disease**	Congenital heart disease, hypertension with cardiac complications, chronic heart failure, ischaemic heart disease, individuals with atrial fibrillation, peripheral vascular disease or a history of venous thromboembolism
5	**Chronic kidney disease**	Chronic kidney disease at stage 3, 4 or 5, chronic kidney failure, nephrotic syndrome, kidney transplantation
6	**Chronic liver disease**	Cirrhosis, biliary atresia

7	**Chronic neurological disease**	Stroke, TIA Individuals with cerebral palsy, severe or profound learning disabilities, Down's Syndrome, multiple sclerosis, epilepsy, dementia, Parkinson's disease, motor neurone disease and related or similar conditions; or hereditary and degenerative disease of the nervous system or muscles; or severe neurological disability. Conditions in which respiratory function may be compromised due to neurological disease
8	**Chronic respiratory disease**	Individuals with a severe lung condition, including those with asthma that requires continuous or repeated use of systemic steroids or with previous exacerbations requiring hospital admission, and COPD, including chronic bronchitis and emphysema; bronchiectasis, cystic fibrosis, interstitial lung fibrosis, pneumoconiosis and BPD
9	**Diabetes mellitus**	Type 1 or 2 DM
10	**Obesity**	Adults with a BMI ≥ 30 kg/m²
11	**Severe mental illness**	Individuals with schizophrenia or bipolar disorder, or any mental illness that causes severe functional impairment
12	**Pregnant women**	All pregnant mothers should be offered the benefits of vaccination between 14-33 weeks of pregnancy. High risk mothers should ideally be vaccinated pre-pregnancy.

3. Pre-Vaccination Assessment (PVA)

Pre-vaccination assessment is an assessment conducted preferably by the treating doctor (i.e medical officer or clinical specialist) to determine the suitability of individual to receive vaccine, timing to receive vaccine and suitable facility for the individual to receive vaccination (i.e hospital or other vaccination centre). The patient can also be assessed by the doctor on duty at the vaccination centre (PPV) according to the suitability to do so. For example, patients with history of allergic reaction may not be under regular follow up.

PVA is conducted by assessing the patient current health condition, reviewing relevant result of investigation, reviewing past medical history, medication history and allergy history. Hence, it is best conducted by the doctor who regularly treat the patient.

Not all patients with co-morbidities require PVA. Furthermore, not all patients in hospitals require PVA. Generally, the patients that require PVA can be divided into **3 groups**. Most patients that require PVA are under hospital follow up:

1. **Immunocompromised patients** - Patients with diseases or on medications that can compromise or suppress their immune system. These patients include those with cancers, those who had organ transplants, those with chronic HIV infection or those on immune-suppressing medications. Not all of these patients will require to go to their respective hospitals for vaccination. Further details are in the following table. **(Section 5.1.2)**

2. **Patients with bleeding tendency - Patient** or on medications that can cause bleeding or interfere with the body's ability to stop bleeding. These include patients with hemophilia, those being followed up due to very low platelet levels and are on high doses of anticoagulants. **(Section 5.4)**

3. **Patients with history of severe allergy** (eg: anaphylaxis) - to vaccine or multiple medications or unknown causes. **(Section 3.7, 3.8,3.9)**

Following PVA, the medical officer/clinical specialist will decide whether:

1. Patient can receive vaccination at any time
2. Patient can receive vaccination but at later time (deferred)
3. Patient cannot receive vaccination at any time (absolute contraindication)

*For details on **"Conditions and Optimal Timing for Vaccination"- Refer Section 3.1**

If the patient can receive vaccination, the doctor needs to decide whether he/she can receive vaccination in the hospital or at any Vaccination Centre in the community. The doctor needs to document result of PVA on the "Slip "Penilaian Kesesuaian Menerima Vaksin COVID-19 Bagi Pesakit Dengan Masalah Kesihatan Tertentu" *(Refer example below).*

Not all patients who fall into one of the 3 groups above need to be vaccinated in hospital-based vaccination center (SPPV). Some may still be suitable for vaccination at the community PPV (eg: PPV Awam or Komuniti) with appropriate observations post vaccination. For those who need to be vaccinated in the hospital, the doctor filling up the PVA form will need to make the necessary arrangements for them to be vaccinated in the hospitals where they are being followed up or at any other SPPV. This can be done by contacting the relevant SPPV, District Health Office of SPPV State Coordinator.

KEMENTERIAN KESIHATAN MALAYSIA

Slip "Penilaian Kesesuaian Menerima Vaksin COVID-19 Bagi Pesakit Dengan Masalah Kesihatan Tertentu"

Hospital/Institusi/ Klinik: _____

Nama Pesakit: _____

No. Kad Pengenalan: _____

No. Telefon: _____

Wad / Klinik Pakar: _____

1. Penilaian telah dilakukan kepada pesakit seperti butiran di atas dan mendapati pesakit *(sila tandakan √ pada ruang yang berkenaan)*:

	Boleh menerima vaksin COVID-19 pada masa ini.
	Pemberian vaksin COVID-19 perlu ditangguhkan. Namun boleh menerima vaksin COVID-19 pada tarikh akan datang iaitu selepas (masukkan tarikh) _____
	Tidak boleh menerima vaksin COVID-19 (*absolute contraindication*)

2. Bagi pesakit yang boleh menerima vaksin COVID-19, pesakit ini disarankan untuk menerima vaksin di *(sila tandakan √ pada ruang yang berkenaan)*:

	Hospital / Institusi _____
	Fasiliti kesihatan/ pusat imunisasi yang berhampiran dengan tempat tinggal

3. Langkah tambahan (cth: Pesakit perlu pemantauan lebih panjang setelah menerima imunisasi)

   _____

4. Hasil penilaian ini sah sehingga; _____

Pakar / Pegawai Perubatan yang menjalankan penilaian:

Tandatangan:

Nama dan Cop:

Tarikh penilaian:

Sila bawa bersama Slip ini ke Pusat Pemberian Vaksin untuk ditunjukkan kepada pegawai bertugas di Stesen 3.

3.1. Condition and optimal timing for vaccination

(Ref: Centers for Disease Control and Prevention. (2021, May 14). Vaccines & Immunizations: COVID-19 Vaccines. https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html)

Conditions	Optimal timing for vaccination	Comments
Acute illnesses that require admission to hospital.	Vaccination can be given once the **person recovers** from the acute illness and can perform his/her usual daily baseline activities and is deemed clinically stable by the treating clinician. Patients with acute neurological conditions (e.g. transverse myelitis, GBS, demyelinating diseases, others;) can receive the vaccine after stabilization and deemed suitable by the treating clinician.	
Persons who previously had SARS-CoV-2 infection	Vaccination should be deferred until the person has recovered from the acute illness (if symptomatic) and has met criteria to discontinue isolation. While current evidence suggests that natural infection with SARS-CoV2 results in good protection against reinfection for at least 3 months, the emergence of viral variants (which might be less susceptible to natural immunity) can be an indication for earlier vaccination. However, if in the event of vaccine shortage, it is recommended to prioritize those uninfected by COVID-19 before.	
Recovered COVID-19 patients who received **anti-SARS-CoV-2** monoclonal antibodies or convalescent plasma as part of COVID-19 treatment.	Vaccination should be deferred for at least 90 days. This is a precautionary measure until additional information becomes available, to avoid potential interference of the antibody therapy with vaccine-induced immune responses. This recommendation applies to people who receive passive antibody therapy before receiving any vaccine dose and to those who receive passive antibody therapy after the first dose of an mRNA vaccine but before the second dose, in which case the second dose should be deferred for at least 90 days following receipt of the antibody therapy.	

	COVID-19 vaccine doses received within 90 days after receipt of passive antibody therapy do not need to be repeated.	
Conditions	**Optimal timing for vaccination**	**Comments**
Persons being quarantined at quarantine centre or under HSO for being a **close contact**.	Vaccination may be given once the persons have completed the required days of quarantine/self-isolation and no new symptoms to suspect active COVID-19 infection.	
Recent immunisation with any other vaccines.	It is recommended that vaccination to be deferred or scheduled at least after 2 weeks before or after COVID vaccine However, administration of other non-COVID vaccines may be allowed within 14 days in certain conditions i.e. whether the patient is behind or at risk of becoming behind on recommended vaccines or are at risk of a vaccine-preventable disease (e.g. tetanus vaccination in pregnant women, during an outbreak or occupational exposures)	
Terminally ill with life expectancy <1 month	Not for vaccination	
Very frail elderly	Those with Clinical Frailty Score 8: Vaccination should still be encouraged if patient is not actively dying and there are no acute medical issues *Refer to Table 1 in Appendix 3 for further details	
Obstetrics & Gynaecology	Refer to Appendix 4	
HIV not on ARTs **and** CD4 count $\leq$350cells/mm^2	Optimal timing of vaccination to be decided after discussion with the health care provider of the patient.	
History of anaphylaxis to vaccines or medications	Please refer to Section 4.2, 4.3	

<table>
<tr><th>Conditions</th><th>Optimal timing for vaccination</th><th>Comments</th></tr>
<tr><td>Solid organ cancers on active chemotherapy, radiotherapy, or immunotherapy (excluding hormonal treatment) in remission or a cancer survivor</td><td>Discuss with patient’s health care provider regarding the optimal spacing for vaccination and the cancer therapy (Refer to Appendix 5)</td><td rowspan="7">COVID-19 vaccine is not a live vaccine, and hence it is NOT contraindicated for the immunocompromised.

Immunocompromised hosts are at high risk of severe COVID-19 infection.

However, there is insufficient data on the efficacy of vaccine.

To balance between optimising efficacy of the vaccine and providing timely protection against COVID-19 infection, optimal timing of vaccination has to be decided after discussion with the health care provider of the patient.

Please refer to COVID-19 Vaccination for Patients with Haematological Disorders (Appendix 6) and Vaccination for Patients with Rheumatic and Musculoskeletal diseases (RMD) and Autoimmune and Inflammatory Rheumatic Diseases (AIIRD) (Appendix 7) and COVID-19 Vaccination for Cancer Patients with Solid Tumours (Appendix 5) for detailed information.</td></tr>
<tr><td>Autoimmune diseases like systemic lupus erythematosus and rheumatoid arthritis, and psoriasis who require long term immunosuppressive treatment</td><td>Discuss with patient’s health care provider regarding the optimal spacing for vaccination and the immunosuppressive treatment.</td></tr>
<tr><td>Patients receiving systemic steroids with a dose ≥20mg of prednisone or equivalent for ≥14days</td><td rowspan="2">Discuss with patient’s health care provider regarding the optimal spacing for vaccination and the immunomodulating agents.</td></tr>
<tr><td>Individuals who are receiving immunosuppressive or immunomodulating
biological therapy such as anti-TNF, rituximab</td></tr>
<tr><td>Transplant recipients:
Solid organ
Bone marrow / stem cell</td><td>At least 3 months after transplantation</td></tr>
<tr><td>Hematological malignancies</td><td>In those receiving intensive cytotoxic chemotherapy, it is advised to delay until ANC recovery.
However, for those on long term therapy or those who are expected to have limited or no recovery of marrow failure, vaccination is recommended as soon as vaccine is available.</td></tr>
</table>

Conditions	Optimal timing for vaccination	Comments
Haemophilia	There are no specific contraindications to vaccination related to complications of haemophilia and other bleeding disorders or their therapies. For patients with severe/moderate haemophilia A or B, the vaccine injection should be given after a prophylactic dose of Factor VIII (FVIII) or Factor IX (FIX). For patients with a basal FVIII or FIX level above 10%, no haemostatic precautions are required.	The bleeding risk can be reduced by application of firm pressure at the injection site for **5 to 10 minutes** afterwards. Use a **25- or 27-gauge needle** to reduce the pressure gradient as it causes less trauma to the tissue. The vaccine should be injected slowly (≥5 seconds) to reduce the risk of tissue damage. Stabilisation of the limb will reduce the risk of a haematoma. The site should not be rubbed or massaged. Inspect the injected limb after several minutes and 4-6 hours later and to report any concerns to the vaccination centre. Please refer COVID-19 Vaccination for Patients with Haematological Disorders for detailed information (Appendix 6)
Patients on anticoagulant (e.g. warfarin) and antiplatelet agents	Patients with stable anticoagulation with INR < 4 on their last scheduled visit can receive IM vaccination without stopping the drug. Patients on concomitant warfarin and anti-platelet therapy, should be managed on an individual basis in consultation with their primary physician. On the day of vaccination, warfarin should be taken **AFTER** the vaccine injection.	
Patients with known thrombocytopenia (platelet count <50,000)	Should defer the vaccination till their platelet counts recover, if possible. For those with chronically low platelet counts, vaccination should be performed in consultation with their primary haematologist.	
Patients taking DOAC or LMWH or fondaparinux	Can delay the dose on the day of vaccination until after the intramuscular injection but do not need to miss any doses.	
Patients with thrombocytopenia	Patients with platelet counts ≥ 50,000 can proceed with vaccination without additional haemostatic support.	

Patients with rare bleeding disorder (including platelet function disorders)	Should be vaccinated in consultation with their primary haematologist.	

3.2. Vaccines for Sub-populations

Sub-population	Vaccines				
	***Cominarty*®** **(Pfizer-BioNTech)**	***CoronaVac*®** **(Sinovac)**	***ChAdOx1-S*®** **(Oxford-Astra Zeneca)**	***Ad26.COV2-S*® *[Recombinant]*** **(Janssen)**	***Convidecia*®** **(CanSinoBio)**
Children / Teenager	**FDA[11]:** • Comparable data for efficacy, immunogenicity and adverse profile **CDC[6]:** • Pericarditis and myocarditis in adolescents 16 years and older • More common after 2nd dose. • Symptoms: Chest pain, dyspnea and palpitation • Self-limiting	No data available *Data not released: ongoing Phase IIb trial (n=500) for child aged 3-17*	No data available	No data available	No data available

Persons below 60 years old	**Recommended**[12]	**Recommended**[3]	**Recommended when other vaccines are not immediately accessible** Risk of TTS[9] • 8 per million doses • Monitor symptoms for 3 weeks after vaccination (reported cases: 5-21 days)	**Recommended when other vaccines are not immediately accessible** Risk of TTS[9] - 7 per million doses (women) - Monitor symptoms for 3 weeks after vaccination (reported cases: 6-15 days)	No data available

Population	**Vaccines**				
	***Cominarty*® (Pfizer-BioNTech)**	***CoronaVac*® (Sinovac)**	***ChAdOx1-S*® (Oxford-Astra Zeneca)**	***Ad26.COV2-S*® *[Recombinant]* (Janssen)**	***Convidecia*® (CanSinoBio)**
Pregnancy[18]	**Recommended** Preferred vaccine in view of safety data. First dose ideally to be administered between 14-33 weeks of gestation. It is not contraindicated beyond this gestation and it is best to discuss with the obstetrician on potential benefits if required.	**Not contraindicated in pregnancy** Weigh benefits risk ratio. May be administered if the patient conceives after the first dose of CoronaVac® or in circumstances where access to mRNA vaccine is limited	**Not contraindicated in pregnancy** Weigh benefits risk ratio. May be administered if the patient conceives after the first dose of ChAdOx1-S®. Discuss with obstetrician on the benefits against potential risk of AZ vaccine in pregnancy especially the rare association of VIIT.	Limited safety data	

Breastfeeding[18]	Recommended	Not contraindicated	Limited safety data
Fertility[18]	Recommended		Limited safety data

For more information on vaccination for pregnancy and breastfeeding mothers:

- Link to **interactive Q&A** (YouTube) – https://youtu.be/gA2b_g3w24Q (BM), https://youtu.be/gA2b_g3w24Q (Eng)
- **E-book** "*Real Issues for COVID-19 Vaccine Immunization & Pregnancy, Breastfeeding Mothers*" – can be accessed at http://nih.gov.my/covid-19/component/content/article/92-e-books/214-real-issues-for-covid-19-vaccine-immunization-pregnancy-breastfeeding-mothers?Itemid=437

Population	**Vaccines**				
	***Cominarty*® (Pfizer-BioNTech)**	***CoronaVac*® (Sinovac)**	***ChAdOx1-S*® (Oxford-Astra Zeneca)**	***Ad26.COV2-S*® *[Recombinant]* (Janssen)**	***Convidecia*® (CanSinoBio)**
Older patients over 60 years old	**Recommended** (based on published phase 3 data)[13]	**Recommended** (based on published phase 2 and interim phase 3 data)[19,21]	**Recommended** • Real-world data from UK (post single dose): 55-70% (overall effectiveness); 75-85% (against hospitalization) [15] • Incidence of AESI is lesser than the younger population [15]	**Recommended** (based on Phase 3 data) • Incidence of AESI is lesser than the younger population [16]	**Awaiting Phase 3 data** Phase 2 data[22]: • May need to consider booster dose as lesser immunogenicity and humoral response observed • No serious adverse effects observed

History of GBS	Recommended[7]	Not recommended[17]	Recommended[7]	Recommended[7]	Not recommended[3]
History of Bell's palsy	Recommended[7,10]	No data available	Recommended[7]	Recommended[7]	No data available
History of thrombo-embolism (or history of thrombosis and thrombocytopenia within 90 days)	Recommended[8]	Recommended[17]	Not recommended[2]	Not recommended[8]	Recommended[3]
Allergic to Polysorbate	Not recommended[4]	Recommended[17]	Not recommended[4]	Not recommended[4]	Not recommended[3]
Allergic to PEG	Not recommended[12]	Recommended[17]	Not recommended[1]	Not recommended[5]	Not recommended[3]

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3.3. Allergy concern of COVID-19 vaccines available in Malaysia

The complete list of components of all the pre-existing COVID-19 vaccines is documented in Chapter 2. The possible allergens of concern that may contribute to the immediate allergic reactions after vaccination are polyethylene glycol (PEG) and polysorbate-80.[1] Polysorbate and PEG are structurally related. PEGs are widely used as excipients and conjugated pharmaceuticals, cosmetic, industrial and food products.[1] Exposure extends from household to perioperative setting, and PEGs are common constituents of a variety of products including wound dressings, PEGylated drugs, and hydrogels as well as tablets, lubricants such as echocardiogram or ultrasound gel, laxatives, bowel preparation and dental floss.[1] PEG allergy is very uncommon as shown in this list, despite its widespread use. Most reported reactions to PEG in the literature are due to high molecular weight PEGs.[1]

Polysorbate-80 is also an excipient in a multitude of medical preparations (e.g, vitamin oils, vaccines, and anticancer agents), creams, ointments, lotions, and medication tablets.[1] People with PEG allergy may also be allergic to polysorbate-80 which is widely used in medicines particularly in biologics, and in processed foods.[1] For a more complete list of medicines and vaccines that contain PEG and polysorbate, please refer to Appendix 1.

Individuals who have tolerated polysorbate-containing injections (e.g. influenza vaccine) are likely to tolerate the COVID-19 Vaccine containing polysorbate-80 such as *ChAdOx1-S*® (Oxford-AstraZeneca), *Ad26.COV2-S*®[Recombinant] (Janssen) and *Convidecia*® (CanSinoBio). Table 1 below shows the allergens of concern that are found in the COVID-19 vaccines available in Malaysia.

Table 1: Presence of PEG and polysorbate-80 in COVID-19 vaccines available in Malaysia.

COVID-19 vaccine	PEG	Polysorbate-80
Cominarty® (Pfizer-BioNTech)	√	X
ChAdOx1-S® (Oxford-AstraZeneca)	X	√
Ad26.COV2-S® *[Recombinant] (*Janssen)	X	√
Convidecia™ (CanSinoBio)	X	√
CoronaVac® (Sinovac)	X	X

The incidence of anaphylaxis reported due to different type COVID-19 vaccines is shown in Table 2. The incidence of anaphylaxis of *Cominarty*® (Pfizer-BioNTech) is reported to be between 4.7-24 cases per million doses inoculated. There is no published real-world data on the anaphylaxis following *Convidecia*® (CanSinoBio) to date.

Table 2. The incidence of anaphylaxis following COVID-19 vaccinations based on reports on adverse event following immunizations in different countries.

COVID-19 vaccine	**Incidence of anaphylaxis** (cases /million doses)					
	CDC US	**MHRA UK** Updated 9/6/21	**Japan** Updated 16/5/21	**Singapore** Updated 23/5/21	**Chile** Updated 27/4/21	**Malaysia** Updated 16/6/21
Cominarty® (Pfizer-BioNTech)	4.7[2,3]	14.2[5]	24[7]	8.8*[8]		6.7[§]
ChAdOx1-S (Oxford-AstraZeneca)		17.5[6]				0[§]
Ad26.COV2-S® [Recombinant] (Janssen)	<0.5[4]					
Convidecia™ (CanSinoBio)						
CoronaVac® (Sinovac)					17[9]	0.8[§]

CDC US - Center for Disease Control and Prevention, United States of America
MHRA UK- The Medicines and Healthcare products Regulatory Agency, United Kingdom
* The incidence reported is for both Cominarty® (Pfizer-BioNTech) and mRNA-1273 SARS-CoV-2 vaccine (Moderna).
[§]Unpublished data, updated 16/6/21 by the National Pharmaceutical Regulatory Agency (NPRA) Malaysia

	Vaccine not used in the country or no available data to date

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3.4. Guidance on the indications and contraindications to COVID-19 vaccinations for selected hypersensitive population

Types of hypersensitivity	Vaccination decision
Drug Hypersensitivities	
• Persons with a history of immediate type of penicillin allergy • Persons with a history of immediate type of antibiotics allergy (other than penicillin) • Persons with a history of an identified immediate type of drug hypersensitivity	**Can receive** COVID-19 vaccines
• Persons with a history of anaphylaxis to penicillin or other types of antibiotics • Persons with a history of anaphylaxis to an identified drug (e.g. neuromuscular blocking agent (NMBA), anesthetic induction agent, local anesthetic, antiseptic)	**Can receive** COVID-19 vaccines However, should be observed longer in a controlled environment.
Persons with multiple oral NSAIDs hypersensitivity (urticaria/angioedema not involving the larynx/bronchospasm)	**Can receive** COVID-19 vaccines *Many will have multiple chemically unrelated NSAIDs cross-intolerant reactions.* *About 15-20% of these will have reactions involving two systems (skin/mucosa and bronchospasm) termed **'blended'** reactions[1], with resolution from antihistamines and corticosteroid institution.*
Persons with NSAIDs-induced fixed drug eruptions or SCARs	**Can receive** COVID-19 vaccines
Persons with NSAIDs-induced **anaphylaxis**	**Can receive** COVID-19 vaccines However, should be observed longer in a controlled environment. NSAIDs-induced anaphylaxis may be due to an IgE-mediated reaction (skin test positive) and **does not** cross react with other chemically unrelated NSAIDs group. *NSAIDs can be a co-factor for food-induced IgE-mediated anaphylaxis, e.g., wheat component (omega-5-gliadin) sensitization should be ruled out

Types of hypersensitivity	Vaccination decision
• Biologics and/or chemotherapy hypersensitivity • PEGylated biologics/chemotherapy hypersensitivity	**Do not give vaccine containing PEG or polysorbate*** May consider other type of COVID-19 vaccine **without PEG or polysorbate (e.g. *CoronaVac*® (Sinovac))** May consider referring for investigations of polysorbate 80 and PEG hypersensitivity.
History of unexplained recurrent anaphylaxis to unidentified injectable medications (e.g. multiple groups of chemically unrelated drugs or idiopathic anaphylaxis)	**Do not give vaccine containing PEG or polysorbate*** May consider other type of COVID-19 vaccine **without PEG or polysorbate (e.g. *CoronaVac*® (Sinovac))** These individuals should be investigated for the underlying cause. Consider referral for PEG and polysorbate 80 testing. If skin test positive for PEG or polysorbate 80, **contraindicated** to receive **vaccine containing PEG or polysorbate**. Consider other types of COVID-19 vaccines **without PEG or polysorbate**. However, should be observed longer in a controlled environment.
Mild allergic reaction (non-generalized urticaria) to an unidentified medication	**Can receive** COVID-19 vaccines
Vaccine hypersensitivity	
Persons with history of anaphylaxis to other non-COVID-19 vaccines	**Do not give vaccine containing PEG or polysorbate*** May consider other type of COVID-19 vaccine **without PEG or polysorbate (e.g. *CoronaVac*® (Sinovac))** May consider referring for investigations of polysorbate 80 and PEG hypersensitivity. Many non-COVID-19 vaccines contain polysorbate 20 or polysorbate 80

** Note: Cominarty® (Pfizer) contains **PEG**.*
*ChAdOx1-S®[recombinant] (Oxford-AstraZeneca), Ad26.COV2-S®[Recombinant] (Janssen) & Convidecia™ (CanSinoBio) contain **polysorbate-80***

Contrast media hypersensitivity	
Persons with history of contrast media hypersensitivity reaction (**not anaphylaxis**)	**Can receive** COVID-19 vaccine
Persons with history of contrast media **anaphylaxis**	**Can receive** COVID-19 vaccine However, should be observed longer in a controlled environment
Persons with history gadolinium-based contrast media hypersensitivity reaction during MRI	**Contraindicated to receive the *Moderna* mRNA vaccine**. **Can receive** *Cominarty*® (Pfizer), *CoronaVac*® (Sinovac), *ChAdOx1-S*® (Oxford, AstraZeneca), *Ad26.COV2-S®[Recombinant]* (JANSSEN) or *Convidecia™* (CanSinoBio) **Gadolinium-based contrast media hypersensitivity reaction has been reported to be due to the excipient **TROMETAMOL[2]**, a component contained in the Moderna vaccine.*
Contact Allergy	
Persons with history of reactions or contact allergy with patch test positive to nickel, perfumes, and cosmetics	**Can receive** COVID-19 vaccines
Identified food, environment and latex	
Persons with history of allergic reaction to specific identified foodstuff (e.g. shellfish, wheat, peanut, soy, cow's milk, egg, gelatin), environment (e.g. house dust mites, pollens), latex	**Can receive** COVID-19 vaccines The current COVID-19 vaccines do not contain derivatives from shellfish, wheat, peanut, soy, cow's milk, egg, gelatin. The vial stopper of all COVID-19 vaccines is made from synthetic rubber. Thus, there is no issue concerning latex contamination.
Persons with convincing history of anaphylaxis to specific identified foodstuff (e.g., shellfish, wheat, peanut, soy, cow's milk, egg), environment, (e.g. house dust mites, pollens), latex	**Can receive** COVID-19 vaccines However, should be observed longer in a controlled environment as a precaution. **Vaccines may be manufactured in a manufacturing facility where trace amounts of e.g. shellfish, wheat, peanut, soy, cow's milk, egg may be present*

Venom allergy	
Persons with history of venom anaphylaxis (e.g., insect or bee or wasp stings)	**Can receive** COVID-19 vaccine However, should be observed longer in a controlled environment. **Persons with history of venom anaphylaxis should be investigated for mast cell disorder* **Persons receiving venom immunotherapy (or other allergen immunotherapy) should be timed accordingly (~ 48 hours interval) with the COVID-19 vaccine to avoid confusion (should an allergic reaction occur)*
Urticaria/Angioedema	
Persons with history of chronic spontaneous urticaria / angioedema (CSU/A)	**Can receive** COVID-19 vaccine However, these individuals should take their normally prescribed daily antihistamine(s) as usual, even on the day of vaccination. These individuals should be observed longer in a controlled environment. **Persons with CSU/A may experience mild (non-generalized) urticaria after vaccination. Urticaria is often triggered by stressors (for these individuals)* **Persons with CSU/A on immunosuppressive therapy such as cyclosporin should be able to receive the currently available COVID-19 vaccines as none are live attenuated vaccines*
Persons with angiotensin ACEi-induced angioedema	**Can receive** COVID-19 vaccines However, should be observed longer in a controlled environment.
Persons with hereditary angioedema type I, II and III or acquired angioedema	**Can receive** COVID-19 vaccines.[3] However, should be observed longer in a controlled environment.

Atopy	
Persons with underlying asthma on medication	**Can receive** COVID-19 vaccines **Underlying asthma is **NOT a contraindication** to receive the vaccine* **Poorly controlled asthma should be assessed by the treating physician for suitability and timing of the COVID-19 vaccination* **Asthmatic persons on **high dose oral prednisolone (>20 mg/day) should defer vaccination** until oral prednisolone can be stopped* **Atopic or eosinophilic asthmatic persons on omalizumab, benralizumab, dupilumab, mepolizumab, reslizumab **can receive** the mRNA or viral-vector COVID-19 vaccines* [4] For inactivated virus vaccines, vaccinations should be placed approximately midway through the treatment interval (i.e., between two applications of the respective biologics). [4]
Persons with allergic rhinitis	**Can receive** COVID-19 vaccines
Persons with atopic dermatitis	**Can receive** COVID-19 vaccines
Mast cell disorder	
Persons with systemic mastocytosis or mast cell activation disorder	**Can receive** COVID-19 vaccines However, should be observed longer under medical surveillance. **Persons with mast cell disorder with raised mast cell tryptase requiring treatment should continue their antihistamines, mast cell stabilizers, imatinib during vaccination* [5]

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3.5. Scheme for contraindications and precautions when considering vaccination for COVID-19

	Proceed with Vaccination	Special Precautions	Vaccination Contraindicated
Patient Characteristics	1. Prior history of allergic reaction (of any severity including anaphylaxis) to an identified food or venom or pet or environmental allergens/ medications/ latex 2. Bronchial asthma 3. Atopy (eczema, allergic rhinitis, allergic conjunctivitis) 4. Family history of allergies 5. Local reaction and non-allergic reactions to a previous dose of vaccine 6. Hypersensitivity to multiple oral non-steroidal anti-inflammatory drugs (NSAIDs) e.g. aspirin, diclofenac acid, mefenamic acid, ibuprofen, naproxen, paracetamol 7. Chronic spontaneous urticaria 8. Angiotensin converting enzyme inhibitor (ACEi) induced angioedema 9. Severe cutaneous adverse drug reactions (SCARs)* or other non-IgE mediated hypersensitivities[#] to identified medications/agents 10. Patients receiving omalizumab, dupilumab or other specific biologics for allergic diseases	1. History of **anaphylaxis or allergic reactions of any severity** towards previous vaccines *(eg influenza, pneumococcal, meningococcal group B, Hepatitis A or B, Human papillomavirus etc)* 2. History of **anaphylaxis** to injectable medicines or substances possibly containing polyethylene glycol (PEG) or polysorbate[¶]. 3. History of **anaphylaxis** to multiple different drug classes 4. History of **idiopathic anaphylaxis**	1. **Severe allergic reactions** (e.g. anaphylaxis, SCARs) after a previous dose or to any ingredient[§] of the COVID-19 vaccine 2. **Allergic reaction of any severity within 72 hours** after a previous dose or to any ingredient[§] of the COVID-19 vaccine.

Actions	• ***Proceed with vaccination*** *according to local guidelines and settings* *Observation period of 15-30 minutes post vaccination*	**Do not administer:** *Cominarty*® (Pfizer) *ChAdOx1-S*® (Oxford-AstraZeneca), *Ad26.COV2-S®[Recombinant] (*Janssen) *Convidecia™* (CanSinoBio) **Can administer CoronaVac® (Sinovac)**	• **Do not vaccinate with the same vaccine in question (refer below):** **1. Cominarty® (Pfizer), ChAdOx1-S® (Oxford-AstraZeneca)** - To administer *CoronaVac*® (Sinovac), 2 doses 3 weeks apart **2. *CoronaVac*® (Sinovac)** - To administer a single dose of Ad26.COV2-S®[Recombinant] (Janssen) or Convidecia™ (CanSinoBio) **3. Ad26.COV2-S®[Recombinant] (Janssen) or Convidecia™ (CanSinoBio)** - Vaccinee does not need a second dose - If booster is needed in the future, to use *CoronaVac*® (Sinovac) • Consider referral to allergists/immunologists if no other vaccine available • Vaccinate alternative second dose in a hospital-based vaccination center

*SCARs – severe cutaneous adverse drug reactions include Stevens-Johnson Syndrome (SJS); toxic epidermal necrolysis (TEN); drug reaction with eosinophilia and systemic symptoms (DRESS); acute generalized exanthematous pustulosis (AGEP); generalized bullous fixed drug eruption (GBFDE) and acute erythroderma.
other non-IgE mediated hypersensitivities include vasculitis, maculopapular eruptions, erythema multiforme, fixed drug eruption, symmetrical drug-related intertriginous flexural exanthema
§ ingredient – please refer to Chapter 2 COVID-19 Vaccines
¶ *Cominarty® (Pfizer)* contains **PEG**. *ChAdOx1-S®[recombinant] (Oxford,AstraZeneca), Ad26.COV2-S®[Recombinant] (JANSSEN) & Convidecia™ (CanSinoBio)* contain **polysorbate-80**. PEG and polysorbate are structurally related, cross-hypersensitivity between these compounds may occur.

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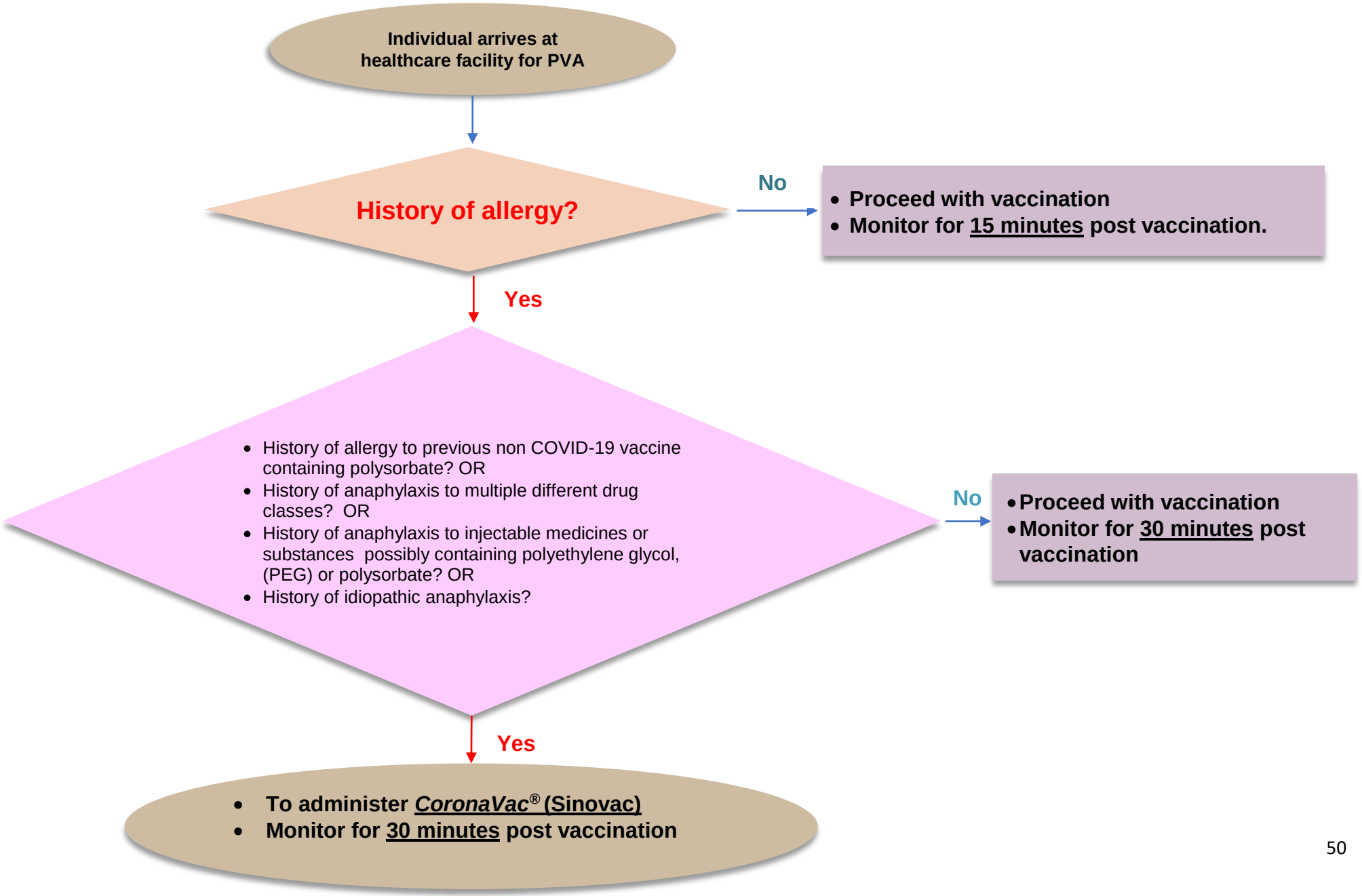
3.6. Flowchart on Pre-vaccination Assessment Process for mRNA or viral vector vaccines on Individual with History of Allergy



3.7. Case scenarios for allergy assessment BEFORE the first dose of COVID-19 vaccine

Allergy details	Vaccination decision	Precaution
50/M with urticaria, lips swelling and shortness of breath (SOB) to penicillin 30 years ago.	**Can vaccinate** Anaphylaxis to penicillin	Observe for **30 minutes** after vaccination
35/F with history of wheals and angioedema to paracetamol, oral naproxen and IM diclofenac. Given adrenaline injection x1, hydrocortisone and chlorpheniramine at casualty when she had angioedema and SOB due to IM diclofenac.	**Can vaccinate** NSAIDs hypersensitivity	
45/F with chronic spontaneous urticaria (CSU). She had history of angioedema and throat swelling to paracetamol, ibuprofen and mefenamic acid. Her symptoms currently controlled with oral cetirizine 20mg bd.	**Can vaccinate** **Continue antihistamines as usual.** CSU and NSAIDs hypersensitivity	
20/M with history of lips swelling and wheals after eating shellfish (prawn and crab). His symptoms resolved spontaneously within 24 hours.	**Can vaccinate** Allergy or intolerance to seafood	
75/F with DRESS to allopurinol 15 years ago. She has eczema after resolution of DRESS under dermatology follow up.	**Can vaccinate** DRESS to drugs other than vaccine is not a contraindication	
45/M with HIV, history of maculopapular rash to sulfamethoxazole and trimethoprim (*Bactrim®)*, CD4 = 240, viral load undetectable. No throat swelling, no shortness of breath.	**Can vaccinate** MPE (type IV hypersensitivity) to sulfamethoxazole and trimethoprim (*Bactrim®)*	
43/F with generalized rash after flu vaccine last year. No throat swelling, no shortness of breath, no angioedema, no syncopal attack.	**Do not give vaccine with PEG or polysorbate** Allergic to previous influenza vaccine. Most influenza vaccines contain polysorbate.*	To administer ***CoronaVac®* (Sinovac).** Observe for 30 minutes after vaccination
67/M flushing and generalized wheals after alcohol and certain preserved/fermented food (sausages, cheese). No angioedema.	**Can vaccinate** Histamine intolerance to alcohol/food that contain high histamine	Observe for **30 minutes** after vaccination

Allergy details	Vaccination decision	Precaution
30/M SJS/TEN overlap to carbamazepine 5 years ago.	**Can vaccinate** SJS/TEN to drugs other than vaccine is not a contraindication	Observe for **30 minutes** after vaccination
66/M holding an allergy card GBFDE to celecoxib.	**Can vaccinate** GBFDE to drugs other than vaccine is not a contraindication	Observe for **30 minutes** after vaccination
58/F had angioedema and wheals associated with SOB after taken Forlax® (Macrogol 4000) for constipation	**Do not give vaccine with PEG or polysorbate** Immediate hypersensitivity to Forlax® (Macrogol 4000). Forlax® contains PEG*.	To administer ***CoronaVac®*** **(Sinovac).** Observe for **30 minutes** after vaccination
70/F with DM, IHD, hypertension and perindopril induced angioedema.	**Can vaccinate** ACE inhibitor induced angioedema	Observe for 30 minutes after vaccination
18/M poorly control bronchial asthma. He is wheezing.	**Defer vaccination**	To get assessment by physician and optimize bronchial asthma control.
33/M DM taking regular metformin and aspirin, had 5 episodes of anaphylaxis occurred during jogging. He took bread an hour before jogging when he had the anaphylaxis. He has an adrenaline autoinjector.	**Can vaccinate** Wheat-dependent exercise-induced anaphylaxis enhanced by aspirin (NSAIDs)	Observe for 30 minutes after vaccination
50/F with chronic spontaneous urticaria (CSU) has an allergy card labelling "multiple drug allergies *to Augmentin*®, cefuroxime, EES, doxycycline, ciprofloxacin, clindamycin, prednisolone and *Piriton*®." Most of her drug reactions were wheals, itch and angioedema. Her CSU is controlled with oral levocetirizine 10mg bd.	**Can vaccinate** Continue antihistamines as usual.	Observe for **30 minutes** after vaccination

Allergy details	Vaccination decision	Precaution
40/M multiple episodes of angioedema, fullness of throat and near syncopal attacks to various food and drink. He had received IM adrenaline, IV hydrocortisone and IV chlorpheniramine a few times at casualty. He was labelled as idiopathic anaphylaxis and is still under assessment at allergy clinic. He has an adrenaline autoinjector.	**Do not give vaccine with PEG or polysorbate** PEG* could be the culprit in idiopathic anaphylaxis.	To administer ***CoronaVac***® **(Sinovac).** Observe for **30 minutes** after vaccination
34/F with a history of oculogyric crisis after IV metoclopramide 5 years ago.	**Can vaccinate** Oculogyric crisis is a neurologic adverse event of metoclopramide, not an allergic reaction.	Observe for 15 minutes after vaccination

***PEG is an ingredient in Comirnaty® (Pfizer-BioNTech). Polysorbate 80 is an ingredient in ChAdOx1 (Oxford-AstraZeneca), Ad26.COV2-S®[Recombinant] (JANSSEN) and Convidecia™(CanSinoBio). PEG and polysorbate are structurally related, cross-hypersensitivity between these compounds may occur.*

3.8. Case scenarios for reactions developed AFTER the first dose of COVID-19 vaccine

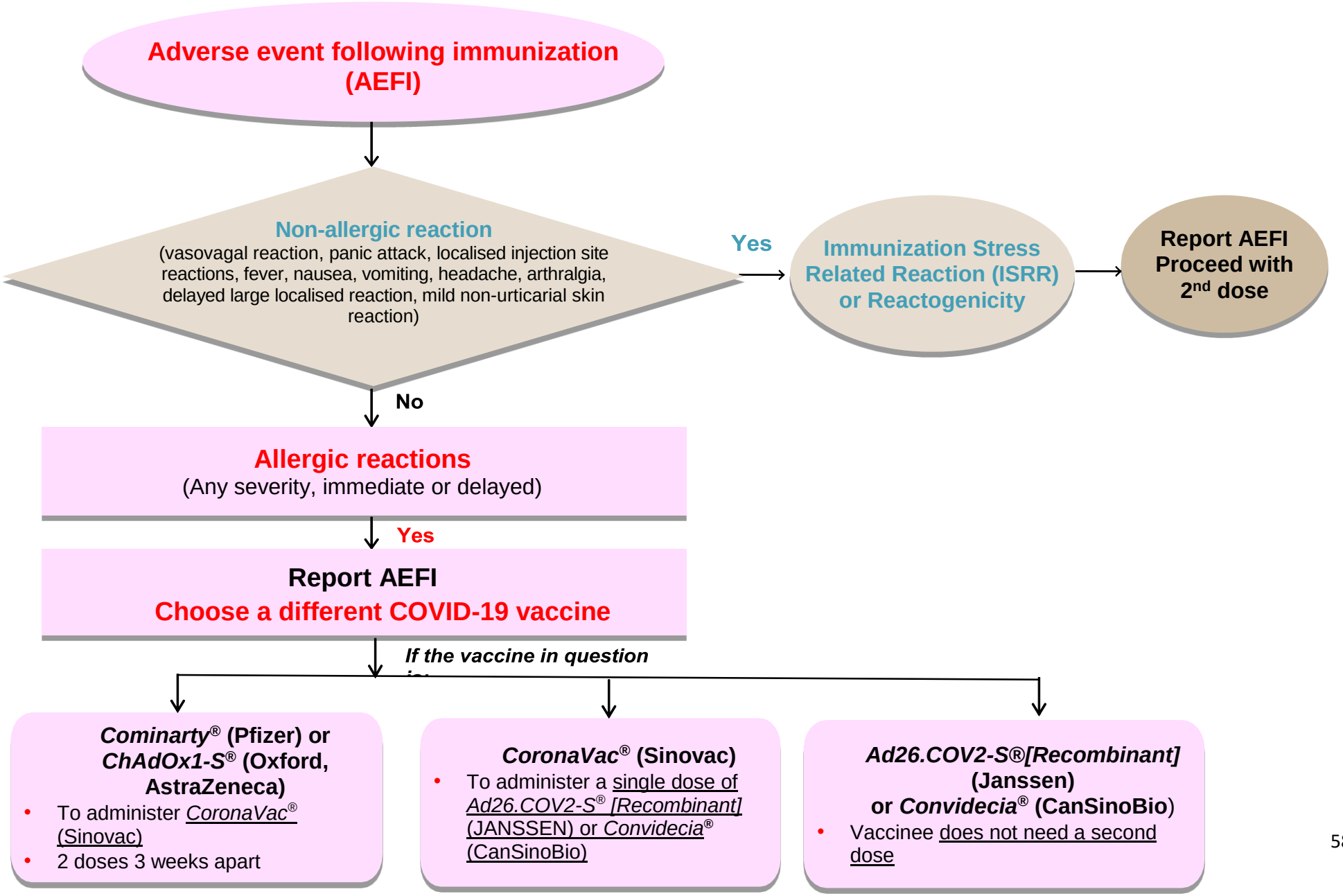
First dose: *Cominarty*® (Pfizer)		
Allergy details	**Vaccination decision**	**Precaution**
35/M with generalized wheals that started 6 hours after the first dose of ***Cominarty*® (Pfizer).** No throat swelling, no shortness of breath, no syncopal attack. Rash took 2 days to resolve with antihistamines.	**Do not give second dose of *Cominarty*® (Pfizer), report AEFI** Allergic reaction (type I reaction, non anapylaxis) to ***Cominarty*® (Pfizer)**	To administer ***CoronaVac*® (Sinovac) as alternative*,** at least 3 weeks from the first dose of *Cominarty*® (Pfizer). Observe for **30 minutes** after vaccination.
35/F with transient fever for a day and painful swelling at injection site after the first dose of COVID-19 vaccine. Injection site erythema and swelling lasted 3 days. She took paracetamol for the fever and pain.	**Can vaccinate, report AEFI** Non-allergic localized side effect.	Observe for **30 minutes** after vaccination.
26/M with generalized hives, facial swelling, and loss of consciousness 15 minutes after first dose of mRNA-COVID-19 vaccine. Documented tachycardia and hypotension. Given IM adrenaline x2, IV hydrocortisone and IV chlorpheniramine and observed overnight at ICU. Discharge well after that.	**Do not give second dose of vaccine, report AEFI** Anaphylaxis to ***Cominarty*® (Pfizer)**	To administer ***CoronaVac*® (Sinovac) as alternative*,** at least 3 weeks from the first dose of *Cominarty*® (Pfizer). Observe for **30 minutes** after vaccination.
28/M developed bronchospasm within 15 minutes after first dose of ***Cominarty*® (Pfizer)**. He has well controlled bronchial asthma. His last asthmatic attack was a year ago and was managed at ICU.	**Do not give second dose of *Cominarty*® (Pfizer), report AEFI** Bronchospasm to ***Cominarty*® (Pfizer)**	
40/M with history of anaphylaxis due to bee sting. Developed generalized urticaria on day-2 post first dose of mRNA-COVID-19 vaccine. No angioedema	**Do not give second dose of *Cominarty*® (Pfizer), report AEFI** Delayed generalized urticaria to ***Cominarty*® (Pfizer)**	

Allergy details	Vaccination decision	Precaution
48/F taking regular prednisolone 10mg daily for underlying autoimmune disease. Developed generalized urticaria associated with itchy throat and nose 1 hour after first dose of mRNA-COVID-19 vaccine. The urticaria subsided 3 days later with antihistamines and high dose of oral prednisolone	**Do not give second dose of *Cominarty*® (Pfizer), report AEFI** Generalized urticaria to ***Cominarty*® (Pfizer)**	To administer ***CoronaVac*® (Sinovac) as alternative*,** at least 3 weeks from the first dose of Cominarty® (Pfizer). Observe for **30 minutes** after vaccination.
35/F with history of severe angioedema many years ago to food and NSAIDs, has been asymptomatic for many years. She took chlorpheniramine 4mg immediately after the first dose of mRNA-COVID-19 vaccine. Developed mild periorbital swelling 12 hours later after vaccination.	**Do not give second dose of *Cominarty*® (Pfizer), report AEFI** Urticaria to ***Cominarty*® (Pfizer)**	
40/F developed diffuse facial flushing and swelling of both ears 2 hours post vaccination with the first dose of mRNA-COVID-19 vaccine.	**Do not give second dose of *Cominarty*® (Pfizer), report AEFI** Angioedema to ***Cominarty*® (Pfizer)**	
40/M developed periorbital swelling without respiratory or systemic manifestations 10 minutes post vaccination with the first dose of mRNA-COVID-19 vaccine.	**Do not give second dose of *Cominarty*® (Pfizer), report AEFI** Angioedema to ***Cominarty*® (Pfizer)**	

First dose: *CoronaVac® (Sinovac)*		
Allergy details	**Vaccination decision**	**Precaution**
29/F developed headache, dizziness, nausea 5 minutes after received the first dose of *CoronaVac®* (Sinovac). No rash observed. No angioedema. All her vital signs were normal.	**Can vaccinate *CoronaVac®* (Sinovac) as second dose, report AEFI** Immunization stress related reactions (ISRR)	Observe for **30 minutes** after vaccination
33/F with history of lip swelling due to rifampicin 20 years ago. Developed anaphylaxis after the first dose of *CoronaVac®* (Sinovac). She had choking sensation, generalized wheals and hypotension requiring intravenous infusion of adrenaline. She was observed in the ICU for a day. She was subsequently discharged well.	**Do not give second dose of *CoronaVac®* (Sinovac), report AEFI.** Anaphylaxis to CoronaVac® (Sinovac)	To administer a single dose of *Ad26.COV2-S®[Recombinant]* (Janssen) OR *Convidecia®* (CanSinoBio) **as alternative,** at least 3 weeks from the first dose of *CoronaVac®* (Sinovac) Observe for **30 minutes** after vaccination
61/F with history of pituitary microadenoma on replacement oral hydrocortisone for past 8 years. She also has history of developing non-generalized rash to multiple classes of drugs since teenage years. Developed hypotension on day 2 after a flu-like symptom following first dose *CoronaVac®* (Sinovac). No wheals or angioedema. No bronchospasm and no choking sensation.	**Can vaccinate *CoronaVac®* (Sinovac) as second dose, report AEFI.** Addisonian crisis post vaccination.	To be closely monitored in the ward for vaccine reactogenicity post second dose and up dosing of her replacement oral hydrocortisone or stat IV hydrocortisone

First dose: *ChadAdOx1S® [recombinant]* (Oxford-Astra Zeneca)		
Allergy details	**Vaccination decision**	**Precaution**
33/F with history of multiple drug hypersensitivities (including chlorpheniramine, loratadine, cetirizine, desloratidine) and chronic spontaneous urticaria/angioedema. Developed hypotonia of lower limbs and flushing 5 minutes after *ChadAdOx1S®* [recombinant] (Astrazeneca-Oxford) vaccine. Admitted to ward for observation. No documented hypotension. No angioedema.	Can vaccinate ***ChadAdOxS1®* [recombinant] (Astrazeneca-Oxford] vaccine as second dose,** report AEFI. **Immunization stress related response**	Refer dermatology to start regular oral non-sedative antihistamines to treat the chronic spontaneous urticaria. Consider using high dose of antihistamine before the second dose of vaccine. Observe for a minimum 30 minutes after vaccination
20/M with no background of allergy. Received *ChadAdOx1S®* [recombinant] (Astrazeneca-Oxford). Within 10 minutes he developed generalized intense pruritus over the ears and palms, followed by lips swelling and stridor. He had tachycardia, hypotension and generalized wheals. Intramuscular adrenaline 0.5mg, intravenous chlorpheniramine 10mg was given. His symptoms resolved with treatment. He was admitted to hospital for overnight observation. He was discharged well the next day.	**Do not give second dose of *ChadAdOxS1®* [recombinant] (Astrazeneca-Oxford].** **Report AEFI.** **Anaphylaxis to *ChadAdOxS1®* [recombinant] (Astrazeneca-Oxford]**	To administer ***CoronaVac®* (Sinovac) as alternative,** at least 4 weeks from the first dose of ***ChadAdOxS1®* [recombinant] (Astrazeneca-Oxford]**. Observe for **30 minutes** after vaccination

3.9. Flow chart for considerations in vaccinating selected groups of hypersensitive population (AFTER 1st VACCINATION)

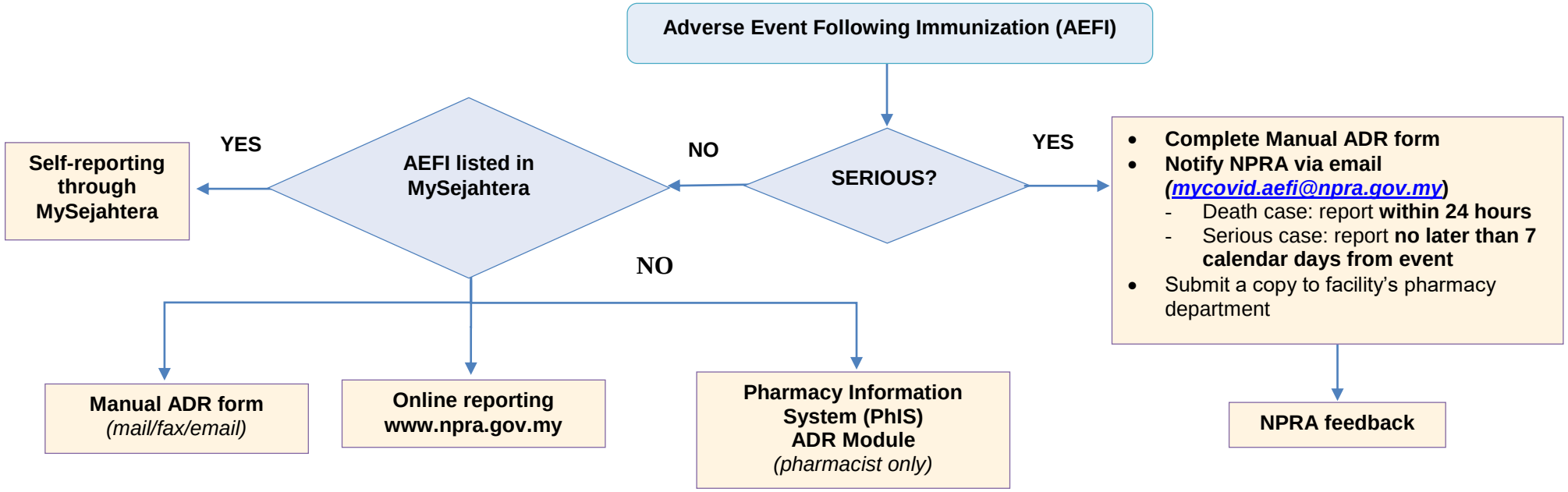


4. Post vaccination

4.1 Post Vaccination Monitoring

a. Everyone who gets a COVID-19 vaccine **SHOULD** be **monitored on-site**.
b. For those with **history of allergy**, observe for **at least 30 minutes** post vaccination.
c. Otherwise, observe for **at least 15 minutes** post vaccination.
d. Vaccination providers should have appropriate medications and equipment such as **epinephrine, antihistamines, stethoscopes, blood pressure cuffs, and timing devices and access to the emergency trolley** at all COVID-19 vaccination sites.

4.2 Reporting of Adverse Event Following Immunization (AEFI)



An AEFI will be considered **serious**, if it:

- results in death,
- is life-threatening,
- requires in-patient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect, or
- requires intervention to prevent permanent impairment or damage.

National Pharmaceutical Regulatory Agency (NPRA). (2021). Reporting ADR. [online] Available at: <https://npra.gov.my/index.php/en/health-professionals/reporting-adr> [Accessed 20 March 2021].
Vaccine-safety-training.org. (2021). MODULE 3 – Classification of AEFIs - WHO Vaccine Safety Basics. [online] Available at: <https://vaccine-safety-training.org/classification-of-aefis.html> [Accessed 20 March 2021]

4.3 Differences between anaphylaxis, vasovagal reaction and panic attack

Characteristics	Anaphylaxis	Vasovagal reaction	Panic attack
Onset	Usually within 15 minutes after immunization, but can occur within hours	Sudden, occur before, during or after immunization	Sudden, occur before, during or after immunization
Cutaneous	• Urticaria, pruritus with or without rash and angioedema (face and tongue) • Warm skin, progressing to clammy and pallor	Pallor, sweating, clammy skin, pallor	Sweating
Respiratory	Upper airway swelling, bronchospasm, respiratory distress, sensation of throat closure/swelling	Normal or shallow	Hyperventilation, sensations of shortness of breath
Cardiovascular	• Hypotension (systolic pressure <90mmHg) • Tachycardia (rapid, weak, irregular)	• Hypotension • Bradycardia (slow, weak but regular)	Tachycardia
Neurological	Anxiety	Lightheaded, weakness, clonic seizure activities	Anxiety, lightheaded, dizzy, paresthesias in lips and fingertips
Gastrointestinal	Nausea, vomiting, abdominal pain, diarrhoea	Nausea, vomiting	Nausea, abdominal pain

Characteristics	Anaphylaxis	• Vasovagal reaction	Panic attack
Treatment	See protocol.	• Place patient in a recumbent position and elevate legs above head (or have patient sit with head between their knees) • Ventilate the room well • Give reassurance	Reassurance
Prevention	Avoid in those who had history of anaphylaxis or severe reactions to previous vaccines including the first dose of COVID-19 vaccine or any ingredient in an COVID-19 vaccine.	• Do not vaccinate a standing person • Before vaccinating ask if he/she tends to faint; if so, ask patient to lie down	May consider psychiatry evaluation before vaccination if the level of anxiety is uncontrollable and disturb the functioning.

5. Frequently Asked Questions

5.1 General

5.1.1 Vaccine Safety	
Can a person get COVID-19 from the vaccine?	No. None of the vaccines approved for use contain live SARS COV-2 virus, so they cannot cause COVID-19 illness. Vaccines prime your immune system to recognize and fight off a disease, but they do not actually cause an infection.
What are the possible side effects of the COVID-19 vaccine? Will a person feel unwell after vaccination?	The side effects may include pain, redness, swelling and itchiness where the vaccine was given. Some people experience local injection site reactions within 1-2 days after the vaccine, but they are usually self-limiting. Other side effects include tiredness, headache, fever, chills, muscle or joint soreness, nausea and vomiting. Most people feel those side effects slightly more after the second dose for mRNA vaccines like *Comirnaty*® (Pfizer-BioNTech).
Are vaccine side effects a good sign?	The side effects are part of the immune response to the vaccine. However, everyone's reaction to the vaccine is different, so the absence of side effects after vaccination does not mean the vaccine is not working.
5.1.2 Vaccine eligibility	
Can a person on immunosuppressive agents be vaccinated? (e.g. SLE, RA)	Yes. To discuss with patient's healthcare provider regarding the safety and optimal timing of vaccination. Please note that there is insufficient efficacy data in immunocompromised hosts. Individuals with immunosuppression may not mount a full immune response to vaccination. The timing of vaccination may vary according to the type of immunosuppressant and a discussion with the health care provider would be beneficial

Can a person with the following underlying conditions receive COVID-19 vaccine? ● DM ● Hypertension ● Dyslipidemia ● Chronic kidney diseases ● Chronic Respiratory diseases: ○ Bronchial asthma * ○ COPD ○ Chronic lung disease e.g. Bronchiectasis ● Chronic heart and vascular diseases ● Obesity, BMI >30 kg/m²	A person with pre-existing chronic illness is more likely to progress to severe disease, hence recommended for COVID-19 vaccination. **Poorly controlled asthma should be assessed by the treating physician for suitability and timing of the COVID-19 vaccination*
Can a person with the following underlying conditions be vaccinated? 1. Solid organ cancers on active chemotherapy, radiotherapy or immunotherapy (excluding hormonal treatment) 2. Patients on long term immunosuppressive treatment who receive : • systemic steroids for > 1 month at a daily dose equivalent to prednisolone ≥ 20mg • immunomodulating therapy 3. Transplant recipients (solid organ/bone marrow/stem cell)	To discuss with the patient's healthcare provider regarding the optimal timing of COVID-19 vaccination. For transplant recipients, vaccination can be given at least 3 months after transplantation if patient is stable. *Notes: Majority of COVID-19 vaccines are not live vaccines; hence it is not contraindicated for the immunocompromised.* *Immunocompromised hosts are at high risk of severe COVID-19 infection. However, there is insufficient data on the efficacy of vaccine in immunocompromised hosts.*
Can PLHIV be vaccinated?	Yes, PLHIV should receive vaccination regardless of CD4 or viral load. However: • PLHIV with lower CD4 counts or has just started on ARVs may suffer from opportunistic infections or IRIS. This may be misinterpreted as post-vaccination side effects. Defer vaccination until patients are more stable.

	• PLHIV with lower CD4 count may not mount full level of protection as the immunocompetent hosts. Defer vaccination until at least 3 months after initiation of ART. • PLHIV in older age group (> 60 years old) or with chronic disease should be prioritised compared to those stable on HAART.
Can a person with chronic liver disease including Chronic Hepatitis B/C be vaccinated?	Yes, a person with stable chronic liver disease may receive vaccination. However, if a person is in the decompensated stage, decision may be made on an individual basis, if the benefits outweigh the risks. Consider prioritization for vaccination after discussion with the healthcare provider.
Can a person with underlying mental illness be vaccinated?	Yes. Individuals with schizophrenia or bipolar disorder, or any mental illness that causes severe functional impairment are recommended to be vaccinated.
Can someone who is a close contact of a confirmed COVID-19 case be vaccinated?	Yes. Once the person has completed quarantine/isolation and has no new symptoms to suggest acute COVID-19 infection.
Can a subject or patient involved in a clinical trial receive vaccination?	Individual who is involved as a subject in a clinical trial need to consult the investigator and study team regarding this matter.
5.1.3 Timing and dosing schedule for vaccine	
How soon after acute illness or surgery can a person be vaccinated?	Vaccination can be given once the person recovers from the acute illness, can perform his/her usual daily baseline activities, and is deemed clinically stable by the treating clinician.
What if a person fails to get the second dose on time?	Anyone who fails to adhere to the prescribed dosing schedule should complete the full vaccination procedure as soon as possible and there is no need to start over.
Can a person receive another (non- COVID-19) vaccine at the same time as COVID-19 vaccine?	COVID-19 vaccination is recommended to be separated by at least 14 days from any other vaccine (before or after). *However, administration of other non-covid vaccines maybe allowed within 14 days in certain conditions i.e whether the patient is behind or at risk of becoming behind on recommended vaccines or their risk of vaccine-preventable disease (e.g., during an outbreak or occupational exposure, tetanus vaccination in pregnant women, rabies, hepatitis B post exposure prophylaxis etc)*

Can a person receive a different vaccine brand as a second dose?	No. Both doses of COVID-19 vaccine series should be completed with the same vaccine brand. *In exceptional situations where a person received the first dose but is unable to complete the series with same COVID-19 vaccine due to medical contraindications e.g. serious AEFI, a different brand of COVID-19 vaccine for the second dose may be considered (Refer to Chapter 4.9)*
Can a person get mixed vaccines from different manufacturers?	No. There are proposed and ongoing studies addressing this subject. Early data on specific vaccine combinations appear encouraging. However, at the moment, mixing of vaccines is not part of the national policy yet except for situations described above. This position may change to reflect data or needs in the future.
Does a person who has completed 2 doses of COVID-19 vaccine need a third booster dose?	The need and timing for COVID-19 booster doses have not been established, and is a subject under study at the moment. No additional doses are recommended at this time.
5.1.4 Vaccine administration error and deviation	
Scenarios of incorrect vaccine administration	**Recommendation of action**
Incorrect **SITE** of injection *Recommended site: deltoid muscle, anterolateral thigh (alternative)*	**Do not repeat dose.** Inform the recipient of the potential for local and systemic adverse events.
Incorrect **ROUTE** of administration (e.g. subcutaneous)	**Do not repeat dose.** Inform the recipient of the potential for local and systemic adverse events. The second dose may still be administered at the recommended interval
Unauthorized **AGE** group	If received dose at age <12 years, **do not administer second dose** until the person becomes eligible to receive vaccination . If age 12 to 17 years and a vaccine **other than** *Comirnaty*® (Pfizer-BioNTech) was inadvertently administered: **Do not administer the second dose of the same vaccine.** Inform the recipient of the potential for local and systemic adverse events. There is inadequate evidence to recommend mix-and-match vaccine at this juncture.

	If benefits outweigh the risk, to consider a repeat vaccination with *Comirnaty*® (Pfizer-BioNTech) vaccine.

Scenarios of incorrect vaccine administration	**Recommendation of action**
Dosage **higher-than-authorized dose** volume administered	Inform the recipient of the potential for local and systemic adverse events. The second dose may still be administered at the recommended interval. However, if local or systemic side effects following vaccination are considered as serious, or are ongoing at the time of the second dose, the decision to administer the second dose may be assessed on a case-by-case basis
Lower-than-authorized dose volume administered (e.g., leaked out, equipment failure, recipient pulled away)	If **more than half** of the dose was administered, do not repeat dose. If **less than half** of the dose was administered or the proportion of the dose cannot be estimated, administer the authorized dose immediately (no minimum interval) in the opposite arm If this dose is the **second dose**, the series is complete, and no additional doses are needed.
Dose administered **within 90 days** of monoclonal antibodies or convalescent plasma for COVID-19 treatment	**Do not repeat** COVID-19 vaccine dose, the series is considered completed. However if person has received ONLY one *Comirnaty*® (Pfizer-BioNTech) or *ChAdOx1-S*® (Oxford-AstraZeneca) vaccine dose, defer administration of second dose for 90 days following receipt of antibody therapy. If the first dose is *CoronaVac* , consider other vaccine as alternatives at interval of after 90 days from receiving antibody therapy , e.g. *Convidecia*® (CanSinoBio) , *Ad26.COV2-S*® (Janssen)

5.2 Neurological-related disorders	
Can a person with a previous history of Bell's palsy receive COVID-19 vaccine?	Yes, may proceed for vaccination considering the benefits outweigh risks. There is 1 case report on persons with recurrent Bell's palsy which was developed post vaccination. However, the causal association with COVID-19 vaccine was not concluded.
Can a person who developed Bell's palsy after the first dose COVID-19 vaccine, to receive a second dose?	Yes, second dose may be given after assessment by clinician. Assessment should be carried out to rule out other causes of CN VII palsy. Management should be according to standard practice and notified as AEFI. To discuss with a physician/neurologist if necessary. Vaccine recipient should be **counselled** regarding: ● effect of corticosteroids (equivalent to prednisolone >20mg OD for 14 days) on the safety and efficacy of COVID-19 vaccines is currently unknown. ● to proceed with vaccination while being treated for Bell's palsy versus delaying vaccination until after completion of treatment.
Can a person who previously had GBS receive COVID-19 vaccine?	Yes, patients who previously had GBS may receive *Ad26.COV2-S*® or *Cominarty*® vaccines. *CoronaVac* and *Convidecia*® are **not recommended** for patients with history of GBS (as stated in their product inserts)
Can a person who had Multiple Sclerosis (MS) receive COVID-19 vaccine ?	Yes, *Cominarty*® and *Ad26.COV2-S*® are considered safe for people with MS and are not likely to trigger a relapse of MS *CoronaVac*® and *Convidecia*® are not recommended for patients with demyelinating diseases or multiple sclerosis (as stated in in their product inlet) Refer to **Appendix 8: Timing considerations for medications related to neurological disorders**
Can a person who has transverse myelitis (TM) receive COVID-19 vaccine?	Yes, *Cominarty*® and *Ad26.COV2-S*® are considered safe for people with TM and are not likely to trigger a relapse of TM.

	CoronaVac® and *Convidecia®* are not recommended until more safety data is available.
In a patient with acute neurological conditions, how soon after the acute event can the person receive vaccination?	Patient with acute neurological conditions (e.g. transverse myelitis, GBS, demyelinating diseases, others;) can receive the vaccine after stabilization and is deemed suitable by the treating clinician.
After an acute stroke event, how soon can the patient receive COVID-19 vaccine?	There is no data available but generally it is recommended that patients with acute stroke should defer vaccination until deemed neurologically and medically stable by treating clinician. The risk of disease and potential benefit of early vaccination after an acute stroke should be assessed individually by the treating physician.
How do we time related medications for multiple sclerosis, neuromyelitis optica and spectrum disorders with COVID-19 vaccines?	Refer to **Appendix 8: Timing considerations for medications related to neurological disorders**
What is the timing consideration for immunomodulatory therapy and COVID-19 vaccination?	Refer to **Appendix 7: Malaysian Consensus on COVID-19 Vaccination For Patients With Rheumatic And Mucoskeletal Diseases (RMD) And Autoimmune And Inflammatory Rheumatic Diseases (AIIRD)**
Will the immunosuppression therapy affect the response to COVID-19 vaccination?	**High dose immunosuppression** (prednisolone >20mg/day for >14 consecutive days, azathioprine >3mg/kg/day, methotrexate >0.4mg/kg/week) may affect response to vaccination than lower conventional doses. Ocrelizumab, rituximab, ofatumumab, and possibly fingolimod, siponimod and others will have a reduced and possibly undetectable antibody response to the COVID-19 vaccines. However, even if antibodies are undetectable or low, other components of the immune system may be triggered by the vaccine and could contribute to vaccine response.

5.3 Cardiovascular related disorders	
Which types of Covid-19 vaccine are potentially related to post-vaccination myocarditis and pericarditis?	mRNA vaccines e.g. C*omirnaty*® (predominantly in male adolescents) *For more information, refer to Appendix 10* Identified in safety report, casual –relationship with vaccine is under review : *ChAdOx1-S*® (Oxford-AstraZeneca) *Ad26.COV2-S*® (Janssen)
What is the incidence of COVID-19 vaccine induced myocarditis / pericarditis?	Available data showed the incidence was 636 cases from total 133 million of second mRNA vaccine administered (≈ 4.78 per 1,000,000 dose)[1]. Globally, the incidence of myocarditis in general population is approximately 10-20 individuals per 100,000/year[2].
What is Systemic Capillary Leakage Syndrome (SCLS)?	It is a very rare serious condition that causes fluid leakage from small capillaries resulting in limbs oedema, hypotension , haemoconcentration and hypoalbuminaemia
Which type(s) of Covid-19 vaccine is/are potentially related to post-vaccination SCLS?	As of current date, adverse event reporting system detected 14 cases of SCLS in relation to *ChAdOx1-S*® (Oxford-AstraZeneca) vaccine . It is best to avoid *ChAdOx1-S*® vaccine in people with history of SCLS

5.4 Haematological disorders, anticoagulant and antiplatelet therapy	
Can patients with thrombocytopenia be vaccinated?	Patients with **platelet count > 50,000** can be vaccinated without additional haemostatic support. Patients with **platelet count < 50,000** should defer the vaccination till their platelet counts recover, if possible. For those with chronically low platelet counts, vaccination should be performed in consultation with their primary haematologist.
Can a patient with haemophilia and other rare bleeding disorders be vaccinated?	For patients with severe/moderate haemophilia, the vaccine injection should be given after a prophylactic dose of Factor VIII (FVIII) or Factor IX (FIX). For patients with a basal FVIII or FIX level above 10%, no haemostatic precautions are required. Patients with other rare bleeding disorder including platelet function disorders should be vaccinated in consultation with their primary haematologists.
Can patients receiving anticoagulants be vaccinated?	1. Warfarin ● Can be vaccinated if INR < 4.0 ● If INR ≥ 4.0, to discuss with the patient's healthcare provider on the optimal timing of vaccination and precautions to be considered. 2. DOAC (e.g. Apixaban, Dabigatran) or LMWH ● Delay the dose on the day of vaccination until after the injection but do not need to miss any dose
If patient has taken warfarin on the day of scheduled vaccination, can patient proceed with vaccination?	Yes. The risk of haematoma formation is reduced by applying firm pressure at the injection site for at least 5 minutes.
Do I need to take another INR before vaccination?	No, unless the patient missed their last scheduled visit.
Can patients with higher intensity anti-thrombotic treatment, for example warfarin with a target INR >4.0 or dual antithrombotic medications be vaccinated?	These patients should be managed on an individual basis and in consultation with their primary physician, to discuss regarding the optimal timing of vaccination.

Are there any special precautions to be taken during vaccination of patients on anticoagulation therapy and bleeding disorder?	Patients receiving anticoagulant therapy or bleeding disorder may develop haematomas in IM injection sites. The risk of haematoma formation is reduced by applying firm pressure at the injection site for at least 5 minutes. Use a 25- or 27-gauge needle to reduce the pressure gradient and cause fewer traumas to the tissue. Vaccine should be injected slowly (≥5 seconds) to reduce the risk of tissue damage. Stabilisation of the limb will reduce risk of haematoma. Bleeding risk can be reduced by application of firm pressure at injection site for at least 10 minutes. The site should not be rubbed or massaged and inspect injected limb after several minutes and 2-4 hours and to report any concerns immediately
Can patients on single antiplatelet therapy (aspirin or clopidogrel) be vaccinated?	Yes. Can continue these medications without any adjustment.

5.5 Post COVID-19 infection	
Should a person who already had COVID-19 infection be vaccinated?	Yes. Vaccination should be deferred until the person has recovered from the acute illness (if symptomatic) and they have met criteria to discontinue isolation.
Should a person who is diagnosed with COVID-19 infection after the first dose of vaccine, get the second dose?	Yes, the second dose should be administered once the person has recovered from the acute illness (if symptomatic) and they have met criteria to discontinue isolation.
Can a person who received convalescent plasma or monoclonal antibodies as part of therapy for COVID-19 infection be vaccinated?	Yes. Defer vaccination at least 3 months after recovery from COVID-19 infection.
Should people who are suffering from Long COVID (Post- acute sequelae of COVID-19) get vaccinated?	Yes, there is no evidence of any safety concerns from vaccinating individuals with COVID-19 infection sequelae.

<table>
<tr><th colspan="2">5.6 Miscellaneous</th></tr>
<tr><td>What are the different VOC (Variants of Concern) of SARS-CoV2?</td><td>WHO describes a SARS-CoV-2 variant that meets the definition of a Variant Of Interest (VOI) and, through a comparative assessment, has been demonstrated to be associated with one or more of the following changes at a degree of global public health significance as a VOC

• Increase in transmissibility or detrimental change in COVID-19 epidemiology; OR
• Increase in virulence or change in clinical disease presentation; OR
• Decrease in effectiveness of public health and social measures or available diagnostics, vaccines, therapeutics.

Currently 4 variants are designated VOC summarised in the table below.
<table><tr><th>WHO label</th><th>Pango lineage</th><th>Earliest sample</th></tr><tr><td>Alpha</td><td>B.1.1.7</td><td>United Kingdom
September 2020</td></tr><tr><td>Beta</td><td>B.1.351</td><td>South Africa
May 2020</td></tr><tr><td>Gamma</td><td>P.1</td><td>Brazil
Nov 2020</td></tr><tr><td>Delta</td><td>B.1.617.2</td><td>India
October 2020</td></tr></table></td></tr>
<tr><td>Will COVID-19 vaccines protect against the SARS-CoV2 variants?</td><td>Variants of the SARS-CoV2 virus are spreading in Malaysia and other parts of the world. Data on the efficacy and effectiveness of vaccines to variants continue to emerge. Reassuringly, these data suggest that COVID-19 vaccines offer protection against most variants, although this information is currently not available for all vaccines. Some variants may cause infection and illness in some individuals even after they are fully vaccinated.

However, most fully vaccinated individuals are expected to be protected from the consequence of hospitalisation and severe disease. Data on the efficacy and effectiveness of vaccines to variants will be continuously monitored, and guidance will be issued to reflect any emerging information.</td></tr>
<tr><td>When can a person donate blood after receiving COVID-19 vaccine?</td><td>Blood donation to be deferred at least 7 days post vaccination. If any mild side effect occurs post vaccination, to defer until 7 days after symptoms resolution.

Individual that is involved as a subject in clinical trial need to consult investigator and study team regarding this matter.</td></tr>
</table>

5.7 Immunization Stress Related Response (ISRR)	
What is ISRR?	ISRR is an AEFI arising from anxiety about immunization. Manifestations include signs and symptoms of vasovagal-mediated, hyperventilation-mediated and/or stress-related neurological and psychiatric reactions after vaccination or even immediately before vaccination.
Should the second dose be administered in a person with ISRR after the first dose?	Yes
What is the management of stress & anxiety post vaccination?	Identify those with needle fear and at risk of having ISRR early. Provide a private and calm space for the vaccination. Communicate clearly, explain & reassure. General principle of managing an acute stress response is with calm, reassuring, positive communication with the vaccine recipient until resolution of symptoms. Patients with vasovagal reaction should be placed in the supine position and practise muscle tension. Once an ISRR is identified, the vaccinator should clearly explain that it was not related to the vaccine product, immunization program or procedure error. The nature of the symptoms which are not harmful and will spontaneously resolve without medication should be explained. More complex presentations such as dissociative neurological symptom reaction with or without non-epileptic seizures warrant multidisciplinary team for medical & psychological assessment.

5.8 Incidence of Adverse Events of Interest– As of June 2021

Adverse Events of Special Interest (AESI) according to WHO definition:

A preidentified and predefined medically-significant event that has the potential to be causally associated with a vaccine product that needs to be carefully monitored and confirmed by further specific studies.
Three newly identified **AESIs** which are notable for healthcare professionals' attention and therefore careful monitoring:

1) Vaccine Induced Immune Thrombocytopenia and Thrombosis (VITT) / Thrombosis with Thrombocytopenic Syndrome (TTS)
2) Systemic Capillary Leakage syndrome (SCLS)
3) Myocarditis/Pericarditis

Adverse events of interest	**Vaccines**					**Remarks**
	***Cominarty*® (Pfizer)**	***CoronaVac*® (Sinovac)**	***ChAdOx1-S*® (Oxford-Astra Zeneca)**	***Ad26.COV2-S*® *[Recombinant]* (Janssen)**	***Convidecia™* (CanSinoBio)**	
Anaphylactic reaction: Incidence of anaphylaxis (cases / million doses)	4.7 - 24	0.8-17	17.5	<0.5	No data	• Refer to *Chapter 4*
Delayed large local reaction: Reactogenicity	16%	No data available	No data available	No data available	No data available	• Median 7 days after first vaccine administration, resolved after a median of 3-4 days. • Reaction responded well to topical corticosteroids, oral antihistamines and/or analgesia. • Most did not recur on second dose of vaccine administration. Those recurred, it occurred earlier (day-2) but less severe.

Adverse events of interest	Vaccines					Remarks
	***Cominarty*® (Pfizer)**	***CoronaVac*® (Sinovac)**	***ChAdOx1-S*® (Oxford-Astra Zeneca)**	***Ad26.COV2-S® [Recombinant]* (Janssen)**	***Convidecia*™ (CanSinoBio)**	
Neurological						
Peripheral facial nerve palsy (Bell's palsy)	4 reports (clinical trial)	No data available	3 reports (clinical trial)	2 reports (clinical trial)	No data available	• Post-vaccination incidence is below the disease background rate and did not identify as signals • People with a previous history of Bell's palsy may receive vaccination
Guillain- Barre Syndrome (GBS)	1 case report	No data available	1 case report	1 report (Clinical trial)	No data available	• Post vaccination GBS are very uncommon. • History of GBS does not preclude a person from receiving COVID-19 vaccine. • *CoronaVac*® and *Convidecia*® are not recommended until more safety data is available
Acute ischaemic stroke	No data available	No data available	Case series (VITT)	No data available	No data available	• In young patients with acute ischemic stroke who have had ChAdOx1S especially **within 1 month** after injection, should be urgently investigated for thrombotic event related to VIIT • Refer to **VIIT algorithm (Appendix 6)**

Adverse events of interest	Vaccines					Remarks
	***Cominarty*® (Pfizer)**	***CoronaVac*® (Sinovac)**	***ChAdOx1-S*® (Oxford-AstraZeneca)**	***Ad26.COV2-S*® *[Recombinant]* (Janssen)**	***Convidecia*® (CanSinoBio)**	
Transverse myelitis (TM)	No data available	No data available	1 report (clinical trial)	No data available	No data available	• Person with previous TM may receive vaccination • *CoronaVac*® and *Convidecia*® are not recommended until more safety data is available
Multiple Sclerosis (MS)	No data available	No data available	No data available	No data available	No data available	• No vaccine preference for those living with MS. The vaccines are not likely to trigger a relapse or have any impact on long term disease progression. • *CoronaVac*® and *Convidecia*® are not recommended until more safety data is available

Adverse events of interest	Vaccines					Remarks
	***Cominarty*® (Pfizer)**	***CoronaVac*® (Sinovac)**	***ChAdOx1-S*® (Oxford-AstraZeneca)**	***Ad26.COV2-S*® *[Recombinant]* (Janssen)**	***Convidecia*® (CanSinoBio)**	
Hematological						
Vaccine Induced Immune Thrombocytopenic Purpura (ITP)	0.8 per million doses	No data available	Reported cases but very rare	Reported cases but very rare	No data available	• Commonly seen within 2 weeks post vaccination. • Degree of thrombocytopenia is marked in ITP post vaccination with platelet count of usually <10 x 10^9. • Can occur in anyone even without previous history of ITP • Transient drop in platelet count seen in patients with pre-existing ITP but will eventually recover. • Some patients will need treatment with steroids and / or IVIG if present with wet bleeding.
Vaccine Induced Immune Thrombocytopenia and Thrombosis (VITT) / Thrombosis with Thrombocytopenic Syndrome (TTS)	No data available	No data available	1 in 150 000 doses However, benefit of the vaccine outweighs the risk of TTS as of publication. Refer to **Appendix 12** for more information.	1 in 250 000 doses	No data available	• Thrombosis is usually seen in an unusual location e.g.: cerebral venous sinus, portal vein, splenic vein • Thrombosis in a common location e.g., deep vein thrombosis, pulmonary embolism, myocardial infarction and other venous or arterial thrombosis are also seen. • More commonly seen in females younger than 60 years old • Commonly occurs between 5-20 days post vaccination: seen up to 30 days post vaccination.

Adverse events of interest	Vaccines					Remarks
	***Cominarty*® (Pfizer)**	***CoronaVac*® (Sinovac)**	***ChAdOx1-S*® (Oxford-AstraZeneca)**	***Ad26.COV2-S*® *[Recombinant]* (Janssen)**	***Convidecia*® (CanSinoBio)**	
Other Autoimmune associated Haematological manifestations	• There have been reported cases of **Aplastic Anemia** and **Acquired Haemophilia** • Association with the vaccine is currently uncertain and requires further investigation and data collection. • Types of vaccines not specific in reports					• To consult haematologist for opinion and further management plan. • Incidences are rare and are treated on a case-to-case basis.
Cardiovascular						
Myocarditis / Pericarditis	4.78 in 1 million doses* (2nd dose administered) **includes data for both Pfizer and Moderna*	No data available	1.1 in 1 million doses	0.5 in 1 million doses	No data available	• Occurs within a week (usually 3-4 days) after second dose of vaccine • Common presentations: chest pain, breathlessness, palpitation, fatigue, low grade fever • Refer to **Appendix 9** for diagnosis and treatment algorithm
Systemic Capillary leakage syndrome (SCLS)	No data available	No data available	14 cases reported	No data available	No data available	• Commonly occurs within 4 days of vaccination (typically after 1-2 days) • Common presentations: hypotension, haemoconcentration, generalised or limb oedema • Other symptoms include fatigue, presyncope or syncope attack, abdominal pain and vomiting • Refer to **Appendix 10** for diagnosis and treatment algorithm

Adverse events of interest	Vaccines					Remarks
	***Cominarty*® (Pfizer)**	***CoronaVac*® (Sinovac)**	***ChAdOx1-S*® (Oxford-AstraZeneca)**	***Ad26.COV2-S*® *[Recombinant]* (Janssen)**	***Convidecia*® (CanSinoBio)**	
Others						
Herpes Zoster, reactivation post-vaccination	Case series	No data available	No data available	No data available	No data available	• Case reports: affecting people above age 50 • May occur in younger age population in patients with autoimmune inflammatory rheumatic disease • Presentation: Skin lesions appear 7-20 days post vaccination, mainly seen after first dose • Neuralgia (prodromal) is reported as early as 2-7 days post vaccination

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Appendix 1

List of vaccines and medications containing PEG and polysorbate

a. Common VACCINES containing POLYSORBATE and PEG

Excipient	Vaccine type	Vaccine	Amount per dose
Polysorbate 20	Influenza	Flublok&Flublock quad	≤ 27.5 µg (Tween 20)
Polysorbate 20	Hepatitis A	Havrix	0.05 mg/ml
Polysorbate 20	Hepatitis A & B	Twinrix	Unknown
Polysorbate 20	SARS-Cov-2 (Sanofi)		
Polysorbate 80	Tdap	Boostrix	≤ 100 µg (Tween 80)
Polysorbate 80	Influenza	Fluad	1.175 mg
Polysorbate 80	Influenza	Fluarix quad	≤ 0.055 mg (Tween 80)
Polysorbate 80	Influenza	Flucelvax quad	≤ 1500 µg (Tween 80)
Polysorbate 80	Influenza	Flulaval quad	≤ 887 µg
Polysorbate 80	HPV	Gardasil & Gardasil-9	50 µg
Polysorbate 80	Hepatitis B	Heplisav-B	0.1 mg/mL
Polysorbate 80	DtaP	Infanrix	≤ 100 µg (Tween 80)
Polysorbate 80	Japanese encephalitis	JE-Vax	<0.0007%
Polysorbate 80	DtaP + IPV	Kinrix	≤ 100 µg (Tween 80)
Polysorbate 80	DtaP + HepB + IPV	Pediarix	≤ 100 µg (Tween 80)
Polysorbate 80	Pneumococcal 13-valent	Prevnar-13	100 µg
Polysorbate 80	DtaP + IPV	Quadracel	10 ppm
Polysorbate 80	Rotavirus	RotaTeq	?
Polysorbate 80	Zoster	Shingrix	0.08 mg
Polysorbate 80	Meningococcal group B	Trumenba	0.018 mg
Polysorbate 80	DtaP+IPV+HepB+Hib	Vaxelis	<0.0056%
Polysorbate 80	SARS-CoV-2 (Astrazeneca) SARS-CoV-2 (Johnson & Johnson) Sputnik V (Gamaleya)		
PEG2000	SARS-CoV-2 (Moderna) SARS-CoV-2 (Pfizer)		

b. Common PEG containing DRUGS

Generic name (brand name)	Molecular weight	General description
Methylprednisolone acetate (Depo-medrol)	PEG 3350	Anti-inflammatory glucocorticoid for intramuscular, intra-articular, soft tissue or intralesional injection
Methoxy polyethylene glycol-epoeitin beta (Micera)	30-kD methoxy PEG butanoic acid	Used to treat anemia in adults with chronic kidney disease
Pegfilgrastim (Neulasta)	20-kD monomethoxy PEG	Used to help reduce the chance of infection due to low white blood cell count in people with certain types of cancer (nonmyeloid), who receive anticancer medicines (chemotherapy) that can cause fever and low blood cell count
Peginterferon alfa-2b (PEG-Intron)	12000 daltons	Treatment of HCV in combination with other antiviral drugs in patients over 5 years of age with compensated liver disease
Medroxyprogesterone acetate (Depo-provera)	PEG 3350	Contraceptive and adjunctive therapy and palliative treatment of inoperable, recurrent, and metastatic endometrial or renal carcinoma
Brilliant Blue G Ophthalmic Solution (TissueBlue)	PEG 3350	Disclosing agent indicated to selectively stain the internal limiting membrane
Sulfur hexafluoride (Lumason)	PEG 4000	Ultrasound contrast agent
Biomatoprost implant (Durysta)	PEG, (unspecified)	Reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Transtuzumab (Herceptin, Herzuma, Kanjinti, Ogivri, Ontruzan)	PEG 3350	Adjuvant treatment of HER2 overexpressing node-positive or node-negative breast cancer
Rilonacept (Arcalyst)	PEG 3350	IL-1 blocker for treatment of cryopyrin-associated periodic syndromes
Perflutren lipid microsphere (Definity)	PEG 5000	Contrast agent used to brighten and clarify images of the heart during echocardiograms

c. Common POLYSORBATE containing DRUGS

Drug class	Generic name (brand name)	Polysorbate
Antiarrhythmic	Amiodarone hydrochloride (generics only)	Polysorbate 80
Antidiabetic	Exanatide (BydureonBcise)	Polysorbate 20
	Insulin glargine (Lantus, Semglee)	Polysorbate 20
	Insulin glulisine (Apidra)	Polysorbate 20
	Dulaglutide (Trulicity)	Polysorbate 80
Antidote	Hyaluronidase (Hylenex Recombinant)	Polysorbate 80
Antifungal	Anidulafungin (Eraxis)	Polysorbate 80
Anti-inflammatory	Interferon beta 1b (Avonex, Plegridy)	Polysorbate 20
	Omalizumab (Xolair)	Polysorbate 20
Antineoplastic	Ofatumumab (Kesimpta)	Polysorbate 80
	Siltuximab (Sylvant)	Polysorbate 80
Antipsychotic	Paliperidone palmitate (Invega Trinza, Invega Sustenna)	Polysorbate 20
	Aripiprazole lauroxil (Aristada)	Polysorbate 20
Antiretroviral	Ibalizumab (Trogarzo)	Polysorbate 80
Antipsoriatic	Adalimumab (Humira, Imraldi)	Polysorbate 20 (Imraldi) polysorbate 80 (humira)
	Golimumab (Simponi)	Polysorbate 80
	Guselkumab (Tremfya)	Polysorbate 80
	Infliximab – dyyb (Inflectra, Remicade, Renflexis)	Polysorbate 80
	Ustekinumab (Stelara)	Polysorbate 80
Antiviral	Interferon-alfa-2b (Intron A)	Polysorbate 80
Biological response modifier	Interferon-gamma-1b (Actimmune)	Polysorbate 20

Drug class	Generic name (brand name)	Polysorbate
Cancer treatment	Ado-trastuzumab (Kadcyla)	Polysorbate 20
	Atezolizumab (Tecentriq)	Polysorbate 20
	Avelumab (Bavencio)	Polysorbate 20
	Bevacizumab (Avastin, Zirabev)	Polysorbate 20
	Daratumumab/hyaluronidase (DarzalexFaspro)	Polysorbate 20
	Denosumab (Prolia, Xgeva)	Polysorbate 20
	Dinutuximab (Unituxin)	Polysorbate 20
	Enfortumab (Padcev)	Polysorbate 20
	Olaratumab (Lartruvo)	Polysorbate 20
	Palifermin (Kepivance)	Polysorbate 20
	Pertuzumab/trastuzumab/hyaluronidase (Phesgo)	Polysorbate 20
	Polatuzumabvedotin (Polivy)	Polysorbate 20
	Tafasitamab (Monjuvi)	Polysorbate 20
	Trastuzumab (Herceptin, Herceptin Hylecta, Herzuma, Kanjinti, Ontruzant, Trazimera)	Polysorbate 20
	Belantamab (Blenrep)	Polysorbate 80
	Brentuximab vedotin (Adcetris)	Polysorbate 80
	Cemiplimab (Libtayo)	Polysorbate 80
	Docetaxel (Taxotere)	Polysorbate 80
	Durvalumab (Imfinzi)	Polysorbate 80
	Elotuzumab (Empliciti)	Polysorbate 80
	Etoposide (Toposar, VePesid)	Polysorbate 80
	Fam-trastuzumab deruxtecan (Enhertu)	Polysorbate 80
	Fosaprepitantdimeglumine (EMEND, Fosaprepitant)	Polysorbate 80
	Inotuzumabozogamicin (Besponsa)	Polysorbate 80
	Ipilimumab (Yervoy)	Polysorbate 80
	Isatuximab (Sarclisa)	Polysorbate 80
	Mogamulizumab (Poteligeo)	Polysorbate 80
	Moxetumomabpasudotox (Lumoxiti)	Polysorbate 80
	Nivolumab (Opdivo)	Polysorbate 80
	Ofatumumab (Arzerra)	Polysorbate 80

Drug class	Generic name (brand name)	Polysorbate
	Pembrolizumab (Keytruda)	Polysorbate 80
	Ramucirumab (Cyranza)	Polysorbate 80
	Rituximab (Truxima, Rituxan, Ruxience)	Polysorbate 80
	Temsirolimus (Torisel)	Polysorbate 80
	Temozolomide (Temodar)	Polysorbate 80
Contraceptive	Medroxyprogesterone acetate (depo-provera, depo-provera CI, Depo-subQprovera 104)	Polysorbate 80
Corticosteroid	Methylprednisolone acetate (Depo-medrol)	Polysorbate 80
	Triamcinolone acetonide (Aristocort forte, Aristopan, Kenalog-40, Kenalog-10, Protherix, Triesence, TriloanSuik, Triloan II Suik, Ziretta)	Polysorbate 80
	Sincalide (Kinevac)	Polysorbate 20
	Tuberculin purified protein derivative (Aplisol, Tubersol)	Polysorbate 80
Disease-modifying antirheumatic drug	Anakinra (Kinert)	Polysorbate 80
	Tocilizumab (Actemra)	Polysorbate 80
Enzyme	Velaglucerase alfa (Vpriv)	Polysorbate 20
	Imiglucerase (Cerezyme)	Polysorbate 80
	Taliglucerase alfa (Elelyso)	Polysorbate 80
		Polysorbate 80
Erythoid maturation agent	Luspatercept (Reblozyl)	Polysorbate 80
Factor Xa inhibitor antidote	Coagulation factor Xa (recombinant), inactivated-zhzo (Adexxa)	Polysorbate 80
Gonadotropin	Follitropin (Menopur, Follistim)	Polysorbate 20
Growth hormone analog	Somatotropin (Nutropin AQ Nuspin 5)	Polysorbate 20
Hematopoietic growth factor	Erythropoeitin (Retacrit)	Polysorbate 20
	Pegfilrastim (Fulphila, Neulasta, Nyvepria, Udenyca)	Polysorbate 20
	Romiplostim (Nplate)	Polysorbate 20
	Darbepoetin alfa (Aranesp)	Polysorbate 80
	Filgrastim (Neupogen, Nivestym, Granix, Zarxio)	Polysorbate 80
Hepatitis B/Hepatitis C agent	Peginterferon (Pegays, Pegintron)	Polysorbate 80

Drug class	Generic name (brand name)	Polysorbate
Hemostatic	Vitamin k (Phytonadione)	Polysorbate 80
Immune globulin	Hepatitis B Immune globulin (HepaGam B, Nabi-HB)	Polysorbate 80
	Rho (d) immune globulin (WinRho)	Polysorbate 80
Immunomodulator	Intereron beta-1a (Avonex, Avonex Pen)	Polysorbate 20
	Emapalumab (Gamifant)	Polysorbate 80
Immunosuppressant	Mycophenolate mofetil (Cellcept IV)	Polysorbate 80
Inflammatory bowel disease agent	Vedolizumab (Entyvio)	Polysorbate 80
Interleukin inhibitor	Sarilumab (Kevzara)	Polysorbate 20
	Dupilumab (Dupixent)	Polysorbate 80
	Mepolizumab (Nucala)	Polysorbate 20
	Secukinumab (Cosentyx)	Polysorbate 80
	Tildrakizumab – asmn (Ilumya)	Polysorbate 80
Kallikrein inhibitor	Lanadelumab (Takhzyro)	Polysorbate 80
Leptin analog	Metreliptin (Myalept)	Polysorbate 20
Macular degeneration agent	Aflibercept (Eylea)	Polysorbate 20
	Ranibizumab (Lucentis)	Polysorbate 20
	Brolucizumab (Beovu)	Polysorbate 80
mAb treatment	Ocrelizumab (Ocrevus)	Polysorbate 20
	Remdesivir (Veklury)	Polysorbate 20
	Romosozumab (Evenity)	Polysorbate 20
	Teprotumumab (Tepezza)	Polysorbate 20
	Atoltivimab/maftivimab/odesivimab-ebgn (Inmazeb)	Polysorbate 80
	Banlanivimab	Polysorbate 80
	Burosumab (Crysvita)	Polysorbate 80
	Canakimumab (Iliris)	Polysorbate 80

Drug class	Generic name (brand name)	Polysorbate
	Casirivimab/Imdevimab	Polysorbate 80
	Eptinezumab (Vyepti)	Polysorbate 80
	Fremanezumab (Ajovy)	Polysorbate 80
	Inebilizumab (Uplizna)	Polysorbate 80
	Raxibacumab	Polysorbate 80
	Natalizumab (Tysabri)	Polysorbate 80
	Dantrolene sodium (Dantrium, Ryanodex)	Polysorbate 80
	Crizanlizumab	Polysorbate 80
	Alirocumab (Praluent)	Polysorbate 20
	Evolocumab (Repaha)	Polysorbate 80
	Belimumab (Benlysta)	Polysorbate 80
	Tenecleptase (Tnkase)	Polysorbate 20
	Alteplase (CathfloActivase)	Polysorbate 80
	Reteplase (Retavase)	Polysorbate 80
	Calcitriol (Calcijex, Rocaltrol)	Polysorbate 20
	Doxercalciferol (Hectorol)	Polysorbate 20
	Vitamins A, B1, B2, B6, C, D3, E, K (Infuvite)	Polysorbate 80

Appendix 2

COVID-19 VACCINE-RELATED ANAPHYLAXIS: DEFINITION AND MANAGEMENT

i. Introduction

Anaphylaxis is a serious systemic hypersensitivity reaction which is usually acute in onset and may result in death[5]. Severe anaphylaxis is characterised by potentially life-threatening compromise in airway, breathing and/or circulation and may present without the classical skin features or circulatory shock[5]. The incidence of anaphylaxis following COVID-19 vaccination is generally rare[25]. Both Pfizer-BioNTech vaccine and Moderna COVID-19 vaccine have reported an anaphylaxis rate at 4.7 cases and 2.5 cases per million doses administered respectively based on the data through January 2021[21].

ii. Early recognition

Diagnosis of anaphylaxis is made clinically based on signs and symptoms[5]. Failure to recognise and delay in treatment could be catastrophic as it can deteriorate rapidly leading to respiratory and cardiac arrest[24]. Most anaphylaxis cases occur within 15-30 minutes post vaccination though it can sometimes take up to several hours for the first symptoms to develop[8]. Anaphylaxis may present as:

System	Symptoms
Mucocutaneous	● Eyes: Periorbital or conjunctival swelling ● Oral mucosa: Lips, tongue or uvula swelling ● Skin: Generalized urticaria, skin redness, itchiness
Respiratory	● Upper airway: Foreign body sensation, stridor, voice hoarseness, sudden increase/excess in nasal secretions, difficulty in swallowing, hypoxia ● Lower airway: wheezing, breathlessness, chest tightness, coughing, decreased peak expiratory flow (PEF), cyanosis, hypoxia
Cardiovascular	● Early features: syncope, dizziness, tachycardia, hypotension, prolonged capillary refill time ● Late features: bradycardia, shock, altered mental status related to reduced cerebral perfusion/hypoxia, cardiac arrest.
Gastrointestinal	● Persistent abdominal cramp ● Vomiting ● Diarrhea

The clinical diagnosis of anaphylaxis can be challenging in some situations[9]. Anaphylaxis may present as a mild allergic reaction initially and it may be difficult to predict whether a seemingly mild allergy could progress to become an anaphylactic reaction. In addition, individual with communication difficulties such as those with cognitive or neurological deficits may not be able to report their symptoms precisely. Mucocutaneous manifestation such as urticaria and angioedema may be absent in some anaphylaxis cases[5,28].

Criteria listed in the table below aid in the diagnosis of anaphylaxis.

Diagnosis criteria for anaphylaxis Anaphylaxis is highly likely if any **ONE** of the criteria presents:	
Criteria 1	Criteria 2
Acute onset of illness (minutes to several hours) with mucocutaneous involvement (either skin, mucosal or both) **AND** at least one of the following: ● Respiratory symptoms/signs (e.g. dyspnea, wheezing, hypoxia, stridor, reduced PEF) ● Episode of hypotension or with associated manifestations (e.g. hypotonia, syncope, collapse, incontinence ● Severe gastrointestinal symptoms (e.g. crampy abdominal pain, repetitive vomiting)	Acute onset of hypotension[1] **or** bronchospasm[2] **or** laryngeal involvement[3] after exposure to a **known*** or **highly likely*** allergen (minutes or several hours), even in the absence of typical skin involvement.

Adapted from the diagnostic criteria of anaphylaxis (WAO) 2020[5]

Note:

**The term highly likely allergen and known allergen referred to the COVID-19 vaccine in the context with post vaccination anaphylactic reaction.*

[1] Hypotension is defined as systolic BP < 90mmHg or reduction in systolic BP greater than 30% from the individual's baseline.

[2] Excludes lower respiratory symptoms triggered by common inhalant allergens or food allergens perceived to cause "inhalational" reactions.

[3] Laryngeal symptoms include stridor, vocal changes, odynophagia.

On the contrary, not all signs and symptoms mentioned above are necessarily a result of an anaphylaxis reaction. Careful assessment and clinical judgement can differentiate anaphylaxis from other mimicking conditions[4]. Below are some differential diagnoses:

Category	Differential diagnosis
Cardiac	Myocardial infarct, arrhythmias
Pulmonary	Acute exacerbation of asthma, acute exacerbation of chronic obstructive airway disease, pulmonary embolism, foreign body inhalation
Neurology	Seizure, cerebrovascular accident
Histamine	Systemic mastocytosis, leukemia, scombroid fish ingestion
Skin flushes	Carcinoid syndrome, post-menopausal
Hypotensive, shock	Hypovolemic, cardiac, or septic shock
Psychological	Panic attacks, hyperventilation syndrome, psychosomatic episodes
Others	Hereditary angioedema, pheochromocytoma

Vasovagal syncope is not uncommon during vaccination[15]. Vasovagal attack may present with transient hypotension with bradycardia and tend to improve with supine positioning and resolve spontaneously[11,23]. In contrast, syncope due to anaphylaxis tend to have persistent hypotension, weak pulse volume and tachycardia[9]. Hypotension and poor peripheral perfusion in anaphylaxis would persist unless intervention such as adrenaline and IV fluid administration are given[23].

b. Anticipating and Managing Anaphylaxis in Vaccination Centres

All vaccination centres should have enough staff, medication, and equipment to recognise and treat anaphylaxis. Healthcare workers who are trained to recognise anaphylaxis and deliver intramuscular adrenaline injection should be readily available at site. Transport should be available to send patients to specialist centres if anaphylaxis is diagnosed. The following equipment should be accessible during anaphylaxis:

Equipment	Drugs
1. Transport Stretcher 2. Emergency Cart or Bag 3. Wheelchair 4. Cardiac monitor or Defibrillator 5. Oxygen regulator 6. Portable Oxygen Source 7. Laryngoscope size 3,4 8. Endotracheal tube size 7, 7.5 & 8 9. Laryngeal mask airway (LMA) size 3 and 4 10. Bag Valve Mask 11. Medications Chart 12. Portable Suction 13. Glucometer 14. Stethoscope 15. Large Bore cannula (16G,18G and 20G)	1. Adrenaline 2. Normal Saline 3. Salbutamol 4. Chlorpheniramine 5. Hydrocortisone 6. Ranitidine

c. Management

If anaphylaxis reaction or anaphylactic shock is suspected, the following steps are critical as part of the initial emergency management:

Acute management

- Get additional help immediately.
- Lie patient in recumbent position with leg raised. In patients who are vomiting or having breathlessness, allow patients to be in the position of comfort[22]. Pregnant patients can be put on the left lateral position.
- The first and most critical treatment in anaphylaxis is adrenaline[5,22]. There is **NO** absolute contraindication for adrenaline administration in anaphylaxis. Administer IM injection of adrenaline 1:1000 0.5ml (0.5mg) preferably over the mid-lateral thigh as soon as possible. This can be repeated every 5-10 minutes, as necessary. If more than three IM injections of adrenaline are required, consider giving intravenous (IV) injection for refractory anaphylaxis.
- Give 100% oxygen supplementation via high flow mask[22].
- Immediate intubation in impending airway obstruction from angioedema.
- Consider nebulized/ MDI salbutamol with persistent bronchospasm.

Treatment for refractory anaphylaxis*

Give IV adrenaline infusion for refractory symptoms despite 3 doses of IM adrenaline and IV fluid boluses. The preferred method of adrenaline infusion will be using an infusion pump[5].

- IV adrenaline infusion can be prepared by adding 3mg adrenaline 1:1000 in 47ml of normal saline in a 50ml syringe. Initial dose can be set at 0.1mcg/kg/min

using an infusion pump (e.g. in a 50kg patient, to start infusion adrenaline at 5ml/hour). Titrate the infusion rate according to the blood pressure and heart rate.

- Alternatively, IV adrenaline infusion can be prepared by diluting 0.5ml 1:1000 (0.5mg) adrenaline in 500ml normal saline if the infusion pump is not available. The initial dose can be set at 2ml per minute (equivalent to 2mcg per minute). This can be gradually increased up to 10mcg/min (10ml/min) titrating the infusion rate according to the blood pressure and heart rate[5].

Patients on beta blocker may not respond adequately to adrenaline[22]. Consider administering IV glucagon 1-5mg over 5 minutes followed by infusion 5-15mcg/min in patients resistant to adrenaline[19]. Rapid administration of glucagon may trigger vomiting[19].

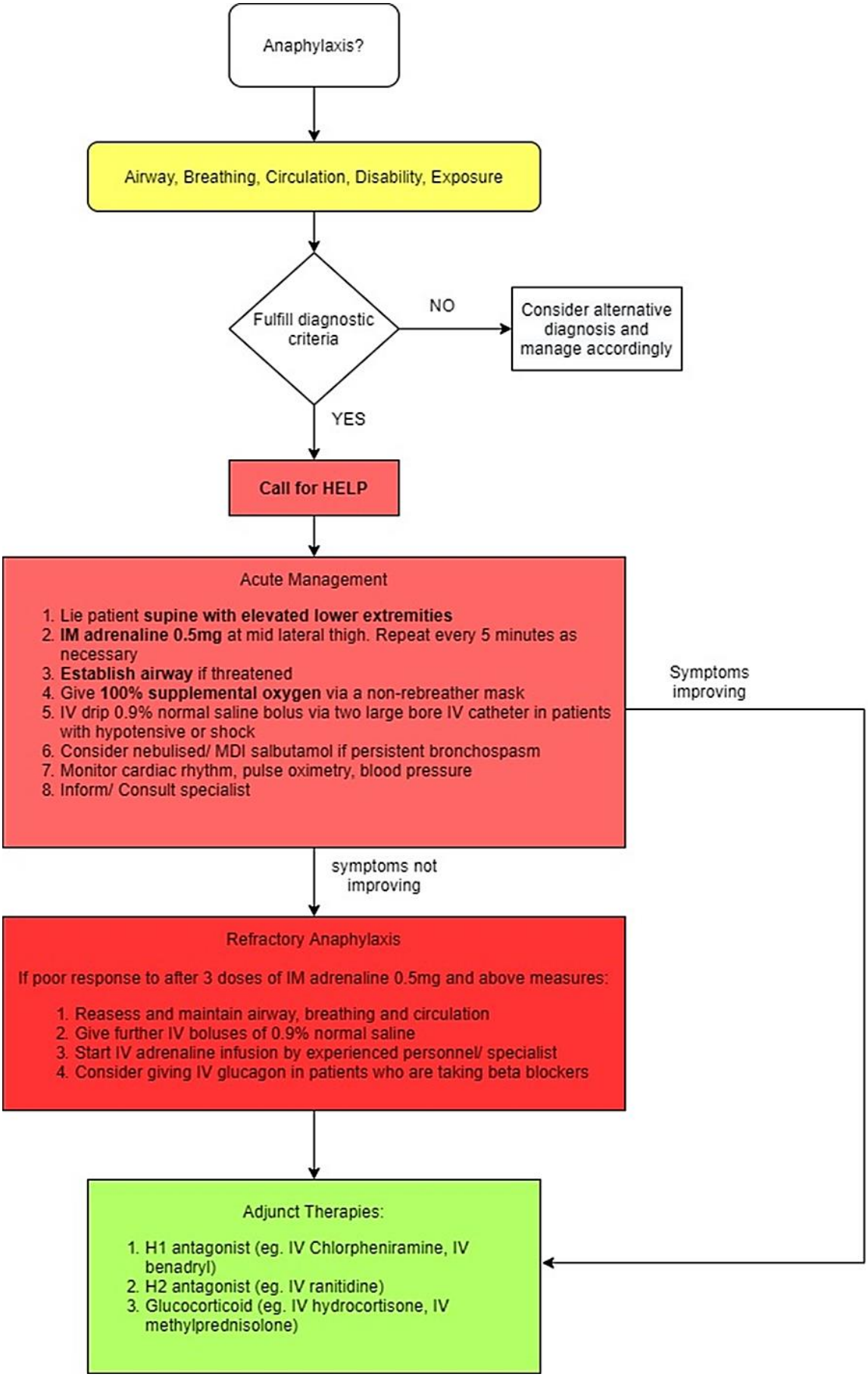
Adjunct therapies[5]

- H1 antagonist: IV chlorpheniramine 10mg
- H2 antagonist: IV ranitidine 50mg
- Glucocorticoid: IV hydrocortisone 200mg
- Monitoring: Pulse oximetry, cardiac monitoring, blood pressure and urine output charting

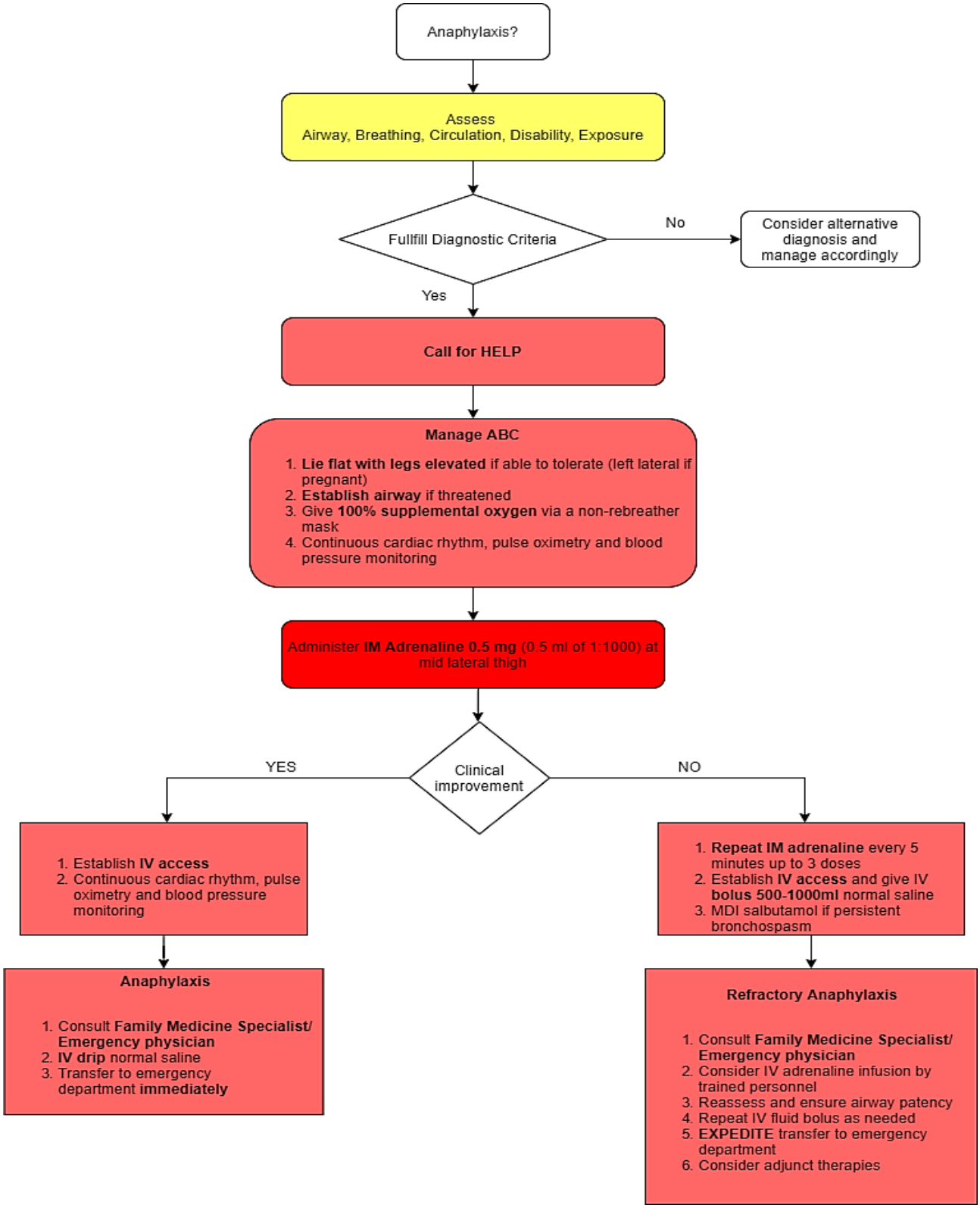
**It is important to consult specialists when encounter refractory anaphylaxis. IV adrenaline should be used only by trained personnel or with guidance from specialists. Glucagon is mostly available in the tertiary hospitals setting.*

Note: **Prioritize** on **adrenaline** administration first over adjunct treatments[11]. While antihistamine and glucocorticoid can relieve symptoms, they do not immediately reverse life threatening airway obstruction or hypotension.

The following flow chart summarizes the management of anaphylaxis



d. Flow Chart for Management of Post Vaccination Anaphylaxis at Vaccination Centers



In the case of confirmed anaphylaxis, adrenaline must be administered as soon as possible. Contact emergency medical services immediately and transfer the patient to a centre with higher medical care for observation for complications and delayed reaction (biphasic phase).

e. Considerations for special population/ groups

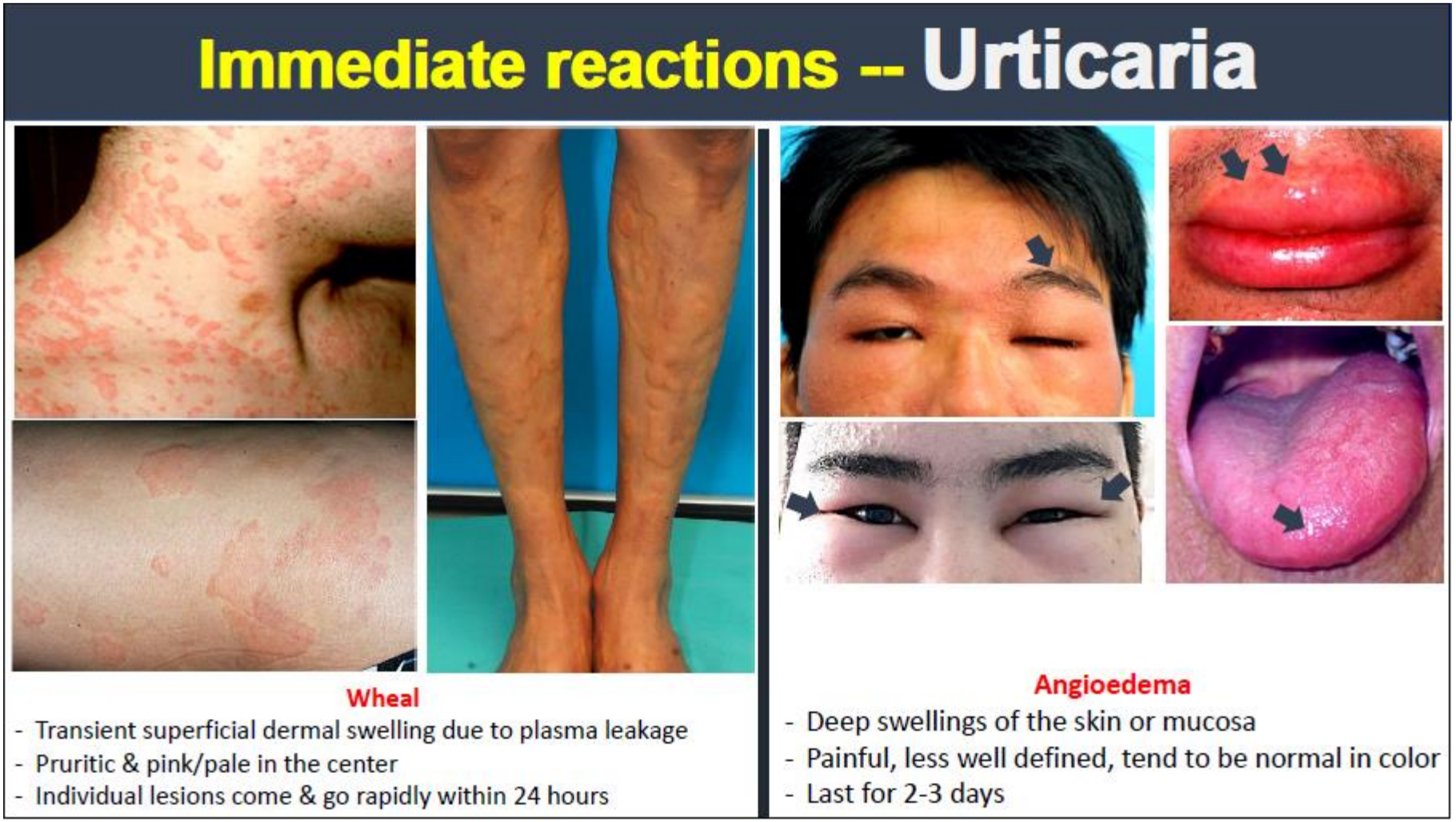
Pregnant patient

The emergency management of anaphylaxis with pregnancy is essentially the same as non-pregnant patients. Early patient transfer to tertiary centers for both maternal and fetal monitoring should be made. If the patient is in shock, emphasis should be given to establish adequate perfusion by rapid administration of intravenous fluid and positioning the patient on the left lateral position or perform manual left uterine displacement to minimise compression of the inferior vena cava in a gravid uterus[6]. It is important to maintain adequate perfusion (SBP> 90mmHg) in pregnant patients as the utero-placental circulation is devoid of autoregulation mechanism and largely depends on the maternal circulation[6].

Elderly patient

Adrenaline administration is the cornerstone for anaphylaxis treatment and is not contraindicated even in elderly with comorbidities such as ischemic heart disease or hypertension. It is important for the vaccination center to have staff who are trained to recognise and manage anaphylaxis so that appropriate treatment is delivered while minimising unnecessary administration of adrenaline.

Immediate reactions: clinical photographs of urticaria and definition



Appendix 3

THE GERIATRIC MEDICINE AND PALLIATIVE MEDICINE FRATERNITY FROM MINISTRY OF HEALTH

Based on current evidence and expert opinions from the geriatric and palliative medicine fraternities, recommendations for COVID-19 vaccination in the elderly frail and terminally ill population are as follows:

1. Persons who are elderly and frail should be ENCOURAGED to have COVID-19 vaccination as the benefits still outweigh risks of COVID-19 infection.
2. Persons with incurable illnesses such as metastatic cancer, dementia, congestive cardiac failure etc. COVID-19 vaccination is still RECOMMENDED unless the person is actively deteriorating with an estimated survival of less than 1 month.
3. Patients requiring palliative care **should not be immediately considered terminally ill** and should be ENCOURAGED to have COVID-19 vaccination if their estimated survival is more than 3 months.
4. Clinical Frailty Scores (CFS) should not be used as the sole criteria to exclude or include an elderly person from COVID-19 vaccination. Persons with high CFS should be further assessed clinically to determine if vaccination is appropriate or to be deferred.
5. Persons who are very frail who receive the COVID-19 vaccination should be monitored post vaccination for at least 72 hours for symptoms of fever, poor oral intake, confusion and weakness which may lead to an acute deterioration in condition. If such symptoms arise appropriate supportive measures should be provided till these symptoms resolve.
6. For persons who lack capacity to decide/consent for vaccination due to conditions such as dementia, stroke, brain injuries etc., family members/careers may decide/consent on behalf of the person.
7. When discussing the role and benefits of vaccination for the elderly frail and palliative care population, it should be mentioned that among the benefits of vaccination would also include the following:
    a. Ease of care and subsequent management in the event of hospitalization or acute illness as isolation procedures may be minimized.
    b. Vaccination will enable better social interaction to occur with family and friends.
    c. Care home residents will protect all other members of the home and minimize risk of outbreaks within the care home.
    d. Preferences for end-of-life care may be more easily fulfilled as there will be less risk of COVID-19 infection and the need for public health procedures.

Table 1: Vaccination criteria for frail elderly

Condition	**Home** ***(Family/carer to register person)***	**Residential Care** ***(Responsible carer in home to register person)***	**Clinical Assessment** ***(performed by any clinician reviewing patient at hospital, outpatient or homecare setting)***
Fit to mild frailty ***(Clinical Frailty Score 1-5)***	**Vaccination is encouraged** - Consent may be by patient or carer	**Vaccination is encouraged** - Consent may be by patient or carer	Pre-vaccination assessment not required
Moderate to severe frailty ***(Clinical Frailty Score 6-7)***	**Vaccination is encouraged** - Consent may be by patient or carer	**Vaccination is encouraged** - Consent may be by patient or carer. - May involve care home management	Patient must be stable in that there are no on-going medical problems such as acute or recurrent/persistent infections or complications where on-going deterioration is anticipated.
Very severely frail ***(Clinical Frailty Score 8)***	**Vaccination should still be encouraged if patient is not actively dying and there are no acute medical issues** - If patient unable to consent then family or carer who is informed of risk & benefits to consent	**Vaccination should still be encouraged if patient is not actively dying and there are no acute medical issues** - If patient unable to consent then family or carer who is informed of risk & benefits to consent. - May involve care home management	Signs of active dying include declining vital signs and clinical condition in the face of medical complications which are not reversible. (eg. Sepsis not responding to antibiotics or severe AKI not for dialysis)

Terminally ill / Patients requiring palliative care	**Vaccination is encouraged unless actively deteriorating with an expected prognosis of less than 1 month)**	**Vaccination is encouraged unless actively deteriorating with an expected prognosis of less than 1 month**	The prognosis of patients requiring palliative care can range from more than 6 months to just a few weeks. Patients in this category should therefore not be excluded from vaccination unless they are in the last stages of their disease trajectory where the expected duration of survival is less than 1 month. Signs of active deterioration includes weekly deterioration in performance status (very disabled to bed bound) and progressive decline in oral intake as well as cognitive function.

GUIDELINES ON COVID-19 VACCINATION IN PREGNANCY AND BREASTFEEDING

Ministry of Health, Malaysia
Version 2
23rd June 2021

Updates

Updates	
I	Safety and efficacy of MRA vaccines among pregnant and breastfeeding mothers
II	Recommendations on Oxford/AstraZeneca, Sinovac, CanSino and Janssen vaccines in pregnancy and breastfeeding
III	Mixing of different types of vaccines in pregnancy and breastfeeding
IV	Simultaneous/co-administration of other types of vaccines in pregnancy
V	Combined oral hormonal contraception and Oxford/AstraZeneca vaccine
VI	Flowcharts on pre & post vaccine assessment of antenatal mothers

Content

Key Recommendations

1) Pregnant mothers are considered vulnerable and are susceptible to severe COVID-19 infections, especially in the second and third trimester.

2) Front liners and those with underlying medical illnesses are at a higher risk of COVID-19 infections. Maternal age of ≥ 40 and BMI ≥ 40kg/m^2 are among identifiable risk factors for severe COVID-19 infection in pregnancy.

3) COVID-19 vaccination should be advocated in pre-pregnancy care, especially for front liners and mothers with identifiable risk factors and also those seeking infertility treatment.

4) Although most pregnant mothers are asymptomatic, the need for ICU admission and mechanical ventilation are higher, particularly with infection by the newer variants of concern. Severe infections in pregnancy are associated with higher risk of pulmonary embolism, iatrogenic prematurity, stillbirth and maternal mortality.

5) Protecting pregnant mothers who are vulnerable, especially those with identifiable risk factors remain a health care priority for vaccination.

6) Based on virology principles, mRNA, vector-based and inactivated vaccines are not contraindicated among pregnant or breastfeeding mothers. Although evidence continues to emerge as more pregnant mothers are included in the study cohort, current data suggests that mRNA vaccines are the preferred option. Live vaccines are contraindicated in pregnancy.

7) The evidence with regards to mixing various types of vaccines and intervals are still being evaluated and until further evidence is available, is it best clinical practice to administer the similar type of vaccine especially among pregnant and breastfeeding mothers.

8) The benefits of COVID-19 vaccines with regards to neonatal protection continues to be evaluated. Current evidence suggests that other routine vaccinations such as Influenza and TDAP can also be safely administered simultaneously without a need for delay or interval between vaccines.

9) Routine pregnancy screening with urine pregnancy test prior to vaccination is not recommended. Vaccination of girls below the age of 18 should be based on an individualized risk assessment and approval by the Ministry of Health (MOH). The FDA has recently approved the use of the vaccines among those above 12 years of age.

Summary of Updates

1) Pregnant mothers remain a vulnerable group

As we continue to review the mortality and morbidity related to COVID-19 infection among pregnant and breastfeeding mothers in Malaysia, they remain a vulnerable group and it is our priority to vaccinate pregnant and breastfeeding mothers.

2) Safety of mRNA vaccines in pregnancy

Based on a recent publication using the “V-safe after vaccination health checker”, no safety signals were associated with mRNA COVID-19 vaccines. This is coherent with the MOH guidelines recommending the Pfizer vaccine among pregnant and breastfeeding mothers in Malaysia. The side effects reported were uncommon, mild, transient and treatable.

Ref: Shimabukuro TT, Kim SY, Myers TR, et al. Preliminary Findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons. N Engl J Med 2021; 384:2273-2282

3) Efficacy of vaccines in pregnancy and breastfeeding

Levels of antibody produced after vaccination with mRNA COVID-19 vaccine is comparable to non-pregnant mothers. This vaccine-induced immune response results in higher antibody titres than natural SARS-CoV-2 infection and is detectable in the cord and breast milk. Whether this confers any protective benefits remains to be seen.

Ref: Gray KJ, Bordt EA, Atyeo C, et al. Coronavirus disease 2019 vaccine response in pregnant and lactating women: a cohort study. Am J Obstet Gynecol. 2021; S0002-9378(21)00187-3. doi:10.1016/j.ajog.2021.03.023

4) First dose of the vaccine is to be administered between 14-33 weeks of pregnancy

Out of an abundance of caution, avoiding vaccination during the critical period of organogenesis in the first trimester is sensible. As the principle of vaccination is to confer protection before the vulnerable late second and third trimester, the current recommendation to administer the first dose of the vaccine during this period remains. The second dose can be administered beyond 33 weeks, based on the specific vaccine’s schedule.

However, vaccination beyond 33 weeks is not an absolute contraindication and can be considered on a case-to-case basis, following individualized risk and benefit assessment.

5) Use of Oxford/AstraZeneca among pregnant and breastfeeding mothers

The Oxford/AstraZeneca vaccine is not contraindicated in pregnancy as it is not a live vaccine. It is best to discuss this with their doctors in order to weight the benefits and risks before making an informed decision.

Although there are no reported concerns with the use of Oxford/AstraZeneca vaccine among pregnant and breastfeeding mothers, there is less published data on this vector-based vaccine compared to the mRNA vaccine. Thus, mRNA-based vaccines such as Pfizer-BioNTech remain the preferred option.

In women who received their first dose of the Oxford/AstraZeneca vaccine and were later confirmed to be pregnant, the recommendation is to receive the second dose of the same vaccine, after 14 weeks of gestation. Vaccine-induced thrombotic thrombocytopenia risk (VITT) is highest following the first dose as compared to the second dose. Furthermore, there is limited evidence with regards to the benefits and implications of mixing different types of vaccines at the time of writing.

It is not contraindicated among breastfeeding mothers, and the WHO Strategic Advisory Group of Experts on Immunization (SAGE) interim guidelines on Oxford/AstraZeneca does not recommend discontinuation of breastfeeding following vaccination.

6) WHO interim guidelines on Sinovac in pregnancy

Coronavac, developed by Sinovac is recommended in pregnancy and breastfeeding mothers as the benefits outweighs the potential risk from the vaccine, despite the lack of safety data related to the use of Sinovac in pregnancy. In principle, live vaccines are contraindicated in pregnancy while Sinovac, being an inactivated vaccine is not.

However, the most robust data available involves the Pfizer-BioNTech mRNA vaccine, where more than 124,000 women were reportedly pregnant at the time of vaccination as of 14th June 2021. Of these, 5100 are involved and enrolled in a registry. The MOH currently recommends the mRNA vaccine as the preferred option, although this may change as new information and data are made available.

In women who have taken the Sinovac vaccine and were later confirmed to be pregnant, it is recommended to take the second dose after 14 weeks of gestation, as the vaccine is not contraindicated in pregnancy. The benefits, safety and efficacy of mixing vaccines in pregnancy is yet to be established.

Ref: World Health Organization. Interim recommendations on the use of inactivated Covid-19 vaccine, Coronavac, developed by Sinovac. 24th May 2021

7) CDC update on co-administration of anti-tetanus toxoid and COVID-19 Vaccines.

The initial recommendation was to defer COVID-19 vaccine for a minimum period of 14 days after administration of another vaccine, such as anti-tetanus toxoid (ATT). However, the experience following the COVID-19 vaccinations now demonstrates that the immunogenicity and adverse profiles are similar and tolerable. The updated CDC recommendations now states that co-administration of vaccines, including on the same visit is acceptable.

Ref: Centers for Disease Control Prevention. Interim clinical considerations for the use of Covid-19 vaccines currently authorized in the United States.

8) Pregnancy and fertility following vaccination

Existing literature remain consistent in stating that all types of COVID-19 vaccines do not affect fertility or future reproductive health. Women who have completed their vaccination can safely embark on pregnancy without delay. However, contraception is recommended between the first and second dose of vaccine.

9) Mixing vaccines and change of dosing interval

The implications of mixing different types of vaccines and changing of dosing interval is still being evaluated in clinical trials and until more robust evidence is available, it is reasonable to maintain the same type of vaccine for now. This is particularly sensible in pregnancy and breastfeeding. The COM-COV trial is one of a handful of trials evaluating the efficacy of mixing vaccines (heterologous schedule) and interim data has shown a higher reactogenicity with Oxford/AstraZeneca and Pfizer-BioNTech. However, the findings may not be applicable to pregnant women since the cohort involved patients above the age of 50.

Ref: Shaw R, Stuart A, Greenland M, et al. Heterologous prime-boost COVID-19 vaccination: Initial reactogenicity data. Lancet 2021. /doi.org/10.1016/S0140-6736(21)01115-6

10) Combined hormonal contraception and Oxford/AstraZeneca

The Faculty of Sexual Reproductive Healthcare (FSRH) of the Royal College of Obstetricians and Gynaecologists (RCOG), does not recommend discontinuation of combined oral hormonal contraception before or immediately after vaccination, in spite of the rare association between the Oxford/AstraZeneca vaccine and VITT. Temporary discontinuation does not render protection against the rare incidence of thrombosis yet increases the risk of unplanned pregnancies. If patients are concerned of their risk and medications, it is best to consult with their doctors first without discontinuing medications and existing contraceptive practices.

11) Vaccination for adolescent mothers above the age of 12 years

The pandemic has seen more than 1.6 million adolescents aged 12-17 in the United States being infected by SARS-CoV2 as of May 2021. This constituted 9% of infections in the country. The efficacy and immunogenicity with mRNA vaccine has already been demonstrated in a randomized clinical trial involving over 2200 adolescents aged 12-15 years old. In fact, as of 31st May 2021, 46,533 adolescents in this age group have been vaccinated in US. The CDC has since expanded the use COVID-19 vaccine to this age group.

The association with myocarditis and pericarditis remains rare and continues to be evaluated. Nevertheless, if an adolescent pregnant mother has significant identifiable risk factors in pregnancy and is flagged as high risk in pregnancy or during breastfeeding, the benefits of vaccinations should be discussed with the patient and family members or guardians. Standard requirement of consent for those below the age of 18 would apply.

Ref: US Food and Drug Administration.Vaccines and Related Biological Products Advisory Committee. 10th June 2021.

Advisory Committee on Immunization Practices. ACIP Evidence to Recommendations for Use of Pfizer-BioNTech COVID-19 Vaccine under an Emergency Use Authorization.

12) Deployment of pregnant or breastfeeding front liners

Pregnant or breastfeeding front liners with no additional risk factors and who have completed their vaccination can continue to provide essential services. This includes direct involvement in managing COVID-19 patients up till the late third trimester as their services are critical with the surge in cases in the country.

13) Single dose vaccines in Malaysia – CanSino & Janssen Vaccines

Malaysia has recently granted conditional approval for the emergency use of two vaccines, produced by CanSino Bio and Janssen. Both are vector-based vaccines and therefore, not contraindicated in pregnancy. However, in view of the limited safety data in pregnancy, the preferred vaccine for pregnant and breastfeeding mothers remains the mRNA vaccine.

Rationale for COVID-19 Vaccination in pregnancy

Pregnant and recently pregnant women with COVID-19 infection are more likely to require intensive care unit admission (1.62, 1.33 to 1.96; I^2=0%; 4 studies; 91606 women) and invasive ventilation (1.88, 1.36 to 2.60; I^2=0%; 4 studies; 91606 women) as compared to non-pregnant women of reproductive age.[1]

These findings were consistent with data from the ongoing prospective COV19Mx cohort in Mexico, where propensity score matching was used to adjust for other risk factors or co-morbidities. Amongst the 5183 pregnant and 5183 non-pregnant matched women, pregnant women had a higher odds of death (odds ratio (OR), 1.84; 95% CI, 1.26–2.69), pneumonia (OR, 1.86; 95% CI, 1.60–2.16) and ICU admission (OR, 1.86; 95% CI, 1.41–2.45) than non-pregnant women. The odds of intubation however, were similar (OR, 0.93; 95% CI, 0.70–1.25).[2]

Severe illness appears to be more common in the second and third trimester. In the UKOSS study, most women were hospitalized in their third trimester or peripartum (n = 342, 81%). The median gestational age at hospital admission was 34+0 weeks of gestation (interquartile range [IQR] 29–38 weeks).[3] A retrospective multicentre study involving 190 women from France and Belgium also showed that women were five times more likely to be admitted to the ICU in the second half, compared to the first half of pregnancy. [4]

The overall rate of preterm birth was 17% (13 to 21%; 30 studies; 1872 women), although the majority were iatrogenic , including to facilitate ventilation. This was a 3-fold increase compared to pregnant women without disease.[1] In another cohort of 64 pregnant women with severe or critical COVID-19 disease, up to 75% of women delivered preterm.[5] Spontaneous preterm birth rate was 6% (3% to 9%; I^2=55%; 10 studies; 870 women).[1]

Thus, vaccinating pregnant mothers with identifiable risk factors not only reduces maternal morbidity and mortality but also reduces fetal morbidity from preterm deliveries.

Safety and efficacy of COVID-19 vaccines among pregnant and breastfeeding mothers

Despite the lack of involvement of pregnant women in the initial clinical trials during development of COVID-19 vaccines, contemporary scientific knowledge indicates that COVID-19 vaccinations among pregnant and breastfeeding mothers are likely to be safe. There is no known risk with giving inactivated virus or bacterial vaccines or toxoids during pregnancy or whilst breast-feeding. Furthermore, pregnant women have been receiving vaccines such as tetanus toxoid, influenza and pertussis vaccination (TDaP) without demonstrable harm to the fetus.[6]

Both the Pfizer-BioNTech and Moderna are mRNA-based vaccines which builds “spike proteins”, mimicking the surface protein of SARS-COV-2 to trigger an immune response. These vaccines do not contain live SARS-CoV-2 and hence is not infective to the pregnant mother and her fetus.

Based on the recent New England Journal of Medicine (NEJM) publication using the V-safe after vaccination health checker, the study concluded that mRNA vaccines were safe to be used during pregnancy without any significant safety signals and this is coherent with the MOH guidelines recommending the Pfizer vaccine among pregnant and breastfeeding mothers in Malaysia. The side effects were uncommon, mild, transient and treatable.

Studies show that the efficacy of the mRNA vaccine is similar in pregnancy as compared to non-pregnant mothers. Although the vaccine induced immune response fared better as compared to those with natural COVID-19 infection, the risk of infection to the fetus is insignificant although the protective benefits remain to be evaluated.

Although there are no reported concerns with regards to the use of Oxford/AstraZeneca vaccine among pregnant and breastfeeding mothers, there is less experience with regards to the use of this vector-based vaccine as compared to the mRNA vaccine. Thus, Pfizer or the mRNA-based vaccine remains the preferred option based on the availability of safety data by the Ministry of Health, Malaysia.

If pregnant mothers are keen to take Oxford/AstraZeneca vaccines in pregnancy, while not contraindicated in pregnancy as it is not a live vaccine, it is best to discuss with their doctors as to weigh the benefits and risk before making an informed decision.

However, the Oxford/AstraZeneca is not contraindicated among breastfeeding mothers, and the WHO Strategic Advisory Group of Experts on Immunization (SAGE) interim guidelines on Oxford/AstraZeneca does not recommend discontinuation of breastfeeding following vaccination.

Coronavac, developed by Sinovac is recommended in pregnancy and breastfeeding mothers as the benefits outweighs the potential risk from the vaccine, despite the lack of safety data related to the use of Sinovac in pregnancy. In principle, live vaccines are contraindicated in pregnancy while Sinovac, being an inactivated vaccine is not.

However, the most robust data available involves the Pfizer-BioNTech mRNA vaccine, where more than 124,000 women were reportedly pregnant at the time of vaccination as of 14th June 2021. Of these, 5100 are involved and enrolled in a registry. The MOH currently recommends the mRNA vaccine as the preferred option, although this may change as new information and data are made available.

In women who have taken the Sinovac vaccine and were later confirmed to be pregnant, it is recommended to take the second dose after 14 weeks of gestation, as the vaccine is not contraindicated in pregnancy. The benefits, safety and efficacy of mixing vaccines in pregnancy is yet to be established.

Women who develop fever after vaccination should be counseled on taking acetaminophen, which is safety in pregnancy and does not alter the immunologic response towards COVID-19 vaccine.

Pre-pregnancy care

All women with identifiable risk factors should be advised to complete their vaccination before embarking on a pregnancy.

Routine pregnancy screening using urine pregnancy test prior to vaccination is not recommended. There are concerns that such measures may increase vaccine hesitancy and put off women against vaccination. It is essential to check for prior allergy risk and those declining vaccinations should be given more information on the benefits and safety of COVID-19 vaccination. Those who are considered vulnerable include:

- Age ≥ 40
- BMI ≥ 40kg/m^2
- Cardiac disease
- Significant lung condition e.g. Tuberculosis/ Severe asthma
- Moderate and severe renal diseases
- Connective tissue diseases such as SLE, Sjogren's Syndrome
- Severe anemia
- HIV patients
- Patients with liver diseases – including Hepatitis B patients on antiviral
- Patients on immunosuppressive therapy
- Organ transplantation (including bone marrow / stem cell)
- Currently undergoing cancer treatment
- History of splenectomy / Apslenia
- Pulmonary embolism or other underlying medical diseases

COVID-19 Vaccines and Fertility

While fertility was not specifically studied in the clinical trials, no loss of fertility has been reported among trial participants or among the millions who have received the vaccines since their authorization. Furthermore, no signs of infertility appeared in animal studies.[16]

There are different viewpoints with regards to the need to postpone conception after vaccination. The American Society for Reproductive Medicine (ASRM) does not recommend delaying pregnancy attempts because of COVID-19 vaccination, including women undergoing fertility treatment. The European Society of Human Reproduction and Embryology (ESHRE) however, recommends a more cautious approach. It suggests postponing the start of assisted reproduction treatments (sperm collection, ovarian stimulation, embryo transfer) for at least a few days after the completion of vaccination (i.e., after the second dose) to allow time for the immune response to settle. It also adds that in the absence of information on the effect of the COVID-19 vaccine on oocytes and sperm, embryo implantation and early stages of pregnancy, and to allow time for antibody development, a more cautious approach could be considered (i.e., postpone the start of ART treatment for up to 2 months).[17,18]

Front line workers, including non-healthcare workers who are at increased risk of repeated exposure to SARS-COV-2 due to the nature of their occupation, should ideally be vaccinated against COVID-19 particularly, if pregnant.

Timing of first vaccination dose in the antenatal period

Vaccinating women early in pregnancy in the setting of a pandemic offers increased emergent protection against the virus. However, such a strategy also potentially reduces the rate of protection towards the end of pregnancy. There is still uncertainty about the duration of protection after completion of the second dose vaccine.

Vaccinating women in the second half of pregnancy protects women against COVID-19 disease which has been associated with greater morbidity in the third trimester.

On the other hand, the first trimester is also a period of great uncertainty for some women and the risk of complications such as miscarriage is also highest. Despite the lack of evidence of harm on fetal/embryonal development from the developmental and reproductive toxicity (DART),[8] out of an abundance of caution to avoid suspicion of connection, even coincidental, between pregnancy and fetal harm, in our opinion, it is reasonable to begin vaccination after the first trimester.

Conceiving prior to completion of vaccination

Women who conceive or find out about their pregnancy after the first dose of vaccination (and prior to the second dose) should be reassured about the overall safety of COVID-19 vaccines based on developmental and toxicity studies (DART).[8] Based on the recent NEJM study, although rates of miscarriage was slightly increased, pregnancy complications such as gestational diabetes and preeclampsia, preterm birth, congenital anomalies and neonatal death were no higher than background rates.[22]

Therefore, pregnant women could be given one of these three options:

Options	Recommendations
Defer second dose till 14 weeks of gestation	Although the manufacturer recommends an interval of no longer than 6 weeks for Moderna/Pfizer for optimal immune response, the UK Joint Committee on Vaccination and Immunization (JCVI) has recommended delaying the 3-week interval to up to 12 weeks, based on the short-term effectiveness quoted below.[23] This is in part, to facilitate rapid high-level uptake of the vaccine
Omit second dose	Short term effectiveness of 52-89% has been reported after a single dose of vaccine, although the duration of this protection remains uncertain.[24,25]
Continue second dose as scheduled	If pregnant women are at high risk of severe disease or repeated exposure to SARS-COV-2, they may choose to continue receiving the 2nd dose of vaccine as scheduled, based on the current safety data reported from v-safe.[22]

For those who have completed their first dose of the Oxford/AstraZeneca vaccine and were later confirmed to be pregnant, the recommendation is to take the second dose of the same vaccine after 14 weeks of gestation. Vaccine-induced thrombotic thrombocytopenia risk (VITT) is highest following the first dose as compared to the second dose. Furthermore, there is limited evidence with regards to the benefits and implications of mixing different types of vaccines at the time of writing.

Similarly, for mothers who have received the Sinovac vaccine and were later confirmed to be pregnant, it is recommended to delay the second dose beyond 14 weeks of gestation as the vaccine is not contraindicated in pregnancy while the benefits, safety and efficacy of mixing vaccines in pregnancy is yet to be established.

Simultaneous / co-administration of other types of vaccines in pregnancy

The initial recommendation was to defer COVID-19 vaccine for a minimum period of 14 days after administration of another vaccine, such as anti-tetanus toxoid (ATT). However, the experience following the COVID-19 vaccinations now demonstrates that the immunogenicity and adverse profiles are similar and tolerable. The updated CDC recommendations now states that co-administration of vaccines, including on the same visit is acceptable.

Similarly, in women who are Rhesus negative and have not been sensitized, anti-D immunoglobulins can be administered as per routine without a need to delay COVID-19 vaccination.

Vaccination and breastfeeding

Many lactating women fall into categories prioritized for vaccination, such as front-line health care workers. Both the WHO Interim Guidance on the use of mRNA-1273 (Moderna) and the Academy of Breastfeeding Medicine do not recommend cessation of breastfeeding for individuals who are vaccinated against COVID-19. Similar to pregnant mothers who were excluded from COVID-19 vaccine trials, there is currently little data for nursing mothers. However, there is little biological plausibility that the vaccine will cause harm and antibodies to SARS-CoV-2 in milk may protect the breastfeeding child.

The vaccine is made of lipid nanoparticles that contain mRNA for the SARS-CoV-2 spike protein, which stimulate an immune response, protecting the individual from COVID-19 illness. During lactation, it is unlikely that the vaccine lipid would enter the blood stream and reach breast tissue. If it does, it is even less likely that either the intact nanoparticle or mRNA would transfer into milk. In the unlikely event that mRNA is present in milk, it would be expected to be digested by the child and would be unlikely to have any biological effects.

While there is little plausible risk for the child, there is a biologically plausible benefit. Antibodies and T-cells stimulated by the vaccine may passively transfer into milk. Following vaccination against other viruses, IgA antibodies are detectable in milk within 5 to 7 days. Antibodies transferred into milk may therefore protect the infant from infection with SARS-CoV-2.[15]

A critical benefit to vaccinating pregnant mothers against pertussis and to a lesser extent, influenza in the third trimester is that the vaccine protects the infant for several months after birth by the transplacental transfer disease-specific serum immunoglobulin G. In this way, antenatal vaccination helps protect not only the mother but also provides neonatal protection. In contrast, the transfer of SARS-COV-2 maternal antibodies to the infant is inefficient when compared to vaccine-induced influenza antibodies. Therefore, it is unlikely that COVID-19 vaccination will provide protection to newborns. No vaccines are currently available to infants or young children.[9,14]

Combined oral hormonal contraception & Oxford/AstraZeneca

The Faculty of Sexual Reproductive Healthcare (FSRH) of the Royal College of Obstetricians and Gynaecologists (RCOG), does not recommend discontinuation of combined oral hormonal contraception before or immediately after vaccination, in spite of the rare association between the Oxford/AstraZeneca vaccine and VITT. Temporary discontinuation does not render protection against the rare incidence of thrombosis yet increases the risk of unplanned pregnancies. If patients are concerned of their risk and medications, it is best to consult with their doctors first without discontinuing medications and existing contraceptive practices.

Vaccination after COVID-19 infection

Some degree of natural immunity is gained after infection with SARS-COV-2 virus. However, it is uncertain how long this immunity might last, although reinfection appears uncommon within 6 months of a PCR-confirmed SARS-COV-2 infection.[13]

Due to the potentially severe health risks posed by COVID-19 and its widespread extent, women who are at risk should still be considered for vaccination against COVID-19.

Care for women declining COVID-19 Vaccination

Women who are at risk but decline vaccination should have an opportunity for further discussion with an Obstetrician and Gynaecologist. This should be documented in their clinical notes. In addition, general measures for prevention of infection such as avoidance of crowds and unnecessary travel, use of a 3-ply mask in public areas, hand hygiene and compliance to standard operating procedures issued by the Ministry of Health should be reinforced.

COVID-19 VACCINATION
IN PREGNANCY AND BREASTFEEDING

1 **IS IT SAFE IN PREGNANCY?**
There is increasing evidence that Covid-19 vaccination is safe in pregnancy.

2 **WHO SHOULD GET VACCINATED?**
All pregnant mothers are susceptible to severe complications from Covid-19. Therefore, vaccination is recommended particularly in women with risk factors such as age above 40, BMI above 40 or have underlying medical diseases.

3 **WHEN SHOULD I GET MY VACCINE?**
Ideally the first dose of Covid-19 vaccine should be given between 14 to 33 weeks. Feel free to consult your doctor if your pregnancy is outside this time frame for more information.

4 **CAN I BREASTFEED MY BABY?**
It is safe to breastfeed after receiving the Covid-19 vaccine as it does not contain live virus. Cessation of breastfeeding is therefore unnecessary.

5 **DOES THE VACCINE PROTECT MY BABY FROM COVID-19 INFECTION??**
Although antibodies have been found in breastmilk, we are unsure if this protects the baby from Covid-19 infection.

6 **WHAT ARE THE SIDE EFFECTS?**
Side effects are transient, uncommon and easily treatable. This includes pain at the injection site, headaches, chills, fatigue and muscle ache.

7 **CAN I RECEIVE OTHER VACCINES SIMULTANEOUSLY?**
Yes, you can receive other routine antenatal vaccines simultaneously.

8 **IF I AM PLANNING TO GET PREGNANT, DO I NEED THE COVID-19 VACCINE?**
Yes, since there is a higher risk of getting severe COVID-19 infection in pregnancy. It is recommended to complete vaccination before embarking on a pregnancy.

9 **WHAT IF I PREVIOUSLY HAD COVID-19?**
Vaccination is also recommended regardless of previous Covid-19 disease. If you have recovered more than 6 months ago, you are unlikely to have protective antibodies.

10 **WHAT IF I HAVE ALLERGIES?**
Women with severe allergies or previous anaphylactic reactions should consult a physician prior to receiving the vaccine.

Source: Guidelines on Covid-19 vaccination in pregnancy and breastfeeding.

CONSULT YOUR DOCTOR IF YOU HAVE ANY QUESTIONS REGARDING COVID-19 VACCINATION IN PREGNANCY TODAY.

JUNE 2021

CONSENT FOR COVID-19 VACCINATION DURING PREGNANCY

Name of proposed intervention

COVID-19 Vaccination during pregnancy (Between 14 to 33 weeks of pregnancy)

Intended benefits

To reduce the risk of severe COVID-19 infection in pregnancy, particularly among high risk mothers
To reduce the risk of COVID-19 infection amongst pregnant frontline workers who are at increased risk of exposure to SARS-COV-2

Frequent Risks associated with COVID-19 Vaccination

i) Pain at the injection site
ii) Headache
iii) Chills
iv) Fatigue
v) Muscle ache

**Your risk may be higher if you are known to have severe allergies or previous anaphylactic reasons. Consult your doctor first.*

Serious Risks

A) **Maternal risk**

Studies among non-pregnant women has shown that serious risks, including anaphylaxis and death from vaccinations are very rare. While there is a lack of safety data among pregnant mothers at this moment, there are no reasons to believe this would differ.

B) **Fetal risk**

No safety concerns have been found in experimental animal studies. However, there is no direct or long term safety data on COVID-19 vaccinations to the fetus.

Alternative options

I understand that I have the option to decline vaccination during pregnancy in view of safety concerns but this may increase my risk of having severe COVID-19 infections, especially if I am considered high risk, which includes ICU admissions, need for ventilation, stillbirth, prematurity and death.

Patient information

I have been given information and resources on COVID-19 including the benefits and risk of having vaccinations in pregnancy. I have been given sufficient time to make my informed decision. I also have been counselled on the various type of available vaccines and its benefits.

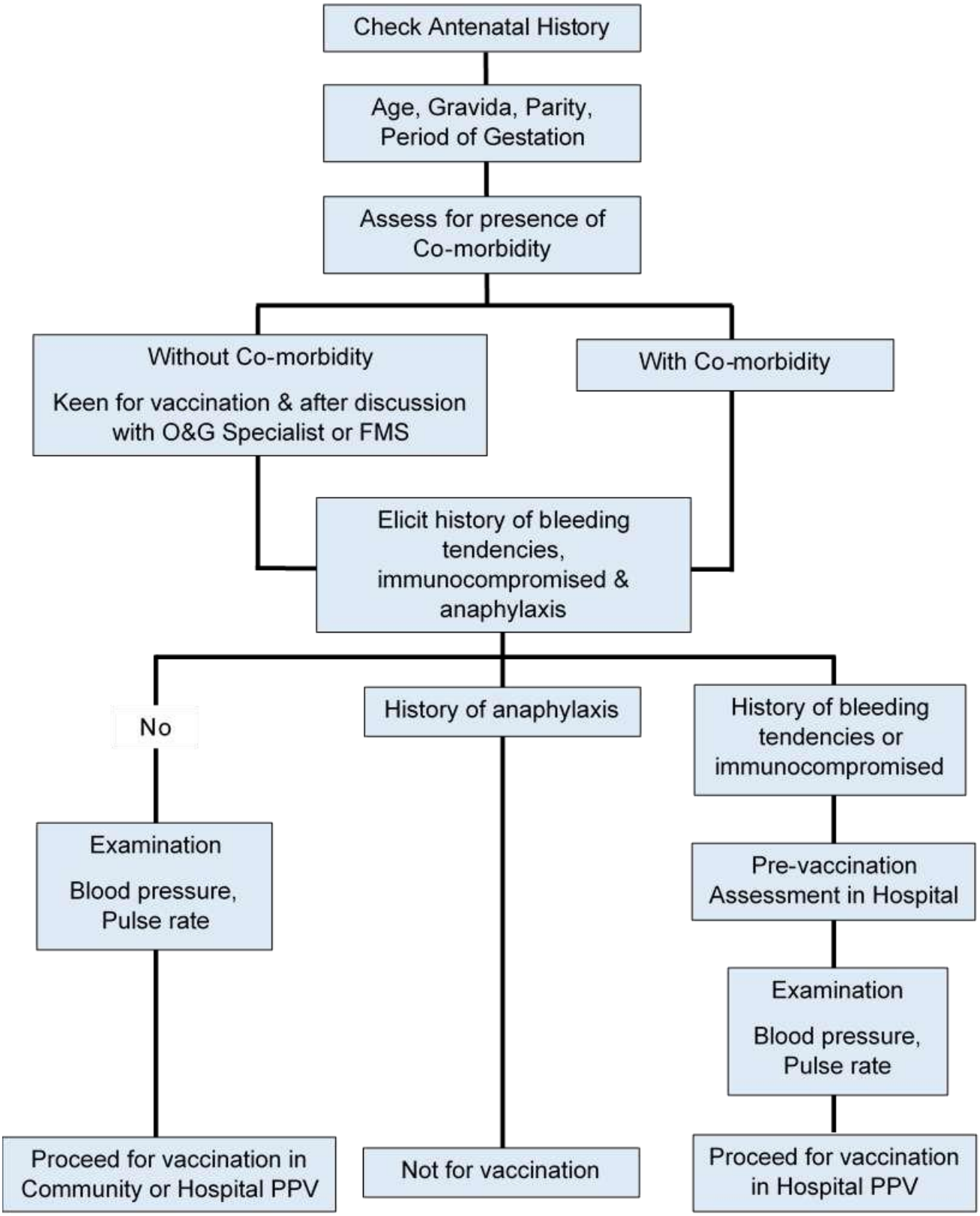
I hereby consent to have the COVID-19 vaccination during pregnancy.

Signature of Mother:
Name:
Identification No:

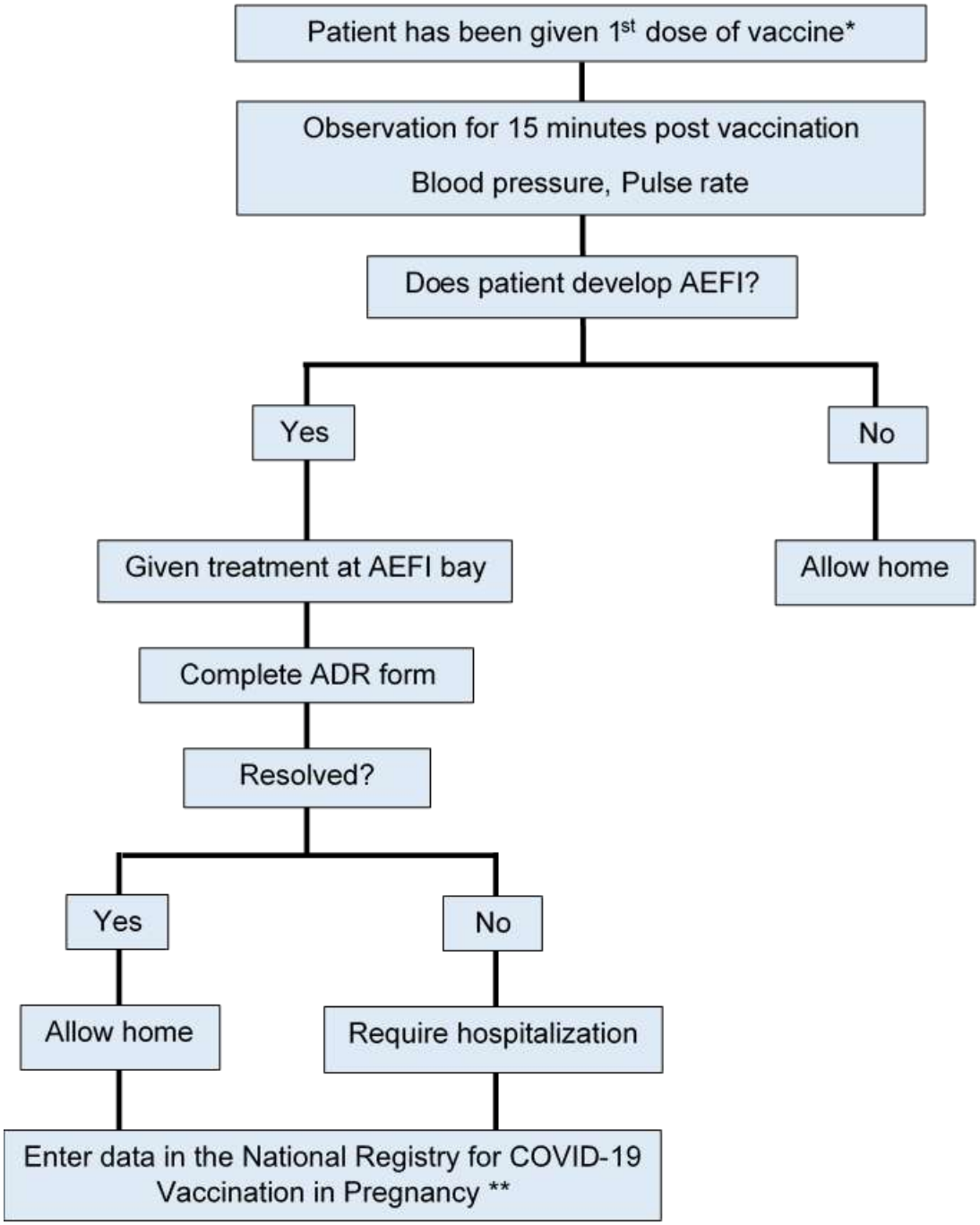
Signature of Doctor
Name:
Stamp:

Witness:
Translator (if required):
Date:

Flow Chart on Pre-vaccination Assessment for Antenatal Mothers on Presentation to Clinic or Hospital (1st Dose)



Flow Chart on Post-vaccination Assessment for Antenatal Mothers



*Any vaccine that has been approved for use in pregnancy by the Ministry of Health, Malaysia

**when available

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Appendix 5

COVID-19 VACCINATION FOR CANCER PATIENTS WITH SOLID TUMOURS

Introduction

This consensus statement is based on reviews of international guidelines on COVID-19 vaccination. Currently none of the authorized COVID-19 vaccines are live virus vaccines. Although data on safety for cancer patients is limited, there are many examples of vaccination for vulnerable patients including cancer patients in countries which rolled out COVID vaccine much earlier than Malaysia and proven that the benefit continues to outweigh the possible adverse effects. It is hence considered beneficial for patients with underlying cancers to receive vaccination against COVID-19. There is interim data indicating lower seroconversion of cancer patients on active treatment. This does not change the benefit derived from vaccination although indicating timing of vaccination could be adjusted for better efficacy. Family members and caregivers are encouraged to have the vaccination for protection of the vulnerable group who are not able to have the vaccination.

DISCLAIMER

This statement is current as of 30th March 2021, and recommendations may change as more data becomes available. Please consult the treating oncologists before vaccination. For further update and information, please refer to the Guidelines for Covid-19 vaccination from MOH Malaysia.

RECOMMENDATIONS

A. Patients on active cancer treatment

The patients who are on active cancer treatment are classified as the patients who are due for the treatment below:

Type of treatment	Status	Recommended timing
Chemotherapy neoadjuvant/ adjuvant/ palliative)	Ongoing treatment	3 months after completed chemotherapy OR earlier up to the discretion of oncologist.
	Due to start chemotherapy	To complete vaccination before and/ or after surgery prior to oncology treatment For urgent chemotherapy for e.g. germ cell tumor or metastatic patients in visceral crisis, chemotherapy should be proceeded WITH NO delay. If vaccination was not given before initiation of oncology treatment, to

		delay until after completion of treatment OR at the discretion of oncologist.
	Completed the last cycle	3 months after completed chemotherapy OR earlier up to the discretion of oncologist.
Hormonal / targeted therapies/ Immunotherapy **e.g., Imatinib/ Pazopanib/ Sunitinib/ Lenvatinib/ Herceptin/ Pertuzumab**	at any treatment time	For vaccination once it is available. The vaccine is relatively safe and recommended; However discussion with treating physician/ oncologist is recommended before the injection.
Checkpoint inhibitors	at any treatment time	once blood count recovers and up to the discretion of oncologist.
Radical/ palliative radiotherapy	at any treatment time	3 months after completed concurrent chemoradiotherapy OR earlier up to the discretion of oncologist. For palliative radiotherapy, once completed treatment and up to the discretion of oncologist.

B. Patients in remission or cancer survivors

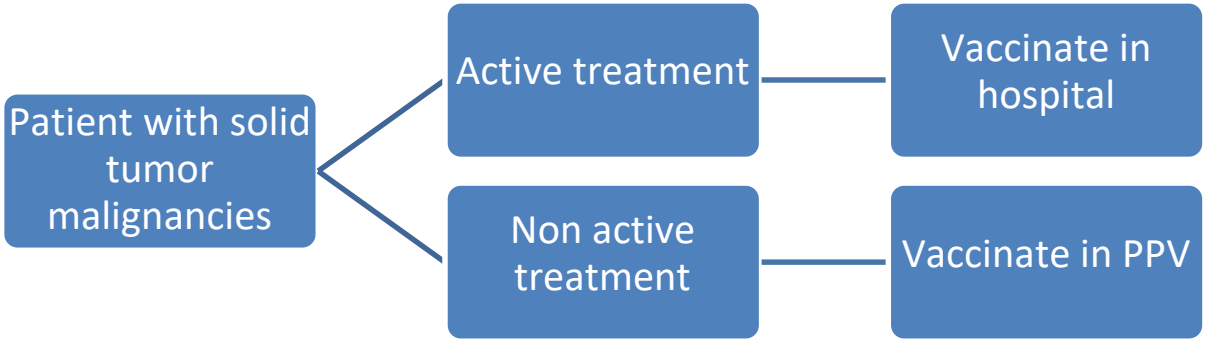
All cancer patients who have completed their treatment for at least three months and are in remission, along with cancer survivors could be vaccinated anytime according to national vaccine guideline.

Patient groups recommended to be vaccinated in hospital. The timing for vaccination is up to the discretion of oncologist.

a. Patient with potential allergy to components in the vaccine e.g. PEG
b. Patients with metastatic disease
c. Thoracic malignancy
d. Patients aged 60 years and above
e. Patient under clinical trials

C. Vaccination Sites for Cancer Patients

a. 6 MOH Oncology Centres – Hospital Kuala Lumpur, Institut Kanser Negara, Hospital Sultan Ismail, Hospital Wanita dan Kanak-kanak Likas, Hospital Umum Sarawak and Hospital Pulau Pinang.
b. Peripheral hospitals – state and major hospitals with specialists providing chemotherapy and palliative care.
c. Pusat Pemberian Vaksin (PPV) – for stable, not on active treatment patients.



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Appendix 6

CONSENSUS STATEMENT FROM MALAYSIAN SOCIETY OF HAEMATOLOGY

COVID-19 VACCINATION FOR PATIENTS WITH HAEMATOLOGICAL DISORDERS

CONSENSUS STATEMENT

Malaysian Society of Haematology

March 2021

BACKGROUND

This consensus statement is based on reviews of international guidelines on COVID-19 vaccination. There is also no preference to the types of vaccine available currently. None of the authorized COVID-19 vaccines are live virus vaccines, hence they are considered safe for patients with underlying haematological cancers or those on immunosuppressive drugs. Family members/ caregivers are encouraged to have the vaccination for protection of the vulnerable group who are not able to have the vaccination. It is crucial that all ought to practice the recommended precaution even after vaccination.

DISCLAIMER

This statement is current as of 22 March 2021, and recommendations may change as more data becomes available. The society and authors will not accept any legal responsibility. Please consult the treating hematologists before vaccination. For further update and information, please refer to the KKM guidelines at covid-19.moh.gov.my.

RECOMMENDATION

A. Patients with Haematological Cancers

- Patients who are undergoing active therapy such as chemotherapy are advised to discuss the risks and benefits of the vaccines prior to considering vaccination.

- Patients who are on long term or maintenance therapy (other than B-cell depleting agents) or have completed treatment can have their COVID-19 vaccination. These include patients with chronic myeloid leukemia, multiple myeloma, lymphomas, chronic lymphocytic leukemia, myelodysplastic syndrome and myeloproliferative neoplasms.

- In patients who are receiving B-cell depleting agents such as anti-CD20 monoclonal antibodies e.g. Rituximab, the vaccine should be administered preferably 6 months after the last dose; if this is not possible, we recommend completing the full course of vaccination at least 4 weeks prior to the next dose of Rituximab.

- Patients who are currently receiving other types of cancer treatment are advised to wait for normalization of blood counts before vaccination.

B. Patients who received Haematopoeitic Stem Cell Transplantation (HSCT) and/or Cellular Therapy

i. Patients can have their vaccination as early as 3 months after autologous HSCT.

ii. Patients can have their vaccination starting from 3 – 6 months after allogeneic HSCT if the risk of community transmission is high. Otherwise, we would recommend deferral beyond 6 months after HSCT.

iii. Patients who have severe, uncontrolled grades III – IV acute graft versus host disease are recommended to defer vaccination until it is controlled.

iv. Consider vaccination in patients with mild chronic graft versus host disease and receiving
    i. ≤ 0.5 mg/kg prednisolone (or equivalent).

v. Consider vaccination in patients who have received Chimeric Antigen Receptor – T cells (CAR-T) 3 – 6 months after completion of treatment.

C. Patients with Bleeding Disorders

i. People with bleeding disorders are not at greater risk of contracting COVID-19 or developing a severe form of the disease.

ii. The vaccine itself does not present any additional safety concerns for these patients but the intramuscular route of administration may increase the risk of bleeding at the injection site.

iii. Patients with a history of allergic reactions to extended half-life clotting factor concentrates containing polyethylene glycol (PEG) should discuss vaccine choice with their physician because some COVID-19 vaccines (e.g. Pfizer-BioNTech vaccine) contain PEG as an excipient.

iv. For patients with severe or moderate haemophilia A or B, the vaccine injection should be given after a prophylactic dose of Factor VIII (FVIII) or Factor IX (FIX). For patients with a basal FVIII or FIX level above 10%, no haemostatic therapies are required.

v. For patients with inhibitors, the vaccine injection should be given after a prophylactic dose of bypassing agent.

vi. Patients on Emicizumab (with or without an inhibitor) can be vaccinated by intramuscular injection at any time without haemostatic precautions and without receiving a dose of FVIII or bypassing agent.

vii. Patients with Type 1 or 2 Willebrand disease (VWD), depending on their baseline von Willebrand factor (VWF) activity levels, should use haemostatic therapies [i.e. tranexamic acid, desmopressin (DDAVP) or VWF concentrate] in consultation with their haematologists. Patients with Type 3 VWD should be given a prophylactic dose of VWF concentrate prior to the intramuscular COVID-19 vaccination.

viii. Patients with platelet counts of 50 x 10^9/L and above can proceed with vaccination without additional haemostatic support. Patients with platelet counts below 50 x 10^9/L should defer the vaccination till their platelet counts recover, if possible. For those patients with chronically low platelet counts, vaccination should be performed in consultation with their primary haematologist.

ix. Patients with other rare bleeding disorders including platelet function disorders should be vaccinated in consultation with their primary haematologists.

x. The currently available COVID-19 vaccines should be administered intramuscularly. There are no data for the subcutaneous route and this should not be done. The smallest gauge needle available (25 to 27 gauge) should be used. Pressure should be applied to the site for 5 to 10 minutes post-injection to reduce bleeding and swelling. Additionally, self-inspection and palpation of the injection area several minutes and 4 to 6 hours later is recommended to ensure that there is no delayed haematoma. Discomfort in the arm felt for 1 to 2 days after injection should not be alarming unless it progressively worsens and is accompanied by swelling. Any adverse events (e.g., haematoma, allergic reaction) should be reported to the haematology clinic or emergency department

D. Patients on Anti-Coagulation and Anti-Platelet Agents

i. Warfarin

- Patients on warfarin can receive intramuscular vaccination if their most recent international normalized ratio (INR) is below 4, without stopping the drug.
- On the day of vaccination, warfarin should be taken after the vaccine injection. The risk of haematoma formation is reduced by applying firm pressure at the injection site for at least 5 minutes.
- Patients on concomitant warfarin and anti-platelet therapy should be managed on an individual basis in consultation with their primary physician.

ii. Direct Oral Anticoagulants (DOAC) and Low Molecular Weight Heparins (LMWH)

- Patients on maintenance therapy with DOAC, LMWH or fondaparinux can delay the dose on the day of vaccination until after the intramuscular injection but do not need to miss any doses.

iii. Anti-platelet agents

- Patients on single agent anti-platelet therapy (e.g. aspirin or clopidogrel) can continue on these medications without any adjustment.

- Patients on dual antiplatelet agents should be managed on an individual basis and in consultation with their primary physician.

E. Patients with Haemoglobinopathies, Enzymopathies and Rare Inherited Anaemias

i. This includes all adults with transfusion-dependent thalassaemia, G6PD (Glucose-6- phosphate dehydrogenase) deficiency and rare inherited anaemias. These patients can receive COVID-19 vaccination.

ii. In patients with splenectomy or functional asplenia, all routine vaccines are likely to be effective and therefore these patients should receive COVID-19 vaccination.

F. Patient with Autoimmune haematological Conditions on Immunosuppression

i. There are no clinical trials of COVID-19 vaccine which enrolled immunocompromised patients. Thus, the efficacy and safety of a COVID-19 vaccine have not been established in the different categories of immunocompromised patients.

ii. The following categories of immunocompromised patients may have attenuated or absent responses to COVID-19 vaccines:

- Primary and secondary immunodeficiencies involving adaptive immunity
- B-cell depleting agents [e.g. anti-CD20 monoclonal antibody like Rituximab]
- T-cell depleting agents [e.g. calcineurin inhibitors, anti-thymocyte globulin]
- Daily corticosteroid therapy with a dose ≥20 mg (or >2 mg/kg/day for patients who weigh <10 kg) of prednisone or equivalent for ≥14 days

iii. The risks and benefits of immunocompromised patients receiving the vaccine should be weighed on a case-by-case basis. If plans to proceed with the vaccination are made, we recommend completing the full course of vaccination at least 2 weeks before the initiation of the planned immunosuppressive therapy or splenectomy. If the patient is receiving or has received immunosuppressive therapy, consider vaccination 6 months after the patient has been taken off immunosuppressive therapy to increase the likelihood of mounting an effective immune response.

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IF YOU HAVE ANY QUESTIONS OR QUERIES, PLEASE CONTACT YOUR HAEMATOLOGIST

Appendix 7

MALAYSIAN CONSENSUS ON COVID-19 VACCINATION FOR PATIENTS WITH RHEUMATIC AND MUSCULOSKELETAL DISEASES (RMD) AND AUTOIMMUNE AND INFLAMMATORY RHEUMATIC DISEASES (AIIRD)

Version 1, 3rd March 2021

GENRAL GUIDANCE

1. There should be a shared decision between the clinician and patient regarding COVID-19 vaccination.

2. Patients with AIIRD should be prioritised to receive COVID-19 vaccination. This is because they are at higher risk of severe COVID-19 infection with a worse outcome compared to the general population.

3. The expected response to COVID-19 vaccination for patients on immunomodulatory treatment is likely to be blunted in its magnitude and duration compared to the general population.

4. A theoretical risk for flare or disease worsening exists following vaccination. However, the benefit of COVID-19 vaccination outweighs the potential risk of new onset autoimmunity.

DISCLAIMER

This consensus was adapted from various international guidelines including the American College of Rheumatology (ACR) COVID-19 Vaccine clinical guidance summary, European Alliance of Associations for Rheumatology (EULAR) view points on SARS-COV-2 vaccination in patients with RMDs and Arthritis and Musculoskeletal Alliance Principles for COVID-19 vaccination in musculoskeletal and rheumatology for clinicians.

RECOMMENDATIONS:

1. RMD and AIIRD patients age 18 years and above should receive vaccination if there are no contraindications.

2. There is no preference for one vaccine over another.*

3. Vaccination should preferably be given when disease is under control.

4. Vaccination should preferably be given before planned immunosuppression if feasible.

5. For patients who are already on immunosuppression, appropriate timing of vaccination may need to be considered. For guidance on timing of vaccination and immunomodulatory therapy, refer to Table 1.

   * *unless there is contraindication for a particular vaccine; Of note certolizumab pegol contains polyethylene glycol (PEG) so patients who have had an allergic reaction to certolizumab pegol should not receive the Pfizer/BioNTech vaccine (as it contains PEG) or any other vaccine that uses PEG as an excipient*.

Table 1: Guidance regarding use and timing of COVID-19 vaccination and immunomodulatory therapies

Medication	Action
DMARDs	
Methotrexate	Hold for 1 week after each vaccine dose*; no modifications to vaccination timing
Leflunomide, Sulphasalazine, Hydroxychloroquine	No modifications to either immunomodulatory therapy or vaccination timing
tsDMARDs	
Tofacitinib, Baricitinib, Upadacitinib	Hold for 1 week after each vaccine dose*; no modification to vaccination timing
bDMARDs	
Infliximab, Etanercept, Adalimumab, Golimumab, Tocilizumab, Secukinumab, Ixekizumab, Ustekinumab Guselkumab	No modifications to either immunomodulatory therapy or vaccination timing
IV Belimumab IV Immunoglobulin SC Denosumab	No modifications to either immunomodulatory therapy or vaccination timing
Immunosuppressives (oral)	
Azathioprine, Mycophenolate, Cyclosporin, cyclophosphamide	No modifications to either immunomodulatory therapy or vaccination timing
Corticosteroids**	No modifications to either immunomodulatory therapy or vaccination timing
IV Cyclophosphamide	Schedule infusion 1 week after each vaccine dose, when feasible
IV Rituximab	vaccinate 4 weeks prior to next scheduled infusion; delay next infusion 2-4 weeks after 2nd vaccine dose if disease activity allows
DMARDs = disease modifying anti-rheumatic drugs; tsDMARDs = targeted synthetic DMARDs; bDMARDs = biologic DMARDs; IV = intravenous; SC = subcutaneous	

**provided disease is well controlled enough to allow for a temporary interruption; otherwise to consider on a case-by-case basis considering circumstances involved*

*** prednisolone-equivalent dose ≥20mg/day, to consider on a case-by-case basis considering circumstances involved*

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Appendix 8

TIMING CONSIDERATIONS FOR MEDICATIONS RELATED TO NEUROLOGICAL DISORDERS

Medications for Multiple sclerosis, Neuromyelitis Optica and spectrum disorders	**Timing Considerations for Immunomodulatory Therapy and Vaccination**
High dose steroid	Consider starting the vaccine at least 3 to 5 days after the last dose of steroid
Beta inferferons	Should not delay timing of initiation of interferons. No medication adjustment required
Glatiramer acetate	Should not delay timing of initiation of interferons. No medication adjustment required
Teriflunomide, dimethyl-fumarate and natalizumab:	Should not delay timing of initiation of interferons. No medication adjustment required
Sphingosine 1 phosphate receptor modulators (Fingolimod, siponimod, ponesimod or ozanimod):	Consider getting fully vaccinated 2 to 4 weeks prior to starting medication. If already on the medication, continue taking as prescribed, no adjustment in medications required
Alemtuzumab	Consider getting fully vaccinated 4 weeks or more before starting medication or 24 weeks or more after the last dose of alemtuzumab
Rituximab/Ocreluzimab	Consider getting fully vaccinated 4 weeks prior to starting infusion or 12 weeks or more after the last dose. Restart 4 weeks or more after the last dose of vaccine
Ofatumumab	Consider getting vaccinated 2 to 4 weeks before starting treatment. If already on treatment, to restart 2 to 4 weeks after the last dose of vaccine
Oral Cladiribine	Consider getting vaccinated 2 to 4 weeks before starting treatment. If already on treatment, to restart 2 to 4 weeks after the last dose of vaccine
C5 inhibitors (e.g. eculizumab, ravulizumab)	No adjustment needed. It is unlikely to diminish a response to any of the COVID-19 vaccines regardless of when administered
For IL-6 receptor inhibition (e.g., satralizumab, tocilizumab)	Vaccination best be scheduled on the third week in a once-per month treatment schedule (or 7 days prior to the next drug dose) but with no pause in therapy

For B cell depleters (e.g. inebilizumab):	Best to vaccinate prior starting therapy, or at a pause in dosing toward the end of a 6 month cycle of therapy and wait 7-14 days after vaccination for next treatment dose.
Immunomodulatory therapy: • Oral: azathioprine, mycophenolate, cyclosporin, cyclophosphamide, prednisolone-equivalent dose <20mg/day, methotrexate • Intravenous cyclophosphamide • Intravenous immunoglobulin	Refer to ***Appendix 7: Malaysian Consensus on COVID-19 Vaccination For Patients With Rheumatic And Mucoskeletal Diseases (RMD) And Autoimmune And Inflammatory Rheumatic Diseases (AIIRD)***

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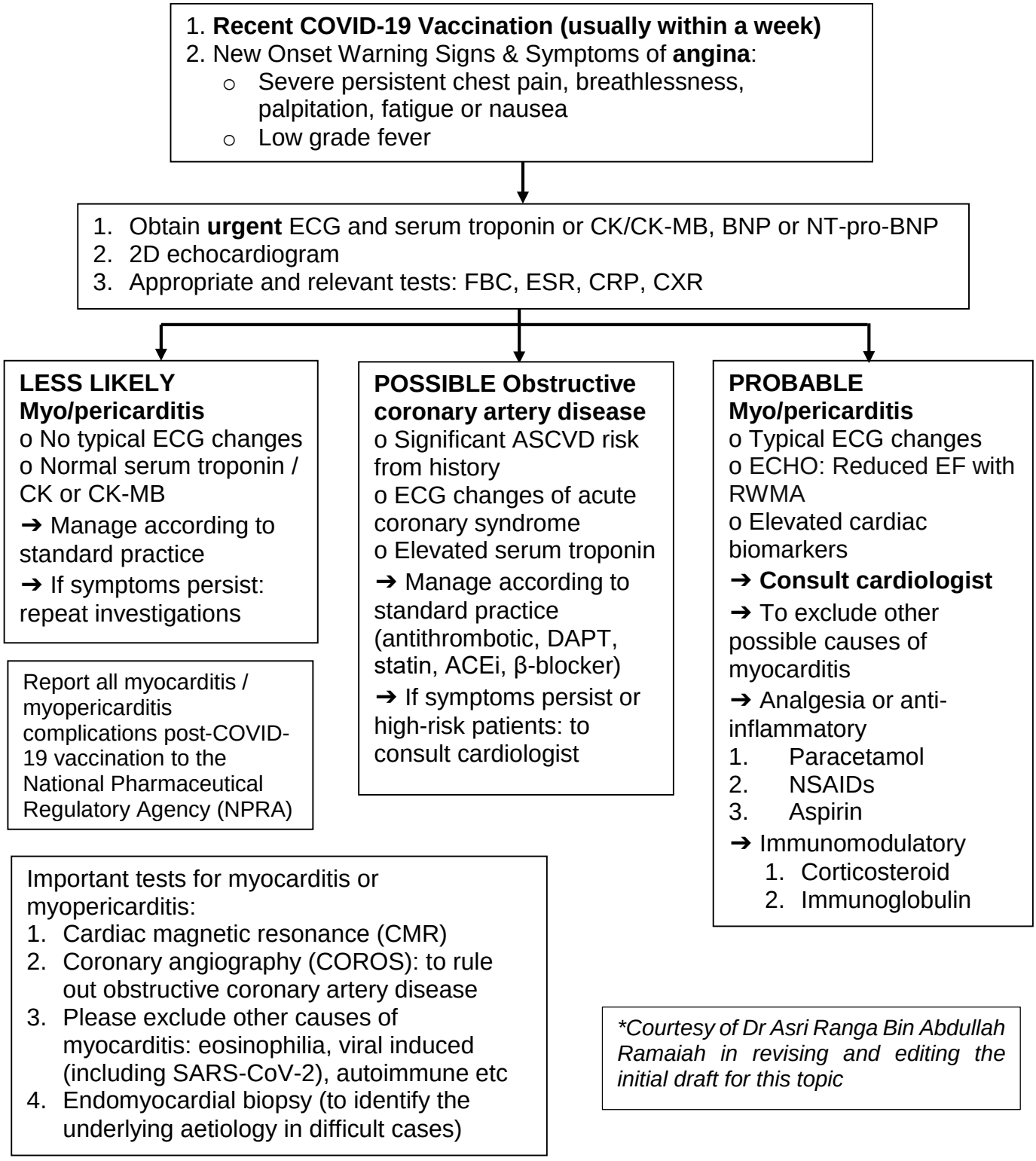
Appendix 9

DIAGNOSIS AND MANAGEMENT ALGORITHM FOR VACCINE-INCUDED MYOCARDITIS / MYOPERICARDITIS

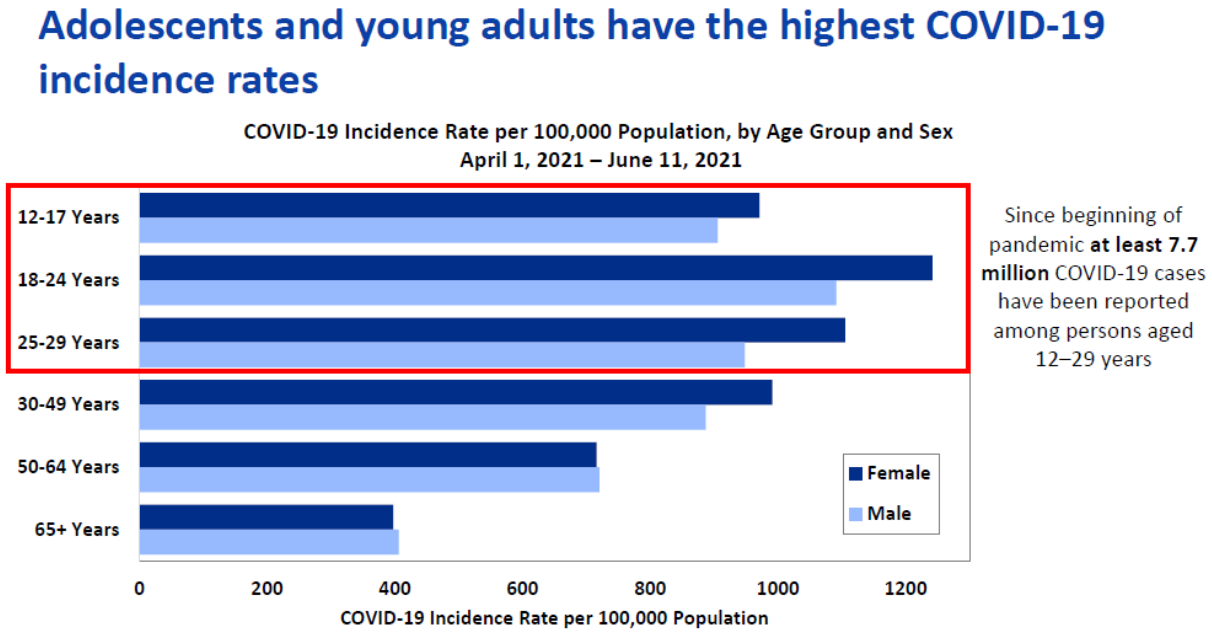


**Courtesy of Dr Asri Ranga Bin Abdullah Ramaiah in revising and editing the initial draft for this topic*

ECG: electrocardiogram, BNP: Brain natriuretic peptide, NT-pro-BNP: N-terminal pro-brain natriuretic peptide, ASCVD: atherosclerotic disease, DAPT: double antiplatelet therapy, ACEi: angiotension converting enzyme inhibitor, NSAIDs: non-steroidal anti-inflammatory drugs, ANA: antinuclear antibody, COROS: Coronary Study, EF: Ejection fraction, RWMA: Regional wall motion abnormalities

Appendix 9

INCIDENCE RATES FOR MYOCARDITIS



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Appendix 10

DIAGNOSIS AND MANAGEMENT ALGORITHM FOR VACCINE-INCUDED SYSTEMIC CAPILLARY LEAKING SYNDROME (SCLS)

1. **Recent COVID-19 Vaccination (within 4 days)**
2. New Onset of **HYPOTENSION** and **PERIPHERAL OEDEMA**
   o Includes syncope / presyncope, tachycardia, breathlessness,

↓

1. Obtain **urgent** FBC, LFT
2. Appropriate and relevant tests include: renal function test, blood culture, CXR, serum lactate and creatinine kinase, ECG, blood gases

↓

LESS LIKELY SCLS

o No evidence of plasma leakage with anasarca.
o No hemoconcentration and polycythemia in FBC.
➔ Manage according to standard practice
➔ If symptoms persist, to look hard for other causes of shock.

Report all systemic capillary leaking syndrome (together with suspected SCLS) and its complications post-COVID-19 vaccination to the National Pharmaceutical Regulatory Agency (NPRA)

POSSIBLE severe sepsis or septicaemic shock

o Features of systemic inflammatory response syndrome (SIRS)
o Absent of polycythemia and haemoconcentration.
o Evident source of infection
➔ Manage according to standard practice (appropriate fluid resuscitation, empirical antimicrobial, ± inotropic support)
➔ Critically ill patients: to consult physician or intensivist

POSSIBLE AND PROBABLE SCLS

o Presence of the following:

- Hypotension (SBP < 90 mmHg)
- Haemoconcentration (Hct > 60% usually)
- Hypoalbuminaemia (< 30 g/L usually)

o Acute / subacute onset of anasarca.
o History of unexplained hypotension and oedema in the past
➔ Appropriate and adequate fluid resuscitation: Balanced crystalloid and/or colloid ± inotrope
➔ Empirical antimicrobial if sepsis cannot be ruled out, appropriate culture must be obtained prior to this.
➔ Urgent IVIG [0.5 - 1.0 g/kg body weight (BW)/day x 2 days]

Important notes for SCLS:

- Patient with past history of SCLC should not be given AstraZeneca *(ChAdOx1-S®[recombinant])* vaccine
- About 80% of the reported cases are associated with monoclonal gammopathy, please send serum and urine paraprotein assays
- Other possible therapeutic options include steroid, β-agonist and theophylline.

FBC: full blood count, LFT: liver function test, ECG: electrocardiogram, CXR: chest X-ray, Hct: haematocrit, IVIG: intravenous immunoglobulin

DIAGNOSIS AND MANAGEMENT ALGORITHM FOR VACCINE-INDUCED IMMUNE THROMBOTIC THROMBOCYTOPAENIA

1. **Recent COVID-19 Vaccination (4 - 30 days)**
2. **New Onset Warning Signs & Symptoms of Thrombosis:**
   - Severe persistent headache / visual change / seizures
   - Severe persistent abdominal pain
   - Limb pain / swelling / coldness
   - Chest pain / shortness of breath

↓

1. Obtain **urgent** FBC, PT / APTT, fibrinogen and D-Dimer and **baseline** Renal function
2. Appropriate symptom-based **imaging**

↓

LESS LIKELY VITT

- Platelet > 150 x 10^9/L
- D-Dimer < 2000 mcg/L or < 4x upper limit of normal (ULN) range
- Normal fibrinogen
- ± Thrombosis on imaging

➔ Thrombosis: Manage according to standard practice

➔ No thrombosis but if symptoms persist: Repeat investigations

Report all thrombotic complications post-COVID-19 vaccination including possible VITT to the National Pharmaceutical Regulatory Agency (NPRA)

POSSIBLE VITT

- Platelet < 150 x 10^9/L
- D-Dimer > 2000 mcg/L or > 4x ULN range
- Low / normal fibrinogen
- No thrombosis on imaging

➔ Consider non-heparin prophylactic anticoagulation [Fondaparinux / Direct Oral Anticoagulant (DOAC)] and / or Intravenous Immunoglobulin (IVIG)

➔ Send sample for confirmatory test*; if positive → **Treat as VITT**

PROBABLE VITT

- Platelet < 150 x 10^9/L
- D-Dimer > 2000 mcg/L or > 4x ULN range
- Low / normal fibrinogen
- Thrombosis on imaging

➔ Send sample for confirmatory test* **and Treat as VITT:**

➔ **Non-heparin** therapeutic anticoagulation (Fondaparinux / DOAC)

➔ **Urgent** IVIG [0.5 - 1.0 g/kg body weight (BW)/day x 2 days]

➔ **Avoid** platelet transfusion

➔ Steroids (e.g. prednisolone 0.5 - 1.0 mg/kg BW) if platelets < 50 x 10^9/L

➔ Consider plasma exchange if platelets < 30 x 10^9/L (despite IVIG or steroids) or fibrinogen level < 1.0 g/L

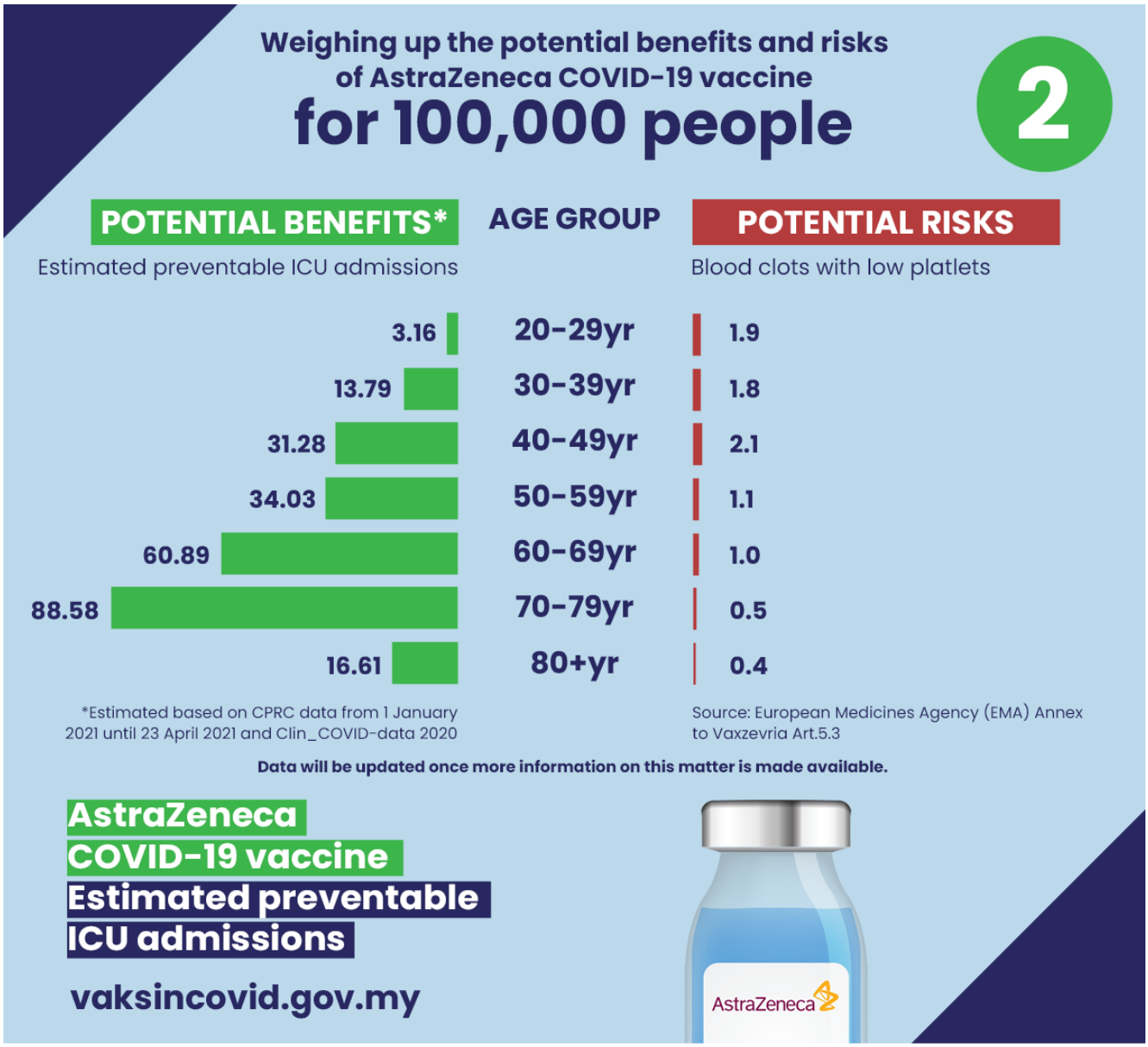
➔ Consult haematologist

***Confirmatory Test: PF4 ELISA Assay**

- Currently offered at Makmal Rujukan Klinikal Hematologi (MRKH), Hospital Ampang
- Send blood sample in 2 plain tubes and 1 EDTA (fresh sample within 4 hours is preferred; if unable to send fresh sample, need to spin-freeze and send frozen sample)
- **Before** sending blood samples / for further information, please contact 03-42896461 or 016-3915825 (after-hours)

Appendix 12

POTENTIAL BENEFITS AND RISKS OF ASTRAZENECA COVID-19 VACCINE



Source: Jawatankuasa Khas Jaminan Akses Bekalan Vaksin COVID-19 (JKJAV)