Obstetrical and Gynaecological Society of Malaysia

Malaysian MATERNAL IMMUNISATION Consensus Guidelines

Obstetrical & Gynaecological Society of Malaysia | 2024

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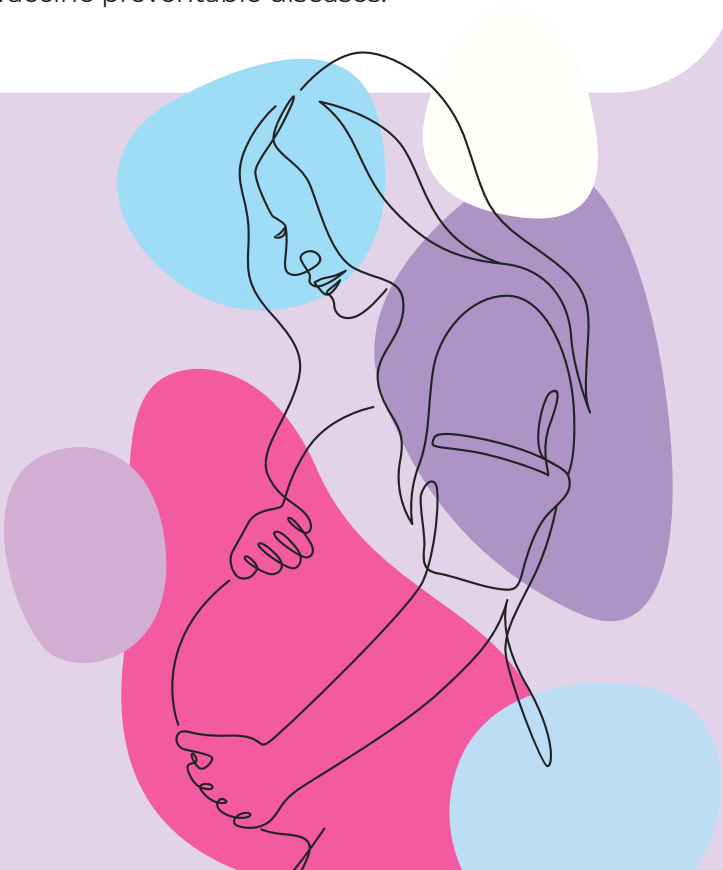
STATEMENT OF INTENT

This guideline aims to offer healthcare providers comprehensive and up-to-date information on maternal immunisation within the local context.

It is formulated based on sound scientific evidence accessible during its development and publication. It's important to note that adhering to these guidelines does not guarantee optimal outcome in all cases.

Therefore, healthcare providers are encouraged to stay updated consistently, in order to make informed decisions and provide the best possible care that will help protect pregnant individuals and their infants from vaccine preventable diseases.



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FOREWORD

Prof Dr Nazimah Idris
President
Obstetrical and Gynaecological
Society of Malaysia

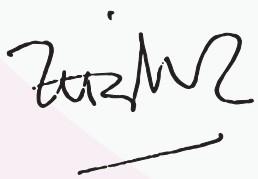
Maternal immunisation is crucial to safeguard the health and well-being of pregnant mothers, their fetuses and newborns from potentially deadly infectious diseases. Pregnant mothers are susceptible to infections because their bodies undergo significant physiological changes that can cause the weakening of the immune system. In some instances, infections during pregnancy can negatively impact fetal development and cause pregnancy complications such as premature birth, low birth weight, miscarriage, and stillbirth. Additionally, newborns and infants below 6 months have immature immune systems and are too young to receive complete vaccination, making them vulnerable to infections and severe complications.

Immunisations such as Tdap, COVID-19, influenza, and RSV provide critical defence against infections that pose severe risks to the mother and fetus during pregnancy and the early months of an infant's life. By vaccinating mothers, we are not only protecting them, but the transfer of maternal antibodies through the placenta will confer passive immunity to the fetuses and newborns. These passively acquired antibodies will help the child fight infections, significantly reducing the risk of severe illness during the crucial first months of life until they are old enough to receive their vaccinations.

Realising the importance of maternal immunisation, the Obstetrical and Gynaecological Society of Malaysia (OGSM) has developed the first Malaysian Maternal Immunisation Guidelines. This long-overdue initiative aims to establish maternal immunisation as a standard of prenatal care. These guidelines provide comprehensive recommendations and strategies to enhance maternal and infant health outcomes, ensuring that mothers and their babies receive the best possible protection from vaccine-preventable diseases.

We hope that these guidelines will serve as a valuable reference for healthcare providers especially those who frequently engage with mothers & mothers-to-be, encouraging them to not only incorporate maternal immunisation into their practices but also in their continuous medical education training programmes. By doing so, we aim to foster an environment where maternal immunisation is universally recognised by clinicians, academicians, healthcare professionals and health policymakers as a vital component of pregnancy care.

I extend my heartfelt gratitude to Professor Jamiyah Hassan, the editorial board and the external reviewers for their dedication to producing these comprehensive and evidence-based guidelines. It is my sincere hope that these guidelines will empower our healthcare providers to promote and advocate for maternal immunisation, ultimately improving the health and well-being of mothers and children across Malaysia.



Prof Dr Nazimah Idris
President
Obstetrical and Gynaecological Society of Malaysia

KEY RECOMMENDATIONS

The following recommendations are highlighted by the Guidelines Development Group (DG) as the key recommendations that answer the main questions addressed in the guidelines and should be prioritised for implementation.

Tetanus, diphtheria and pertussis vaccine (Tdap)

1. Tdap vaccination is recommended during each pregnancy, from 16 weeks to 36 weeks of gestation.

Influenza

1. Pregnant women should receive inactivated influenza vaccine in any trimester of each pregnancy.

COVID-19

1. mRNA-based vaccines are recommended in pregnancy.
2. An additional dose of COVID-19 vaccine should be considered in pregnancy regardless of vaccination status, preferably beyond 12 weeks of gestation.

Respiratory syncytial virus (RSV)

1. Currently, there is a highly efficacious vaccine yet to be available for pregnant women in Malaysia. When available, it is recommended to be given between 32 to 36 weeks of each pregnancy.

Level of Evidence

Definitions of levels of evidence by the Canadian Task Force on Preventive Health Care 2001.

Level	Study Design
I	Evidence from at least one properly randomised controlled trial
II-1	Evidence obtained from well-designed controlled trials without randomisation
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or group
II-3	Evidence from multiple time series with or without intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
III	Opinions of respected authorities based on clinical experience; descriptive studies and case reports; or reports of expert committees

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE

GUIDELINES DEVELOPMENT AND OBJECTIVES

GUIDELINES DEVELOPMENT

The Development Group (DG) for this guideline consisted of obstetricians, gynaecologists, and academicians, both from the public and private sector. These professionals are actively involved in the field of maternal immunisation in Malaysia.

Twenty meetings were conducted with the Editorial Board members to discuss and develop the guidelines.

The development journey commenced with a comprehensive needs assessment to identify gaps and challenges in existing maternal immunisation practices. This involved a thorough review of current literature, examination of national and international guidelines, and an assessment of the needs within our healthcare setting.

This guideline was developed through a rigorous review of the latest scientific evidence, drawing insights from clinical trials, epidemiological studies, and global research on maternal immunisation.

The formulation of the guidelines involved synthesising the gathered insights into clear and actionable recommendations. The team structured the guidelines to address critical aspects including vaccine safety, efficacy, scheduling, and communication strategies to improve vaccine uptake. Practicality and relevance to our local healthcare setting were paramount considerations.

A draft version of the guideline underwent comprehensive internal review by the development team, followed by a rigorous feedback process by the external reviewers. The external reviewers provided valuable insights, which were carefully considered and incorporated to enhance the guidelines.

The guideline was refined and revised following the feedback from the external reviewers. The final document represents a consolidated and well-balanced set of recommendations for our maternal immunisation.

OBJECTIVES

This guideline aims to:

- assist healthcare providers across all levels of the healthcare system to integrate maternal immunisation with maternal and child health services.

- mitigate the risk of vaccine-preventable diseases in expectant mothers and their infants, by providing evidence-based recommendations for immunisations.
- offer comprehensive and clear guidelines as well as equip healthcare professionals involved in maternal care with the knowledge and skills needed to confidently administer vaccines and counsel expectant mothers.
- standardise maternal immunisation practices to ensure consistency and efficacy in maternal care.

TARGET POPULATION

- Women actively planning or considering pregnancy
- Pregnant women
- Postpartum women

TARGET GROUP / USERS

This guideline will serve as a reference on maternal immunisation to those who are involved in the field of maternal and child health at any healthcare level including:

- Doctors
- Allied health professionals
- Trainees and medical students
- Professional medical bodies
- Pharmacists
- Policy makers
- Patients and their caregivers/advocates

HEALTHCARE SETTINGS

Primary, secondary, and tertiary care settings

APPLICABILITY OF GUIDELINES AND RESOURCE IMPLICATIONS

Maternal immunisation can contribute significantly to the reduction of maternal and neonatal morbidity and mortality associated with vaccine-preventable diseases. Therefore, the Maternal Immunisation Guidelines has been developed to provide evidence-based recommendations for the immunisation of women who are planning to get pregnant, pregnant women, and postpartum women within our healthcare setting.

This guideline is applicable to all healthcare professionals involved in maternal care, including but not limited to obstetricians, gynaecologists, medical officers, midwives, and nurses.

This guideline provides comprehensive recommendations for maternal immunisation to ensure the well-being of both mothers and their infants. All healthcare providers and practitioners involved in maternal care are encouraged to familiarise themselves with this guideline to deliver optimal care. The recommendations within this document are to be applied within our healthcare facility and align with current national and international standards.

Implementing the recommendations in this guideline may require an initial investment of time and resources. However, the long-term benefits in terms of improved maternal and child health are invaluable. Adequate training, educational materials, and communication strategies will be essential to successfully integrate these recommendations into our existing healthcare practices.

IMPLEMENTATION OF THIS GUIDELINE

- Healthcare professionals involved in maternal care should familiarise themselves with the recommendations in this Maternal Immunisation Guidelines. Training programmes are encouraged to ensure a thorough understanding of the guidelines, vaccination protocols, and updated immunisation information.
- Patient education is an important component for the successful implementation of the maternal immunisation programme. Educational materials can be downloaded from the OGSM website to aid discussions with patients, ensuring effective communication about maternal immunisation and addressing their concerns.
- The guidelines can be integrated into the protocols of maternal and child healthcare within our healthcare setting.
- A digital and hard copy of the Maternal Immunisation Guidelines will be distributed to relevant healthcare professionals in the country. Updates and revisions will be conducted whenever required.

ABBREVIATIONS

Abbreviation	Description
ACE2	angiotensin-converting enzyme 2
ACOG	American College of Obstetricians and Gynecologists
ADHD	attention deficit hyperactive disorder
AEFI	adverse events following immunisation
AOR	Adjusted Odds Ratio
aP	acellular pertussis
ASD	autism spectrum disorder
ATAGI	Australian Technical Advisory Group on Immunization
ATT	anti-tetanus toxoid
CANVAS	Canadian National Vaccine Safety
CDC	Centers for Disease Control and Prevention
CFR	case fatality rate
CPRD	Clinical Practice Research Datalink
CPSs	Capsular polysaccharides
dNK	decidua Natural Killer cells
DTP3	diphtheria-tetanus-pertussis
DMARDs	disease-modifying anti-rheumatic drugs
EVT	Extravillous trophoblast
Fab	antigen-antibody region
Fc	constant region
FDA	Food and Drug Administration
FHA	filamentous hemagglutinin
FIM	fimbriae
FVS	fetal varicella syndrome
GBS	Group B Streptococcus
GMCs	geometric mean concentrations
HIV	human immunodeficiency virus
HLA-C	Human Leukocyte Antigen-C
HLA-E	Human Leukocyte Antigen-E
HLA-G	Human Leukocyte Antigen-G

Abbreviation	Description
HPV	Human papillomavirus
HR	hazard ratio
ICP	immunocompromised persons
IDO	Indoleamine-2,3-dioxygenase
Ig	immunoglobulins
IgG	immunoglobulins G
ILF	leukemia inhibitory factor
JE	Japanese encephalitis
LMIC	low- and middle-income countries
M1	Macrophages 1
M2	Macrophages 2
MADRAC	Malaysian Adverse Drug Reaction Advisory Committee
MMR	Measles, mumps, rubella
MNTE	maternal and neonatal tetanus elimination
MOH	Ministry of Health
MSIDC	Malaysian Society of Infectious Diseases and Chemotherapy
NPRA	National Pharmaceutical Regulatory Agency
pIgR	polymeric Ig receptor
PIPS	Pertussis Immunisation in Pregnancy Safety
PRN	pertactin
PT	pertussis toxin
PWID	People who inject drugs
PWUD	People who use drugs
RSV	Respiratory Syncytial Virus
RSVpreF	RSV prefusion F
SC	secretory component
SIgA	Secretory IgA
STI	sexually-transmitted infections
TBE	Tick-borne encephalitis
Td	Tetanus-diphtheria

Abbreviation	Description
TH1	T Helper cells 1
TH2	T Helper cells 2
TH17	T Helper cells 17
Tdap	Tetanus, diptheria and pertussis
Teff	T effector
T reg	T regulatory cells
TT	Tetanus toxoid
USA	United States of America
UK	United Kingdom
VAERS	Vaccine Adverse Event Reporting System
VITT	Vaccine-induced thrombosis and thrombocytopenia
VOC	variants of concern
VPCI	Vaccine Policy Collaborative Initiative
VSD	Vaccine Safety Datalink
WHO	World Health Organization
wP	whole-cell pertussis vaccine

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VACCINE QUICK GUIDE

Stages / Vaccines	Pre-conception*	During pregnancy
Recommended		
COVID-19	✓	Any trimester (preferably second trimester)
Inactivated Influenza		Any trimester (every pregnancy)
Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap)		16 – 36 weeks (every pregnancy)
Respiratory Syncytial Virus (when available)		32 – 36 weeks
Additional Vaccine to Consider		
Pneumococcal		
Meningococcal conjugate (MenACWY) **Meningococcal serogroup B (Men B)**		
Hepatitis A		
Hepatitis B	✓	
Measles-mumps-rubella (MMR)	✓	
Varicella	✓	
Rabies		
Human Papillomavirus (HPV)		
Polio (non-live/inactivated)		
Typhoid (non-live/ inactivated)		

May be given during pregnancy in certain circumstances	Contraindicated in pregnancy	May be given after Delivery
		✓#
		✓#
		✓#
		✓#
✓		✓
✓		✓
✓		✓
✓		✓
	✓	✓^
	✓	✓^
✓		✓
		✓
✓		✓
✓		✓

* Pre-conception vaccination: live vaccine should be completed by 4 weeks prior conception.
# Recommended after delivery if not received during pregnancy.
^ Recommended if no evidence of immunity during pregnancy

SECTION 1

BACKGROUND

1.1 Introduction to Maternal Immunisation

Maternal immunisation describes vaccinating women before, during, or after pregnancy. Pregnant women are more susceptible to infections. For these women, infections like influenza could result in more severe outcomes than for non-pregnant women.[1] Increasing susceptibility to infectious diseases in pregnancy is due to the immunological changes that women undergo during pregnancy, and understanding these changes will give more insight into the impact of vaccines on pregnant women. Maternal immunisation confers benefits to both mother and fetus and the potential to reduce morbidity and mortality in the newborn during their most vulnerable period.

The immune system of a pregnant mother is adapted to a hypo-immune state to allow for the survival of the semi-allogenic fetus, and this will increase the susceptibility of pregnant women to infectious diseases like influenza and pertussis.[2] Antibodies produced by maternal immunisation will protect pregnant women and newborns from vaccine-preventable infectious diseases. Despite pregnancy being a slightly hypo-immune state, studies have shown that a pregnant immunogenic response to the vaccines is not inferior to non-pregnant women, as demonstrated in the Tdap vaccination study.[3] Vaccine-specific antibodies are transferred transplacentally with increasing efficiency as the trimester progresses,[4] and the immunoglobulin G (IgG) subclass produced by vaccines containing protein antigens is transferred with the highest efficiency.[5] Vaccine specific antibodies are also transferred via breastmilk to protect newborns.[6] Addressing the safety profile and efficacy of the vaccine

will provide confidence for pregnant mothers to accept maternal immunisation.

The world faced three major influenza outbreaks in the 20th century: in 1918, 1957, and 1958.[7] The "Spanish flu, which occurred in 1918–1919, resulted in an estimated 50 million deaths worldwide and served as a warning of the impact of infectious disease on global health.[8] Influenza is a significant public health threat, and global preparedness for developing the influenza vaccine has become an important public health preventive strategy. The H1N1 outbreak in 2009 and the COVID-19 pandemic in 2020 strengthened the need for a global public health preventive strategy, especially for at-risk populations, including pregnant mothers. The pandemic H1N1 influenza infection has reported severe adverse events when the disease is contracted during pregnancy, including hospitalisation and ICU care, and increasing the risk of preterm births and stillbirths.[9] The landmark study by Zaman et al. has demonstrated that infants born to mothers vaccinated with influenza vaccine were 63% less likely to have laboratory-confirmed influenza in the first six months of life.[10]

In 1989, the World Health Assembly called for the elimination of neonatal tetanus, and the World Health Organization (WHO) reported, in 1996, that an estimated 787,000 deaths from tetanus were prevented in 1995 with tetanus vaccination.[11] Tetanus continues to be a significant problem, especially in developing countries, and in 1999, WHO, in collaboration with UNICEF and UNFPA, renamed the tetanus elimination programme as the maternal and neonatal tetanus elimination (MNTE) programme to achieve the goal of elimination by 2005.[12] The MNTE programme has led to a 94% reduction in neonatal tetanus deaths globally from 200,000 to an estimated 49,000 in 2013.[13]

Centers for Disease Control and Prevention (CDC) has also recommended influenza and Tdap vaccinations for pregnant women.[14] Infants under six months of age are more vulnerable

to infections from influenza and pertussis before they complete the primary vaccination. Immunisation of pregnant mothers is an important strategy in protecting the infants below six months of age against vaccine-preventable diseases through maternal transplacental transfer of vaccine-specific antibodies.

These Malaysian Maternal Immunisation Guidelines will address the current research available on the most important vaccine preventable infectious diseases that can affect pregnant mother, including tetanus, influenza, pertussis, diphtheria, COVID-19, and respiratory syncytial virus. Vaccines that are on the horizon, including Group B Streptococcus, Zika, CMV and Malaria, will be reviewed. We hope these guidelines will be useful to all healthcare providers in the country.

1.2 Rationale of Immunisation Pre-Conception and After Delivery

Maternal Immunisation Pre-conception

The physiological changes during pregnancy result in relative immune suppression, which will increase the risk of acquiring infectious diseases in pregnant mothers.[15(Level II-2)] Acquiring infection in pregnancy can lead to increased maternal morbidity and may lead to congenital malformation.[16(Level III)] Hence, every woman should update her immunisation status prior to conception. In Malaysia, the recommended vaccines for women who are in the reproductive age range follows the Malaysian Immunisation Guidelines for adults.[17(Level III)] The opportunity to discuss pre-conception immunisation can be taken when the women seek medical advice in the pre-pregnancy clinic or opportunistically during a visit to health facilities.

The status of vaccination can be evaluated through immunisation history, health records and serum antibodies. The recommended

live vaccines should be completed 4 weeks or 28 days prior to conception.[18(Level III), 19(Level II-2)] The inadvertent administration of a live vaccine during the pre-conception period or early stages of pregnancy does not warrant termination of the pregnancy.[20(Level III)] Instead, it is important to offer reassurance to the individual on the theoretical risk to the fetus.[19(Level II-2)]

Every woman should have immunity status checked against measles, mumps, rubella, varicella and hepatitis B during pre-conception period.[21(Level III), 22(Level III)] There are additional vaccines to be considered during pre-conception period depending on risk factors, public health, epidemiological concerns or individualised special circumstances. These vaccines include hepatitis A, influenza, meningococcus and pneumococcal (Refer to Table 1).[16(Level III), 22(Level III), 23(Level III)]

Immunisation After Delivery

Pregnancy is a window of opportunity to increase awareness of immunisation during and after pregnancy. In situations where vaccination in pregnancy cannot be provided, the "cocooning" strategy can be implemented where the mother and everyone who will be in contact with the newborn can be vaccinated. This provides moderate impact of protection to the newborn.[24(Level III), 25(Level II-2)] Theoretically, breastfeeding will confer additional protection to the newborn through the breastmilk. As live vaccines are contraindicated during pregnancy, women who have missed the opportunity to take the recommended pre-conception vaccines or the recommended vaccines during pregnancy, will have the opportunity to take the vaccines after delivery.[15(Level II-2)] Most live and non-live vaccines are safe for breastfeeding.[26(Level III), 27(Level II-2)] Table 1 provides a summary of the list of recommended vaccines after delivery.

Table 1: Summary of recommended vaccines during pre-conception and after delivery[16(Level III), 22(Level III), 23(Level III)]

PRE-CONCEPTION	AFTER DELIVERY
Recommended: • Measles, Mumps & Rubella (live) • Hepatitis B • Varicella (live) • COVID-19 **Additional Vaccines to consider:** • Influenza • Pneumococcal • Hepatitis A • Meningococcus	**Recommended:** • Measles, Mumps & Rubella (live) • Hepatitis B • Tdap • COVID-19 • Varicella (live) Additional Vaccines to consider: • Influenza • Pneumococcal • Meningococcus • Hepatitis A • Polio (non-live) • Typhoid (non-live) • Rabies • Human papillomavirus (HPV)

1.3 The Immune System

Innate Immune Response

The innate immune response is the first line of defence and gives an immediate response against foreign invasion. It is non-specific and has a wide range of mechanisms involving specific cells, molecules, and multiple pathways that initiate an inflammatory response.[28,29,30,31,32,33]

The Adaptive Immune Response

The adaptive immune response is divided into humoral immune response (B-cell mediated) and cell-mediated immune response (T-cell mediated). It is the second line of defence and involves the production of antibodies (immunoglobulins) from plasma cells and memory cells. It takes several days to weeks to become protective. However, upon re-exposure to the antigens, it will respond rapidly to neutralise the infection or toxins which may give a protective lifelong immunity.[34,35,36] The interaction of the innate and adaptive immune response facilitated by the immune system components results in an efficient immune response.[28,37,38] **(Table 2)**.

The cell-mediated immune response is primarily T-cell mediated. There are several types including T helper cells, cytotoxic T cells, and regulatory T cells. The T helper cells are involved in stimulating B cells to secrete antibodies, the cytotoxic T cells eliminate virus-infected cells, intracellular organisms, and tumour cells, and the regulatory T cells dampen the immune response.[31] There are 2 populations of T helper cells which are TH1 and TH2 cells. The TH1 produces cytokines such as IFN-γ, TNF-β, and IL-2 stimulate cell-mediated responses, whereas the TH2 cells secrete the set of cytokines such as IL-4, IL-5, IL-6, IL-9, IL-10 and IL-13, which are primarily involved in the activation of B cells into antibody-secreting plasma cells.[30,39]

Table 2: Components of the immune system[3,4]

Immune response	Components		Effects
Innate	Skin	Physical barrier.	Prevent entry of microorganisms.
Innate	Enzymes	Tears, saliva, mucous.	Trap and lyse microorganisms.
Innate and Adaptive	Cells	Ciliated epithelial cells, Phagocytes (Dendritic cells, macrophages, neutrophils, mast cells and basophils), Professional APC (Dendritic, macrophages, B cells), Natural Killer cells (NK cells).	Propels microorganisms outside the body. Phagocytes process and phagocytose the pathogen after being recruited to the infected site. Dendritic cells and macrophages are found in tissue and act as sentinel cells which detect, engulf and digest pathogens to fragments and present them to the adaptive immune response in lymph nodes. NK cells are lymphocytes that kill virus/tumour infected cells by releasing granzymes/ perforins to immediately kill the virus infected cells. APC present antigens to TCR of T cells.
Innate and Adaptive	Effector cells	B cells, cytotoxic cells, T helper cells.	Carry out specific activity in response to stimulation such as NK cells, plasma cells, cytotoxic T cells, T helper cells.

Immune response	Components		Effects
Innate and Adaptive	Molecules	Receptors — PRR, TLR, Acute phase proteins MHC BCR	Molecules expressed on the membrane surface of macrophages, DC, initiating the interaction between self PRR and non-self-cells (pathogen-PAMP). Cause Fever. MHC are molecules that help to discriminate cells that are “self” from “non-self”. BCR are molecules expressed on the B cell surface membrane and present antigens to T cells.
Innate and Adaptive	Chemicals	Cytokines — IL, IFN, TNF	Initiating a cascade of the immune response process i.e. T cell activation, recruitment of other polymorphonuclear (PMN) cells, cell differentiation, proliferation, etc. IL mediate interactions between leukocytes. IFN inhibits viral replication.
	Pathways	Complement, clotting, kinin	Promote opsonisation, stimulate clotting mechanisms and pain

APC: antigen presenting cells, DC: Dendritic cell, PRR: Pathogen Recognition Receptors, TLR: Toll-like receptors, PAMP: pathogen-associated molecular patterns, TCR: T cell receptor, MHC: Major histocompatibility complex, IL: Interleukins, IFN: Interferon, TNF: Tumour necrosis factor.

The immunoglobulins

The immunoglobulins (Ig) or antibodies are used interchangeably. They are produced by plasma cells which originates from B cells. Naive B cells which express IgM and IgD receptors on the membrane surface, after being activated by T cells, will go into class switching leading to specific antibody isotypes i.e. IgA, IgD, IgE, IgG, and IgM. These antibodies have specific functions and contributions to the immune response. Two of the isotypes have subclasses, i.e., IgG1, IgG2, IgG3, IgG4 and IgA1, IgA2.[28,31] B cells also will go through a process called hypersomatic mutations which increase the affinity to specific antigens and increase antibody diversity. The process requires the involvement of immune molecules such as the TCR, APC, costimulatory signals, and protein signalling.[40]

The immunoglobulin (antibody) is made up of two heavy (VH) and two light chains (VL). The heavy chains determine the antibody isotype (Figure 1). The F_{ab} is the site where the antibody binds to the antigen whereas the Fc is the constant region that determines the consequences of the binding on the effector cells.[41] During class switching, the constant region (F_c) is changed but the antigen-antibody region (F_{ab}) remains the same. Therefore, the affinity to the antigen is the same, but they can interact with different effector molecules.[41]

IgG and serum IgA are both monomers composed of two heavy chains and two light chains. The subclass IgA2 is in the form of a dimer joined by J-chains and is called Secretory IgA (SIgA). They are transported to the mucosal surfaces by a secretory component (SC).[42]

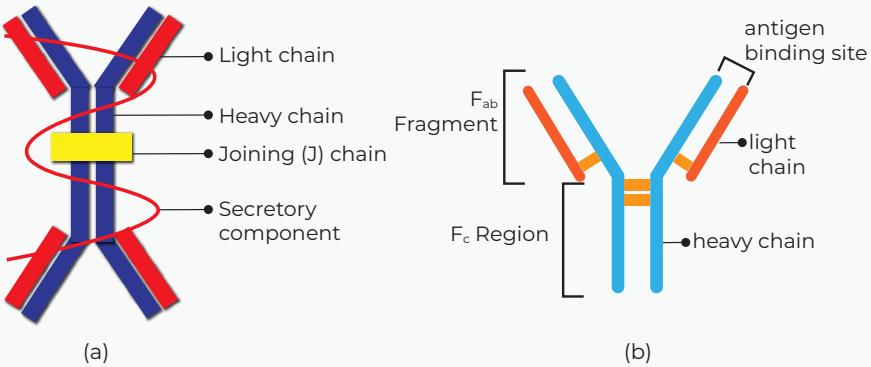


Figure 1
(a) Schematic diagram of the basic structure of immunoglobulin
(b) IgA2 subclass which is a dimeric form.

Antibodies have several properties. Their functions are mainly the destruction and elimination of pathogens through complement fixation, opsonising bacteria, promoting phagocytosis, and facilitating direct killing. **(Table 3)**[31]

Table 3: Classes, properties and functions of antibodies.

Antibody	Properties/ Functions
IgG	• Four subclasses: IgG1, IgG2, IgG3, IgG4 • Distributed equally between blood and extracellular fluid and the only antibody subclass that is transported across placenta. • IgG2 is particularly important in defence against polysaccharides antigens.
IgM	• Highly effective at agglutinating pathogens
IgA	• Two subclasses: IgA1, IgA2. • Highly effective at neutralising toxins. • Particularly important at mucosal surfaces.
IgE	• Majority of IgE is bound to mast cells, basophils and eosinophils. • Important in allergic disease and defence against parasite infection.
IgD	• Function in B-cell development.

Hypersensitivity

Hypersensitivity occurs when there is an inappropriate or exaggerated immune response to an antigen or allergen which results in tissue injury and can cause autoimmune diseases or immunodeficiency.[31,43] Hypersensitivity is grouped into 4 types. Type I, II, and III involve antibodies as effector molecules, and Type IV is T cell-mediated. Type I is the most common type of reaction. Type I and Type III hypersensitivities can be associated with vaccination. A summary of hypersensitivity reactions is shown in Table 4.[39,43,44]

Table 4: Hypersensitivity reactions

	Type I	Type II	Type III	Type IV
Antigen	Allergens such as pollens, active vaccine component.	Cell or matrix associated antigen (patient's own cell)	Soluble antigen	Soluble antigen/ cell-associated antigens
Onset	Immediate	Hours to days	1–3 weeks	Delayed (Days to weeks)
Mediators	IgE-mediated	IgG or IgM	Immune complex-mediated	T-cell mediated
Mechanism	F_c portion of IgE dependent mast cell or basophils activation releasing histamines/ leukotrienes/ prostaglandins causes vasodilation.	F_c portion of IgG/IgM dependent phagocytes or NK or complement results in opsonisation.	Deposit of immune complexes in tissue resulting in activation of complement and inflammation.	Over stimulation of T cells, macrophages/ eosinophils which results in cytokine production and inflammation.

	Type I	Type II	Type III	Type IV
Examples	Anaphylaxis, asthma, allergic rhinitis, angioedema	Haemolytic anaemia	Serum sickness, Arthus reaction	Contact dermatitis, tuberculin reaction

Primary and secondary immune responses

Primary immune response occurs when the antigen is presented to the immune cells for the first time. The secondary immune response is a result of stimulation of the memory cells and results in a higher amount of IgG than IgM **(Figure 2)**. The unstimulated or "naïve" B cells will produce IgM upon activation with antigen, which takes 5–10 days to produce. The other antibody classes (IgG, IgA and IgE) will be produced 1–2 weeks later. Upon re-exposure with the same antigen, the memory B cell will rapidly secrete antibodies dominated IgG antibodies.[40]

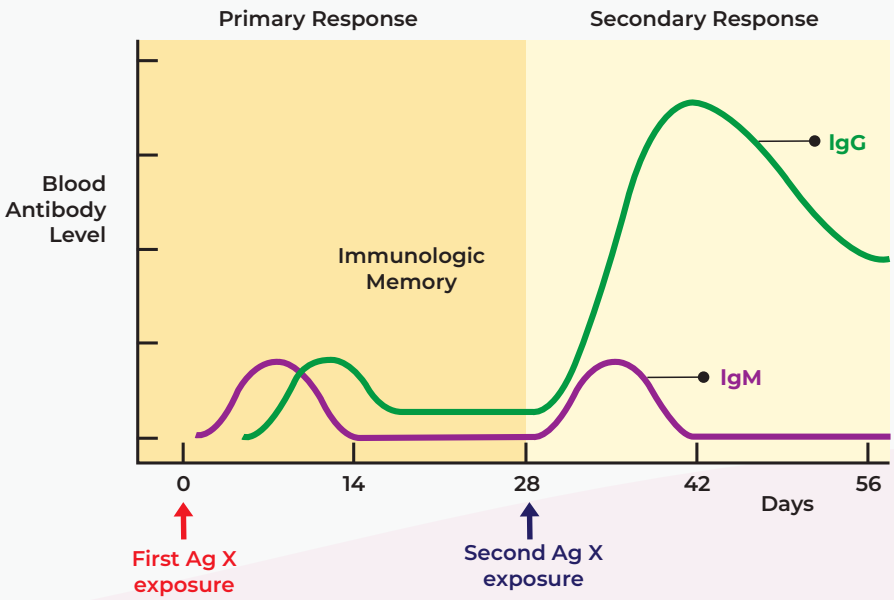


Figure 2: The primary and the secondary immune response.

1.4 Immunological adaptation in pregnancy

Pregnancy is a semi-allogenic state that involves a complex immune adaption (tolerance), evading maternal immune response in which immune activity is effectively diminished thus preventing the fetus from rejection.[39,45]

In normal pregnancy, there is an increase in the number of immune cells. NK cells are abundant in the maternal decidua (75%), followed by macrophages (20–25%) and dendritic cells (1–2%).[39] In the first trimester, implantation by the trophoblastic cells is crucial and has been an integral function of uterine NK cells and the dendritic cells. The NK cells recognise the HLA-G expressed by the trophoblastic cells thus allowing immune privilege and inhibiting the killing activity. The dendritic cells promote decidua formation through the angiogenic response in remodelling spiral arteries and inhibiting vascular maturation. Syncytiotrophoblast tissue also lacks class I and class II MHC antigens, which results in a lack of determinants required for maternal T cell activation.[39]

The maternal immune cells are constantly being modulated, not suppressed. The presence of protein molecules in the trophoblastic cells and their interactions with their ligand on the immune cells such as the Fas/FasL and CTL4 co ligand molecules leads to the modulation and apoptosis of maternal T cells.[39] The production of progesterone, estradiol, prostaglandin D2 (PGD2), and leukemic inhibitory factors in normal pregnancy promotes TH2 type of cytokines environment in early trimester. The cytokines profiles of TH2 such as IL-4 and IL-10 as well as the presence of macrophages and the subpopulation of regular T cells (Tregs) help to maintain immune tolerance towards paternal fetal antigens.[39,45,46,47]

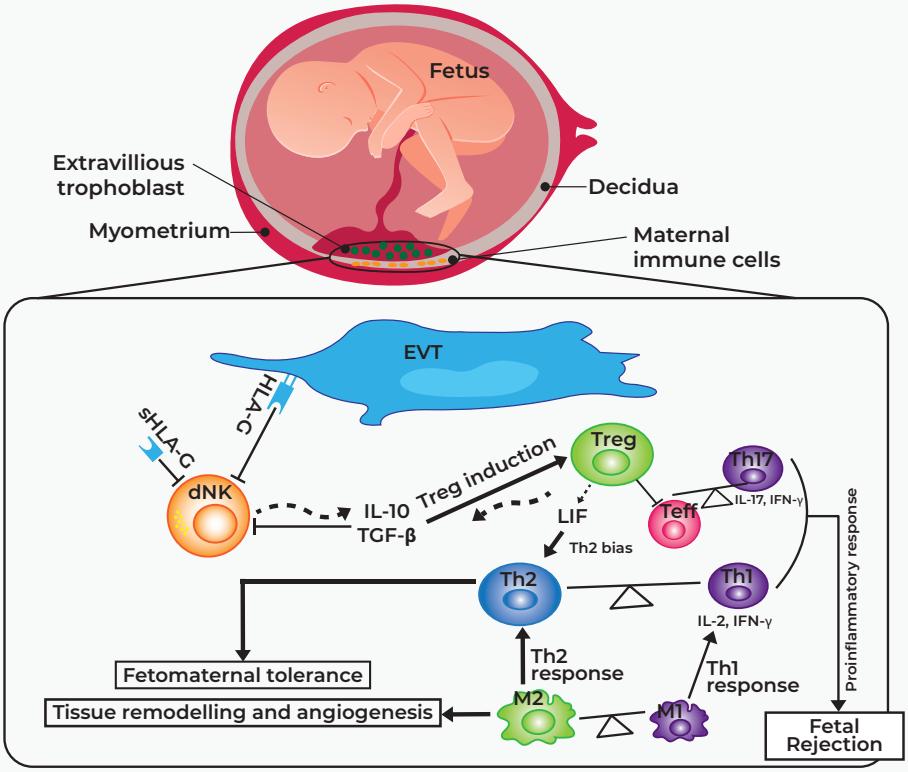


Figure 3: A simplified schematic diagram of immune tolerance in pregnancy.[48]

EVT: Extravillous trophoblast, HLA-C: Human Leukocyte Antigen-C, HLA-E: Human Leukocyte Antigen-E, HLA-G: Human Leukocyte Antigen-G, dNK: decidua Natural Killer cells, IDO: Indoleamine-2,3-dioxygenase, M1: Macrophages 1, M2: Macrophages 2, TH1: T Helper cells 1, TH2: T Helper cells 2, TH17: T Helper cells 17, T reg: T regulatory cells, Teff: T effector, ILF: leukemia inhibitory factor

A normal pregnancy will have three distinct immunological phases. The first phase involves a pro-inflammatory process to support implantation and placentation. A blastocyst will invade the endometrium initiating an inflammatory response, damaging the lining and trophoblast replacement of the maternal blood vessels to secure adequate placental-fetal supply.[39]

The second phase is the anti-inflammatory phase (TH2 environment), to allow the fetus to grow and develop. In the third phase, there will be an influx of immune cells promoting a pro-inflammatory immune state as a preparation for the expulsion of the fetus and rejection of the placenta.[39]

The fetal immune system develops early in the gestation. The hematopoietic cells differentiate into B cells in the liver by 8 weeks of gestation and in the bone marrow by 12 weeks of gestation. IgG and IgA are present by the second to early third trimester (20-30 weeks of gestation). Low levels of IgM can be found at term. However, in response to infection, IgM is increased but limited to certain antigens.

Maternal infection with gram-negative bacteria will stimulate the production of primarily IgM, which cannot cross trans placentally thus increasing the risk of infection in the fetus.[39]

In pregnancy, there is a passive transfer of maternal antibodies of IgG and IgA antibodies across the placenta and into breast milk respectively.[49] This is critical since it protects against infectious disease and immune development for the infant in the first year of life.[6] The level of fetal serum IgG showed a positive correlation with gestational age compared to maternal serum levels which showed a significant negative correlation throughout the pregnancy. (Figure 4).[49]

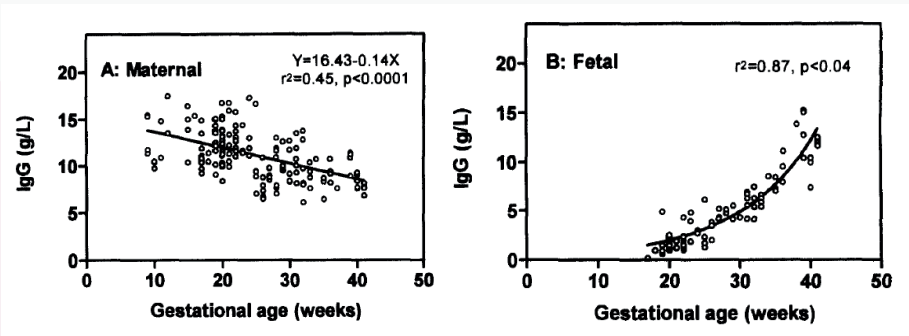


Figure 4: Level of IgG in foetal serum and reduction in maternal serum as the gestation approaches term.[49]

The immunoglobulin IgG transfer occurs through the binding of the maternal IgG antibody Fc fragment to the neonatal Fc receptors (FcRn) on syncytiotrophoblasts(Figure 5).[6] IgG isotype 1, the antibody induced following vaccination with vaccines containing protein antigens is preferred to be transported across the placenta compared to IgG isotype 2 which is induced by vaccines containing polysaccharide antigens.[50]

SIgA is the most predominant antibody in human breast milk.[51] The source of this IgA is from the antibody secreting plasma cells in the interstitial space of the mammary glands which is in a dimeric form.[52] This Fc region of dimeric IgA will bind to the polymeric Ig receptor (pIgR) to form pIgR-IgA complex which will be trancytosed from the basolateral surface of the mammary epithelium cells to the alveolar lumen.[6] Once the complex reaches the lumen, a portion of the pIgR (the secretory component) is cleaved off to release Ig forming SIgA to diffuse in human breast milk.[53](Figure 6)

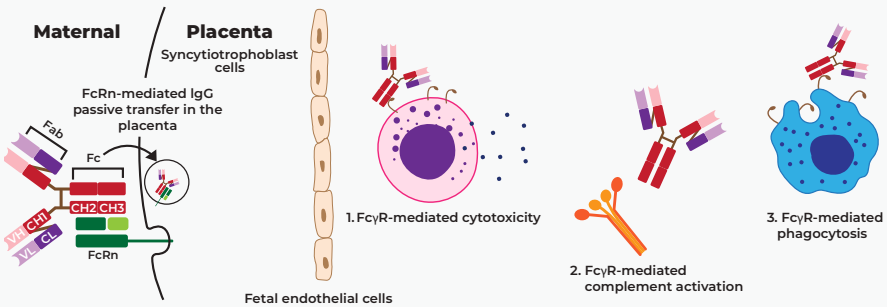


Figure 5: Schematic diagram showing the passive transfer of IgG via the FcRn of the immunoglobulins which binds to the FcRn of the syncytiotrophoblast cells to facilitate immune response in fetus through
1)FcyR-mediated cytotoxicity,
2) FcyR-mediated complement activation,
3) FcyR-mediated phagocytosis.

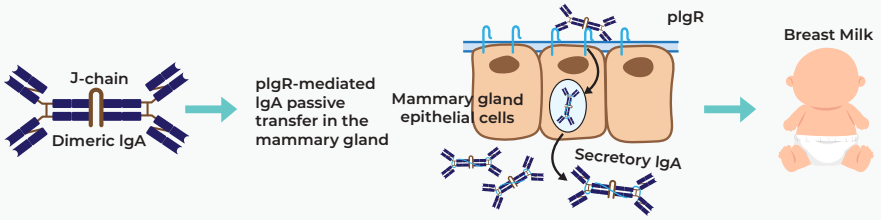


Figure 6 Diagram showing the transfer of Dimeric IgA (SIgA) via the pIgR in the mammary glands which provides protective mucosal surface to the neonates.

Maternal vaccination will provide the maximum amount of antibodies and for some diseases, this is the only option to offer passive protection to neonates immediately after birth.[50]

Maternal antibodies are very effective in protecting neonates and infants. These antibodies will protect against bacterial infection up to 6 months. Maternal antibodies wane over 6–12 months.[54] Maternal antibodies may however interfere with the neonate's humoral immune response thus inhibiting their immune response after vaccination.[55] This so-called "blunting" effect has also been observed following natural infection.[55] The long-term consequences of this phenomenon remain to be determined.[55] A systematic review done by Switzer et al found that vaccine effectiveness was not adversely affected by the relative blunting of the infant's immune response to some of the acellular pertussis-component vaccines.[56] Infants are also found to have high antibody concentrations during the first months of life, which again correlate with protection against pertussis.[57]

- Passive maternal transfer of antibodies to the fetus can occur only through IgG (transplacental) and IgA (breastmilk)
- IgG isotype 1 (vaccines containing protein antigens) is preferentially transported across the placenta compared to IgG isotype 2 (vaccines polysaccharide antigens).

1.5 Basic Vaccinology

A vaccine is a biological product that contains either an antigen derived from a pathogen or a synthetic product representing a component of the pathogen.[37] Vaccination aims to induce immune protection by the production of antibodies mediated by long-lived memory cells in the adaptive immune response[37,49] (Figure 7). The desired antibody response should have the ability to neutralise any biological effects from the pathogens, have a level above the protective threshold and produce long-lasting memory.[37] The clinical outcome of the vaccine includes the prevention of infection, reduction in disease severity, or a decrease in hospitalisation due to the diseases.[37] Traditionally, vaccines are classified into two categories: live and non-live vaccines.[37,49]

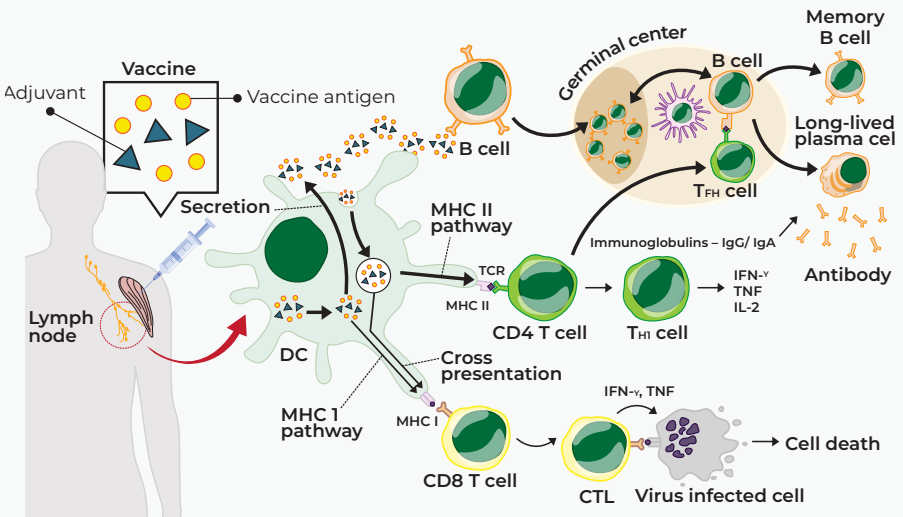


Figure 7 Vaccine-induced immune responses

During vaccination, both innate and adaptive immune responses are involved in which the dendritic cells at the tissue site will present the antigen to the T cells in the lymph nodes through the MHC II and TCR interactions. This in turn will activate B cell proliferation and differentiation into antibody-secreting plasma cells and memory cells.

Vaccines provide herd immunity since it helps to protect against asymptomatic infection and colonisation thus reducing the rate of infection and transmission.[37] Some vaccines require multiple doses at specific intervals to sustain the antibody level above the protective threshold which is the foundation of life-long immunity.[54] Booster doses will help antibodies to rise after rapidly declining.[37,54]

Vaccines help to control the spread of the disease and reduce complications. The BCG vaccine which is mediated by T cell immunity prevents severe manifestations such as tuberculosis meningitis and military TB in children and animal studies have shown that this vaccine reduces the spread of *M.tuberculosis* bacteria in the blood.[37]

In infant immunisation schedule, a series of priming doses are administered at less than 6 months of age followed by booster dose given by 12-15 months of age. This is to provide the earliest protection as possible before the level of maternal antibodies had waned. It is also known that in infants, the immune response is not as robust as in children. This could be due to several factors which has been mentioned previously i.e., the interference from maternal antibodies acquired in utero via placental transfer, that regulate B cell response and reduce the ability of viral replications (in the case of live vaccine). However, as infants grow, there is age-dependent physiological process which increases the antibody level.[37]

Type of Immunity

Passive and Active immunity

Passive immunity is immunity or protection acquired due to the transfer of preformed antibodies or antitoxin to an unimmunised individual.[37] This temporary immunity will last for a few weeks to months due to the degradation of the antibody.[37] Example of this immunity is the passage of maternal antibodies across the placenta (IgG) and into breast milk (IgA).[46,49] With this passive immunity, the infant will have the same type of antibodies as the mother and protect the infant for a few months after birth from infections.

Active immunity is immunity or protection produced by a person's immune system after being stimulated by an antigen such as natural infection or via vaccination.[58] It will be either antibody-mediated or cell-mediated and usually last for many years.[36,37,58]

1.6 Type of Vaccines

Live Attenuated Vaccine

These vaccines contain live virus particles that have been weakened to keep them from causing disease. They create a strong immune response

Some attenuated vaccines might not be suitable for people with compromised immune systems

Inactivated Vaccine

These vaccines contain **whole virus** particles, that have been **killed or inactivated** to keep them from causing disease.

They are safer as the virus is already dead

Inactivated vaccines require booster doses as the immunity conferred by these vaccines is weaker than live vaccines.

Replicating Viral Vector Vaccine

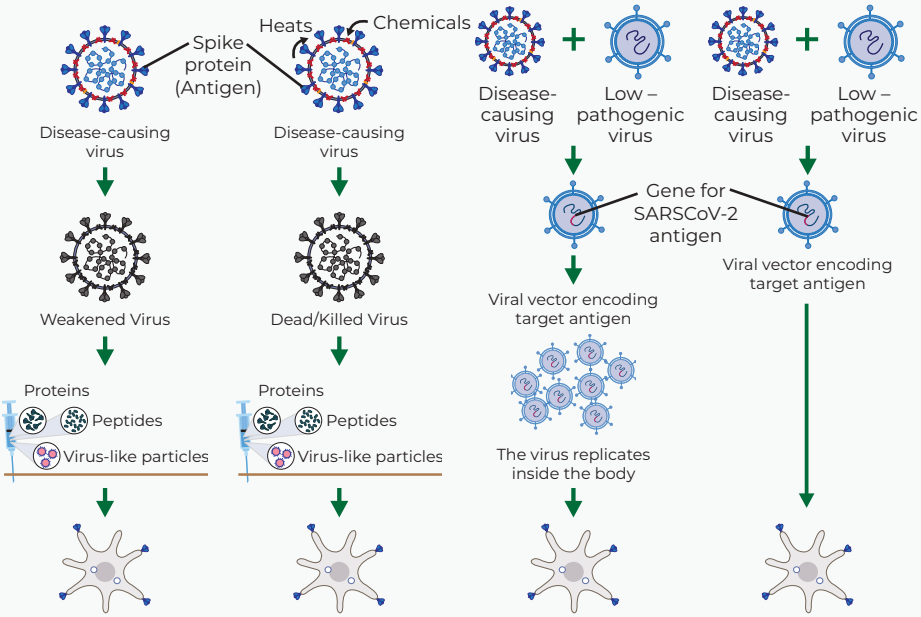
These vaccines use **low-pathogenic viruses,** which are largely harmless, and alter them into **viral vectors** that will produce some of the same proteins as the disease-causing virus.

This creates a **strong immune response,** but may not work for people who are already immune to the low pathogenic virus.

Non-replicating Viral Vector Vaccine

These vaccines are **similar** to **replicating viral vector** vaccines except that they cannot replicate inside the body as the key viral replication genes is deleted from the low pathogenic vector virus.

Improved **efficacy and safety,** but require high doses to confer immunity.



Antigen is presented to the immune cells on **Antigen Presenting Cells**

Immune Response and Memory

Currently used in:
MMR (Measles/mumps / rubella)
Chickenpox

Antigen is presented to the immune cells on **Antigen Presenting Cells**

Immune Response and Memory

Currently used in:
Polio

CoronaVac

Antigen is presented to the immune cells on **Antigen Presenting Cells**

Immune Response and Memory

Currently used in:
Used in veterinary medicine

Antigen is presented to the immune cells on **Antigen Presenting Cells**

Immune Response and Memory

Currently used in:
Ebola

Covid vaccines such as "Ad26.COV2-S, ChAd-Ox1/nCov-19, Ad5-nCoV-S"

Adapted from Murray E.[59]

Inactivated Vaccine

These vaccines use **DNA plasmids** containing a **gene for SARSCoV-2** along with additional genetic elements that will produce some of the same **antigenic proteins** as the disease-causing virus.

They are easy to develop and produce. There is no risk of infection but there is a possibility that the immune system does not fight against the antigen (tolerance to the antigen).

Replicating Viral Vector Vaccine

These vaccines use a piece of **messenger RNA (mRNA)** that will produce some of the same **antigenic proteins** as the disease-causing virus.

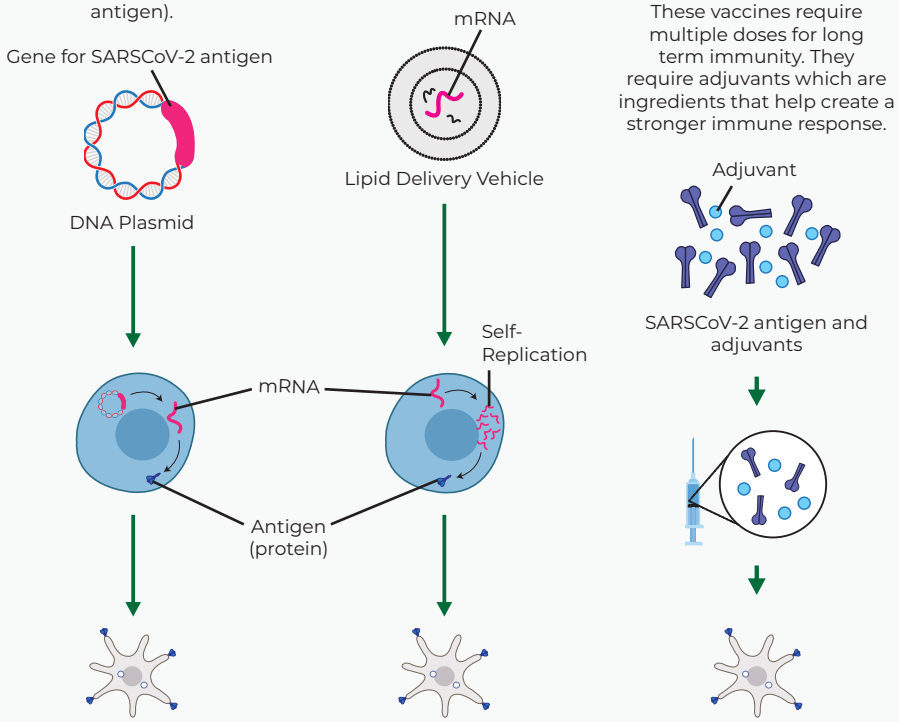
Risk of being integrated to the host genome is averted but, sometimes the RNA molecules may trigger an unintended immune response in the body.

Non-replicating Viral Vector Vaccine

These vaccines use **antigenic protein** from the disease-causing virus **without any genetic material.**

They are relatively safer as there is no genetic material, and they cannot replicate inside the body. They focus the immune response on the most important part of the virus for protection.

These vaccines require multiple doses for long term immunity. They require adjuvants which are ingredients that help create a stronger immune response.



Antigen is presented to the immune cells on **Antigen Presenting Cells**

Antigen is presented to the immune cells on **Antigen Presenting Cells**

Antigen is presented to the immune cells on **Antigen Presenting Cells**

Immune Response and Memory

Immune Response and Memory

Immune Response and Memory

Currently used in:
No currently available human DNA vaccines

Currently used in:
Ebola

Covid vaccines such as “Ad26.COV2-S, ChAd-Ox1/nCov-19, Ad5-nCoV-S”

Currently used in:
No currently available human DNA vaccines

1.7 General Advice on Immunisation Delivery

1.7.1. Management, Storage and Disposal of Vaccines

Vaccines are sensitive biological substances where its potency can be compromised by temperature variation or direct exposure to sunlight.[60] The cold chain of vaccine must comply with the approved guidelines to maintain potency.[61] (Refer to Appendix 1)

All vaccines must be stored in the original package in the vaccine-specific refrigerator at +2 °C and +8 °C,[61,62] and the temperature of the refrigerator checked twice daily.[62] The refrigerator must be connected to an emergency backup power supply with an alarm system in place. Lyophilized (freeze-dried) varicella-containing vaccines may also be stored frozen but should not exceed a temperature below -50°C.[61] Once the lyophilized vaccines are transferred to a refrigerator, they should not be refrozen, e.g. Varivax[63], ProQuad (MMRV)[64].

COVID-19 vaccine (Comirnaty) requires ultra-low temperature storage and transport (-90°C to -60°C) from the manufacturer. Upon receipt, the frozen vaccine can be stored either at -90°C to -60°C or +2°C to +8°C.[65]

Healthcare personnel are responsible for ensuring that the patients receive vaccines that are not compromised in efficacy from heat or cold temperatures.[66] The vaccine should only be removed from the refrigerator just directly before it is administered to the patient. Unused vaccines that have been removed from the cold chain must be disposed of appropriately in the biohazard containers.[66]

Manufacturers' package inserts should be referred to for the most up-to-date storage and handling recommendations for specific vaccines and diluents.[66]

Live vaccines that require reconstitution must be administered as soon as possible after they have been reconstituted and discarded according to the manufacturer's guidelines. For example, the varicella vaccine should be discarded if not utilised within 30 minutes after reconstitution, whereas the measles, mumps, rubella (MMR) vaccine can be refrigerated and stored in a dark place for up to 8 hours after reconstitution. When in doubt about the appropriate handling of a vaccine, vaccination providers should contact that vaccine's manufacturer.[67]

1.7.2. Route and Site of Administration

Healthcare personnel should always perform hand hygiene before administering vaccines. Wearing gloves is not necessary unless there is a likelihood of contact with infectious bodily fluids or the person giving the vaccine has open sores on their hands.[67]

The routes for vaccine administration include oral, subcutaneous, and intramuscular.[68] The current licensed oral vaccines include those for polio, rotavirus and cholera.[69,70,71,72]

Subcutaneous injections are administered into the fatty tissue found below the dermis and above the muscle layer. Vaccines that can be given subcutaneously include those for inactivated polio, MMR, varicella zoster, and pneumococcal.[68]

Intramuscular injections are administered into the deltoid muscle using the appropriate needles. The majority of individual and combination vaccines are administered intramuscularly.[67]

1.7.3. Simultaneous Vaccinations

Simultaneous administration of vaccines is defined as giving more than one vaccine on the same day, at separate anatomic sites, and without combining them into a single syringe.[73]

Any non-live vaccine can be given concurrently with another non-live vaccine or live vaccine without compromising the immune response.[73] If two live vaccines are not administered simultaneously, a minimum 28-day interval is required between the two,[73] as the immune response to one live vaccine might be impaired if it is administered within 4 weeks of the other.[73]

There is no minimal interval required for sequential administration of a non-live vaccine with another non-live or live vaccine.[73]

1.7.4. Temporal Deferral of Immunisation

Immunisation should be deferred if vaccine poses a greater risk of serious adverse reaction to the recipient. However, immunisation can be considered in cases where the protective benefits of vaccine outweigh the risks.[74]

The presence of a moderate or severe acute illness, with or without fever, is a precaution to all types of vaccination.[74,75] A mild acute illness (e.g., diarrhoea or mild upper-respiratory tract infection), with or without fever, is not a precaution, and vaccines may be given.[76]

Immunocompromised individuals may experience severe or fatal reactions from live-attenuated vaccinations due to uncontrolled replication of the virus. Therefore, vaccination should be deferred. Severely immunosuppressed patients with congenital immunodeficiency, leukaemia, lymphoma, or generalised malignancy should not receive live vaccines.[74] Live-attenuated vaccines should also be deferred for patients on high-dose systemic corticosteroids, until at least 3 months after the completion of treatment. The same rules apply to immunosuppressed individuals who are receiving cancer chemotherapy.[17, 74]

Guillain-Barré syndrome occurring 6 weeks or less after a previous dose of tetanus toxoid-containing vaccines or influenza vaccines is a precaution against repeat immunisations.[74,75]

History of type III (Arthus-type) hypersensitivity reaction after a previous dose of diphtheria toxoid or tetanus toxoid vaccine is a precaution to these vaccines; vaccination should be deferred until at least 10 years have elapsed since the last tetanus-toxoid-containing vaccine.[74,75]

1.7.5. Post Vaccination Care

Patients should receive after-care instructions that include advice on how to handle common side effects such as injection site pain and fever, and when to seek medical attention.[77]

Life threatening anaphylaxis following vaccination is rare. Healthcare providers must be competent in recognising adverse events and skilled in providing emergency treatment.[77]

1.7.6. Adverse Event Following Immunisation (AEFI)

All medical events following a vaccination are considered vaccine adverse events. A side effect, often known as an adverse reaction, is an undesirable outcome of a vaccination. Adverse reactions include local reactions of pain, swelling and redness at injection sites.[74] Vaccine adverse reactions may include allergic reaction to the components of vaccines; for example, Type III hypersensitivity (Arthus reaction) from diphtheria and tetanus toxoid.[74] The occurrence of anaphylaxis with vaccination is about 1 per million doses.[78] (Level II-2)

All new side effects or adverse events must be reported to the National Pharmaceutical Regulatory Agency (NPRA) under the Ministry of Health Malaysia and will be investigated by the Malaysian Adverse Drug Reaction Advisory Committee (MADRAC).[17] (Refer to Appendix 2)

SECTION 2

VACCINES RECOMMENDED DURING PREGNANCY

2.1 Tetanus, diphtheria and pertussis (Tdap)

RECOMMENDATION 1

Tdap vaccination is recommended during each pregnancy, from 16 weeks to 36 weeks of gestation.

Burden of disease

Pertussis

Pertussis, or whooping cough, is a respiratory infection caused by the bacteria *Bordetella pertussis*, a Gram-negative coccobacillus.[79,80 (Level III)] Adults, adolescents and children with pertussis infections have milder disease compared to infection in infants younger than 6 months which can be life-threatening.[79,80 (Level III)] Analysis of data from United States showed that the highest mortality rates occur in infant less than 4 months of age (too young to be vaccinated), who have an incomplete vaccine dose.[81 (Level II-3)] The most common complication, and the cause of most pertussis-related deaths, is secondary bacterial pneumonia. Neurologic complications in young infants with pertussis include seizures and encephalopathies.[82 (Level III)]

Pertussis remains endemic and continues to be a public health concern despite high vaccination coverage among children in both developing and developed countries.[79,80 (Level III)] Most countries face a cyclical trend in pertussis rates. The resurgence in some countries

is multifactorial, which includes waning of immunity, pathogen adaptation, an increase in surveillance systems and variable vaccine uptake, and inadequate booster coverage.[83]

Globally, the incidence of pertussis increased from 4.6 million in 2021 to 9.2 million in 2022.[84 (Level II-3)] In the United States of America (USA), historically, the incidence of pertussis was more than 100,000 cases per year before the introduction of the pertussis vaccine in the 1940s and dramatically reduced to fewer than 10,000 cases by 1965. The upward trend was then observed from the 1980s to 2019. More than half of the pertussis cases were in the age group less than 1 year old compared to the older age group.[85 (Level II-3)] In the United Kingdom (UK), the total number of reported pertussis cases from 2012 to 2022 was 7,947 cases and about 3.95% of pertussis cases were in infants of less than a year old.[86 (Level III)] In this group (less than 1 year old), majority of pertussis cases were in infants less than 3 months old.

The reported cases of pertussis in Asia in 2018 according to WHO were 17,532 in the Southeast Asia region (total population: 1,982,238,000; diphtheria-tetanus-pertussis (DTP3) coverage estimate of 89%).[87] The prevalence of PCR-confirmed pertussis was 4% in the Southeast Asia region. Meanwhile, the case fatality rate (CFR) for pertussis among infants in low- and middle-income countries (LMIC) was 7.2% (95% CI, 3.6–11.8%). Mortality occurred mostly in infants less than 6 months of age.[88] A study in Thailand showed that pregnant mothers were more susceptible to pertussis due to a low level of antibody against *Bordetella pertussis*.[89 (Level II-2)]

In Malaysia, the number of pertussis cases is high and follow global cyclical trend. The reported number of cases in 2021 was 11 cases, with 95% vaccine coverage and incidence rate of 0.3 per 1 million. The number of cases increased to 101 in 2022, with 97% vaccine coverage and incidence rate of 3 per 1 million.[84 (Level II-3)] This upswing had also been observed in 2014/2015 and 2018/2019.[84 (Level II-3)]

A recent study in Malaysia (2022), involving seven states, showed a high incidence of confirmed pertussis among infants younger than 6 months (12.7%).[90] (Level II-2) The majority of the confirmed cases were infants less than 2 months of age, who had not received their primary vaccination (44.6%, n = 25/56).[90] (Level II-2) There were also higher numbers of mothers who tested positive for recent or acute pertussis infection in mother of confirmed pertussis cases (14.3%;n=8/56) compared to mother of test -negative cases (3.4%;n=13/385;p=0.0003).[90] (Level II-2)

The antenatal vaccination for pertussis began in the USA in 2011, followed by the UK in 2012 after an outbreak of pertussis among infants, and subsequently adopted by many other countries.[83,91] (Level II-2), [92] (Level III) In the Southeast Asia region, Singapore has recommended the maternal Tdap vaccine in their national program. In Philippines and Thailand, the recommendation for Tdap vaccine is from their national society of physicians and healthcare professionals.[93] Malaysian Society of Infectious Diseases and Chemotherapy (MSIDC) recommends maternal Tdap vaccination in its Guidelines for Adult Immunisation.[17] (Level III)

The rationale for maternal immunisation against pertussis is to offer passive protection to infants from birth by the vaccine specific maternal antibody transfer via the placenta to the fetus until they receive their primary series of immunisation against pertussis. Maternal immunisation will close the two-month gap of vulnerability for pertussis infection.[83]

Tetanus

Tetanus is a life-threatening disease caused by the toxin from the bacterium *Clostridium tetani*.[94] (Level III) The exotoxin from this bacterium acts at the myoneural junction of skeletal muscle and in the spinal cord causing muscular rigidity and contractions which can lead to respiratory and cardiac failure.[95]

In Malaysia, anti-tetanus toxoid (ATT) immunisation for pregnant mother was implemented in 1976.[95]

The maternal coverage for tetanus has significantly reduced the incidence of tetanus in the neonatal period. In 2022, the incidence rate of neonatal tetanus was 0.04 per 100,000 population.[96 (Level III)] The global WHO's MNTE goal is to achieve <1 case of neonatal tetanus per 1000 live birth.[97 (Level III)]

Diphtheria

Diphtheria is an acute respiratory infection caused by toxigenic Corynebacterium diphtheriae, or in rare cases, Corynebacterium ulcerans.[98 (Level II-3)] Exotoxin from the bacilli causes tissue damage, elicits prodromal symptoms and inflames the membranes of the pharynx, tonsils, larynx, heart, or nerves.[98 (Level II-3),17 (Level III), 99 (Level III)]

Globally, the incidences of diphtheria were between 0.7-3.4 per one million total population (year 2013-2023).[100 (Level III)] Diphtheria outbreaks continue to be recorded as a result of poor childhood immunisation coverage.[101 (Level III)] In 1998, WHO advised all countries to switch tetanus vaccination for pregnant and reproductive-age women to tetanus diphtheria (Td) in response to a diphtheria outbreak in certain regions and to provide double protection.[102 (Level III)]

Diphtheria incidence in Malaysia spiked from 0.1 per one million total population in 2021 to 0.4 per one million total population in 2023.[100 (Level III)]

2.1.2 Available Vaccines

Tdap

The components of the Tdap vaccine are tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (aP). [82(Level III), 17 (Level III)]

There are two types of pertussis vaccines; 1) whole-cell pertussis vaccine (wP) (which is available in some countries) and 2) acellular pertussis vaccine (aP). Only acellular pertussis-containing vaccine is licensed for use by pregnant mothers. Acellular pertussis vaccines differ in the number and concentration of antigen components, bacterial clones used during production, methods of purification and detoxification, adjuvants, and preservatives.[82 (Level III), 94 (Level III)]

There are no licensed stand-alone acellular pertussis vaccines available. It is produced as a combination of pertussis toxin (PT) with other antigens, which are filamentous hemagglutinin (FHA), pertactin (PRN), or fimbriae (FIM) types 2 and 3. It also contains a small amount of adjuvant in the form of aluminium (0.33-0.39 mg).[17 (Level III), 103 (Level III)]

2.1.3 Immunogenicity and Effectiveness

Immunogenicity

The administration of the Tdap vaccine in pregnant women results in robust antibody responses against the antigens present in the vaccine. This primarily induces IgG1 antibodies, which are actively transported through the placenta to the newborn, offering passive protection until the infant's primary vaccination.[104 (Level II-2)] The antibody transfer begins as early as second trimester of gestation[105] and shows positive correlation with the gestational age.[49 (Level II-2)]

The antibody response to Tdap vaccine were similar among pregnant and non-pregnant women.[106 (Level I)] Pregnancy did not affect the quality of IgG and memory B cell responses to Tdap immunisation. Moreover, a higher concentration of vaccine-specific IgG, IgG subclasses, and IgG Fc-mediated effector functions was detected in cord blood compared to maternal blood.[107 (Level II-2)] Study in adult showed that aP-containing vaccine was independent of the pre-immunisation antibody titre, and to lesser extent induce TH2 response.[108 (Level III)]

Level of antibody response towards Tdap in maternal sera and cord blood was significantly higher in Tdap vaccinated mother.[83,106] (Level I) Greater antibody in cord blood reflected good antibody transfer across the placenta during pregnancy.[109] (Level I) The geometric mean concentrations (GMCs) of maternally transferred pertussis antibodies in cord blood were 8.5–20.7-fold higher for Tdap-vaccinated mother compared to unvaccinated mother.[110] (Level I)

Tdap vaccination is recommended for every pregnancy regardless of pregnancy interval because Tdap-specific antibodies from the aP-containing vaccine exhibit a relatively short-lived presence, with levels significantly declining within a year post-vaccination.[111](Level II-2) Despite this decline, vaccinated women still maintained higher antibody levels than those who did not receive the vaccine during pregnancy. This waning process suggests the need for re-vaccination in each pregnancy for optimal neonatal protection.[112] (Level III) The decline in Tdap-specific antibodies also observed among infant of Tdap-vaccinated mother. However, the level of antibody in infant at 6 weeks is still acceptable considering IgG to PT is more than 10 IU/ml (97% at birth vs 67% at 6 weeks).[113] (Level II-2)

There is no concern over the theoretical interference in immune response when combining antigens in Tdap. Historically, a single ATT vaccine was first produced in 1924, and the immunogenicity of tetanus is increased by addition of adjuvant.[94] (Level III) Since then, the tetanus vaccine has been combined with other vaccines for many years without causing any increase in adverse effects or compromising the immunogenicity or vaccine response to each of its components.[97] (Level III)

Breastfeeding

Breastfeeding may provide an additional layer of protection through the transfer of pertussis-specific secretory IgA and a smaller IgG antibody in breast milk. Elevated levels of pertussis-specific antibodies have been found in the breast milk of vaccinated women, particularly in the colostrum, suggesting a potential, protective effect against pertussis in breastfed infants.[83]

Effectiveness

Evidence was consistent to show that infants whose mothers received prenatal vaccination have a higher level of antibodies at birth and persist up to 2 months of age compared to non-vaccinated mother.[106 (Level I)]

In PERTINENT Study, vaccine effectiveness (VE) in preventing pertussis in infants less than 3 months of age range between 90.9% and 91.0%. VE in infants younger than 6 months of age ranged from 39% to 46%.[114 (Level I)] Maternal pertussis immunisation reduced pertussis hospitalisation by 58.3 to 90.5%in infant less than 2 months of age.[114 (Level I)] More importantly, a study in England showed the effectiveness of preventing pertussis-related deaths in newborns reached up to 95%.[115 (Level II-2)]

The benefits of the maternal Tdap vaccine are observed particularly in the subgroup of preterm infants, who are at a higher risk for pertussis-related complications. A cohort study in the United States showed that the prenatal vaccine demonstrated protective hazard ratio (HR) of 0.11 in preventing pertussis infections in preterm infants under the age of 6 months.[116 (Level II-3)] This data is very encouraging as it indicates that maternal immunisation can offer substantial protection even to those infants who are most at risk due to their prematurity.[116 (Level II-3)]

2.1.4 Vaccine Safety

There is a large amount of evidence available to show that Tdap is safe for both the mother and the unborn baby during pregnancy.

The earlier UK observational cohort study utilising the UK Clinical Practice Research Datalink (CPRD), involving 20,074 vaccinated pregnant women, showed no increased risk of adverse pregnancy events, which are stillbirth, maternal or neonatal death.[117 (Level II-2)] A national observational study in New Zealand showed Tdap in pregnancy did not increase adverse maternal outcomes.[118 (Level II-2)]

An observational cohort study in the USA, utilising the Vaccine Safety Datalink (VSD), involving 26,229 Tdap-vaccinated pregnant mothers, showed no increased risk of preterm delivery, small for gestation age, or hypertensive disorder of pregnancy.[119 (Level II-2)] A systematic review by Vygen-Bonnet S et al. with a pool of 199,846 pertussis-vaccinated mothers found no increased risk of stillbirth, neonatal death, preterm birth, low birth weight, congenital malformation, neonatal septicaemia, or admission to the NICU.[120 (Level I)] In one study, there was a slightly decreased risk of pre-eclampsia and eclampsia observed.[120 (Level I)]

Findings of very small risk of chorioamnionitis in the vaccination cohorts were not significant compared to the large number of women receiving maternal pertussis each year. There were many confounding factors and heterogenicity of the data that limit the adjusted analysis.[119 (Level II-2), 120 (Level I), 121 (Level I)] Furthermore, Pertussis Immunisation in Pregnancy Safety (PIPS) Study in New Zealand showed no increase in chorioamnionitis.[118 (Level II-2)]

A study addressing the concern of whether there is an association between Tdap vaccination during pregnancy and the development of autism spectrum disorder (ASD) or attention deficit hyperactive disorder (ADHD) found no significant association with a HR of 0.85 (95% CI: 0.77–0.95) in the former and HR of 1.0 (95% CI: 0.88–1.14) in the latter.[122 (Level II-2), 123 (Level II-2)]

Adverse Events

In pregnancy, only aP-containing vaccine is licenced to be used. The aP-containing vaccine has an improved reactogenicity profile over the wP-containing vaccine.[82 (Level III), 94 (Level III)] The most common side effect after the Tdap vaccination is pain at the injection site (75.8%) and headache (33.3%). The other common side effects are erythema or redness at injection site (9.1%), swelling or induration at the injection site (9.1%), malaise (12.1%), myalgia (15.2%), and fever (3.0%). Most of these symptoms are mild and resolve within 72 hours. The risk of anaphylaxis is very rare and develops in less than one in 500,000 vaccinations.[106 (Level I), 124 (Level III)]

The safety of repeated immunisations in every pregnancy has been studied. A retrospective cohort study showed that the recent Tetanus vaccine (prior to 2 years) does not increase the risk of acute adverse events (fever within 3 days [2.1/10000 vs 3.5/10000p = 0.70], allergic reactions within 3 days [2.1/10000 vs 1.4/10000p = 0.73], local reactions within 3 days [4.2/10000 vs 11.2/10000; p = 0.35]), or adverse birth outcomes (preterm delivery [6.6% vs 6.8%; p=0.08], low birth weight [4.7% vs 5.1%;p=0.31], or small gestational age [9.0% vs 9.1%;p=0.88]) after Tdap vaccination in pregnancy compared to control.[125 (Level II-2)]

The Vaccine Adverse Event Reporting System (VAERS) in United States which is a national vaccine safety surveillance program, has not found any adverse safety concerns for mother and fetus following Tdap vaccination.[126 (Level III), 127 (Level III)] In Malaysia, all new side effects or adverse effects must be reported to the NPRA for evaluation. (Refer to Appendix 2)

2.1.5 Contraindications

Tdap vaccine is contraindicated in mothers who have a history of anaphylaxis from a previous dose of Tdap vaccine or any of its components.[82 (Level III)]

2.1.6 Timing and Schedule

All pregnant women should be offered the Tdap vaccine between 16[128] (Level III) and 36 weeks[82] (Level III) of gestation in each pregnancy. The evidence showed that neonatal pertussis antibodies were observed when the vaccine was given as early as early second trimester.[129] (Level II-1) In an open-label randomised controlled trial, IgG antibody concentrations against two of the three pertussis antigens were found to be equivalent in infants whose mothers received the Tdap vaccination during the second or third trimester.[130] (Level II-3) In one study, Tdap immunisation in the second trimester significantly increased neonatal antibodies compared with the third trimester.[129] (Level II-3)

An interval of 2 weeks between administration and delivery is needed to achieve optimal concentration.[131] (Level III) Tdap vaccine can be given after 36 weeks. However, it is less effective in providing passive protection to the newborn.

Cumulative time between Tdap vaccination and childbirth enhances immune responses and antibody levels.[132] (Level II-2), 133 (Level II-3) Although antibody transfer is less effective in preterm births, preterm infants born to vaccinated mothers showed sufficient cord blood antibodies compared to those born to non-vaccinated mothers.[132] (Level II-2)

Recommendations on the timing of maternal Tdap vaccination vary across many countries (Refer to Table 5)

“Cocooning” is a strategy to reduce pertussis transmission from mothers or family members to infants by vaccinating the mother and anyone who is in contact with the infant. WHO position paper 2015 states that the vaccination of pregnant mother is the most cost-effective strategy and more favourable than cocooning.[80] (Level III) A large cohort study from the California Immunization Registry, which involved 74,791 women, showed that vaccination during the prenatal

period was 85% more effective than postpartum vaccination in preventing neonatal pertussis.[134] (Level II-3)

2.1.7 Unknown previous tetanus vaccination status

The incidence of neonatal tetanus is around 0-0.1 per 1,000 live births, and Malaysia achieved MNTE before 2000.[135](Level III), [136](Level III)

When a pregnant mother's past tetanus status is unknown or incomplete, ATT/Tdap is administered at quickening, followed by Tdap four weeks later.

2.1.8 Special circumstances

The Tdap vaccine is a non-live vaccine, making it a safe option for administration to pregnant mothers with special circumstances, such as human immunodeficiency virus (HIV). An open label phase IV clinical trial in South Africa showed that Tdap vaccination for pregnant women with HIV was safe and had similar solicited adverse events as with HIV-uninfected mother. Antibody respond was observed though lower than in HIV-noninfected mother.[137] (Level II-2)

Although there has been no specific study on the Tdap vaccine in mothers in other special circumstances (such as those with cancer or immunosuppressive conditions), the recommendation for administering the Tdap vaccine to adults in these special circumstances does not indicate any significant safety concerns.[138] (Level II-2)

Table 5: Recommendation of timing for maternal Tdap immunisation and year of introduction by countries. (adapted from Kandeil et al., 2020[114] (Level I)

Country	Timing of Tdap Immunisation	Year of Introduction
Argentina	From 20 weeks	2012
Australia	28–32 weeks	2014
Bahamas	Each pregnancy	No information
Belgium	Each pregnancy	2012
Brazil	20 weeks	2017
Canada	Each pregnancy	2012
Chile	27–36 weeks	2016
Colombia	From 26 weeks	2012
Costa Rica	From 20 weeks	2012
Czech Republic	28–36 weeks	2015
Denmark	From 32 weeks	2019
El Salvador	From 28 weeks	No information
England	From 16 weeks	2016
Mayotte	18–39 weeks	2018
Honduras	26–37 weeks	2012
Hong Kong	Second to third trimester	2019
India	27–36 weeks	2013
Ireland	27–36 weeks	2013
Italy	Third trimester	2017
Korea	27–36 weeks	2014
Mexico	After 20 weeks	2012
Netherlands	22 weeks	2018
New Zealand	28–38 weeks	2013
Panama	Pregnant women	2012
Paraguay	Pregnant women	-
Peru	26–37 weeks	-

Country	Timing of Tdap Immunisation	Year of Introduction
Philippines	Pregnant women and postpartum	2015
Portugal	20–36 weeks	-
Qatar	27–36 weeks	2017
Singapore	16–32 weeks	2017
Slovenia	Soon after 24 weeks	2017
Spain	Pregnant women	2014
Switzerland	Pregnant women	2013
Taiwan	28–36 weeks	2012
UK	16–32 weeks (updated 2016)	2012
Uruguay	Pregnant women	-
USA	27–36 weeks	2012

2.2 Influenza

RECOMMENDATION 2

Pregnant women should receive inactivated influenza vaccine in any trimester of each pregnancy (Evidence Level I).

2.2.1. Introduction

Influenza virus

Influenza is an RNA virus of the orthomyxoviridae family, with four sub-types A, B, C, and D.[139] The most clinically significant influenza viruses are types A and B, which cause seasonal epidemics.[140]

Influenza A strains are classified based on two surface proteins of the virus: hemagglutinin (H) and neuraminidase (N). Hemagglutinin enables viral attachment to host cells, and neuraminidase facilitates the virus's subsequent release from the infected cells.[139] A(H1N1) and A(H3N2) are the most common influenza A subtypes at present.[140] Both humans and animals are susceptible to the influenza A virus.[141] The current influenza A(H1N1) viruses are related to the 2009 "swine flu" pandemic virus.[139]

Influenza B viruses are divided into two lineages: B/Yamagata and B/Victoria.[140,142] The virus is slower to mutate and is more commonly found in children and at long-term care facilities, college campuses, and military camps.[141]

Clinical presentation

The clinical manifestations of influenza in pregnancy are similar to those in the general population, typically beginning with sudden onset of fever, headaches, myalgia, and malaise. Respiratory symptoms, such as cough, sore throat, and runny nose, are common.[143] Vomiting and diarrhoea were frequently reported among infected individuals during the 2009–2010 H1N1 influenza pandemic.[144]

The average incubation period of influenza is two days (ranges from 1–4 days).[140] The duration of viral shedding is between 4–7 days and can be detected as early as 48 hours before the onset of symptoms.[143]

Seasonal epidemics occur mainly during winter; typically, between October and May in the Northern Hemisphere.[141] In tropical regions (including Malaysia), influenza may occur throughout the year, causing outbreaks more irregularly.[143]

Burden of disease

An estimated 1 billion cases of influenza are reported annually, of which 3–5 million are severe cases. Additionally, influenza-related respiratory deaths account for between 290 000 and 650 000 cases (0.1–0.2% case-fatality rate).[140,145] Due to its non-notifiable disease status in Malaysia, there are lack of comprehensive surveillance reports on influenza, including hospitalisation rate and deaths. The actual disease burden in this nation remains unclear for now.[146]

Influenza infection is relatively common during pregnancy, affecting up to 11% of pregnant women in the second and third trimesters.[147] Pregnant women are more susceptible to severe influenza infection and hypoxaemia due to pregnancy-related cardiopulmonary changes such as increased heart rate and stroke volume, higher oxygen consumption, and reduced pulmonary capacity.[148,149] Influenza is associated with an increased risk of pneumonia in pregnant women[150] and available data suggest that influenza complications are most common during the third trimester.[151]

According to a meta-analysis of 152 observational studies, the majority of which were carried out during the 2009 pandemic, pregnant women with influenza had a two-fold hospitalisation rate than non-pregnant individuals [OR 2.44 (95% CI 1.22–4.87)].[152]

Pregnant women had a substantially high risk of mortality due to 2009 influenza A(H1N1). In the United States, pregnant women accounted for 5% of all pandemic influenza deaths, despite making up less than 1% of the population.[151] The observed mortality rate for pregnant women was also high during the 1918 and 1957 influenza pandemics.[143] According to estimates, pregnant women in the UK were four times more likely to die during a severe influenza season than during a regular season.[153]

Fever is a common symptom of influenza and can have a negative effect on a developing fetus.[154,155] Exposure to hyperthermia in pregnancy during the embryonic and fetal development stages may

result in miscarriage or a wide range of structural and functional defects, with the central nervous system being the most at risk.[154] A recent meta-analysis highlighted an association between first-trimester influenza infection and non-chromosomal birth defects.[156]

Influenza is also associated with neonatal complications such as preterm delivery, low birth weight, and stillbirths.[143,157,158,159] Data from the United States showed that pregnant women with H1N1 infection who were admitted to intensive care units (ICU), were more likely to have a preterm delivery [adjusted relative risk, aRR 3.9 (95% CI 2.7–5.6)] and a low birthweight infant [aRR 4.6 (95% CI 2.9–7.5)].[158] Similarly, recent Korean data indicated that maternal influenza infection significantly increased the risk of preterm birth [OR 1.41 (95% CI 1.33-1.49) and low birth weight [OR 1.20 (95%CI 1.14-1.26)] irrespective of gestational age.[159]

A meta-analysis of retrospective cohort and case-control studies found that influenza A infection in pregnancy carried greater risks of low birth weight (RR 1.71, 95% CI 1.03–2.84), and stillbirth (RR 2.36, 95% CI 1.05–5.31).[157]

Rationale for maternal immunisation

Maternal immunisation with influenza vaccine is the main strategy to prevent influenza infections among pregnant women and will reduce the severity of influenza infection. There are significantly fewer hospitalisations of vaccinated pregnant women during influenza season than that of unvaccinated pregnant women.[160]

Another important aim of maternal immunisation is to prevent influenza infections in infants <6 months of age, who are particularly vulnerable to severe disease but too young to receive vaccination.[160] Protection in this age group relies on the transplacental transfer of antibodies from the mother[161] as well as maternal antibodies in the breast milk after delivery.[162]

2.2.2 Available Vaccines

Inactivated or live attenuated influenza vaccines come in two forms: **trivalent** formulation contains antigens of 2 influenza A subtypes (H1 and H3); and 1 influenza B virus (Yamagata or Victoria lineage), while **quadrivalent** covers 2 influenza A and 2 influenza B viruses.[145] Research has shown that, when compared to trivalent vaccination, quadrivalent vaccines reduce death, morbidity, and the need for healthcare services.[163,164] Pregnant women are advised to receive inactivated vaccines as live vaccines are contraindicated in pregnancy due to the risk of fetal viraemia.[15]

The influenza strains (Northern and Southern strains) for the vaccine are updated biannually based on recommendations from the WHO.[139]

Influenza vaccines are produced using three different methods: egg-based, cell-based, and recombinant technology. Inactivated egg-based vaccines are the most commonly used nowadays.[145] Inactivated vaccines contain purified H and N antigens instead of whole virions, as the latter is associated with a high rate of adverse reactions.[145]

Recombinant influenza vaccines (RIVs) consist of purified influenza antigens produced using the recombinant DNA technology and contain no preservatives, or egg protein.[141,145] The RIVs can be manufactured quickly in the event of a pandemic or an egg shortage. The production process also avoids egg-adaptive mutations of the vaccine viruses, which may reduce vaccine effectiveness.[141]

Individuals who are or might be pregnant during the Influenza season are advised to receive **inactivated quadrivalent influenza vaccine (IIV4) or the recombinant quadrivalent influenza vaccine (RIV4), regardless of trimester.**[145,165]

2.2.3 Immunogenicity & Effectiveness

Immunogenicity

A single dose of influenza vaccine in pregnancy is sufficient to produce the required immune response. A randomised study demonstrated that a single dose of inactivated 2009 A (H1N1) influenza vaccine given in the second or third trimester of pregnancy, is highly immunogenic. The data showed that 93–97% of women were seropositive with haemagglutinin inhibition (HAI) antibody titres ≥ 1:40. The antibody titres in cord blood were 1.81–2.96-fold higher than in the maternal blood at delivery.[166] (Level I)

While influenza vaccines can be given at any time in pregnancy, vaccination in the third trimester provides better disease protection as it results in a greater immune response and transplacental antibody transfer to the fetus. A meta-analysis of sixteen studies showed that the antibody response to the flu vaccine was 1.33–1.96-fold higher in women vaccinated during the third trimester of pregnancy, than during earlier gestation. The evidence also suggested that vaccination later in pregnancy increased antibody transfer to the fetus by 1.21–1.64-fold.[167] (Level II-2)

A prospective observational cohort study during the 2002–2005 influenza seasons found that infants born to influenza-vaccinated mothers had higher antibody titres, at birth and at 2–3 months old, compared with infants of unvaccinated mothers.[168] (Level II-2)

Efficacy

The efficacy and effectiveness of maternal influenza vaccination in preventing influenza infection in mothers and infants have been extensively studied. A Norwegian national registry study of 117,347 pregnancies during the 2009–2010 influenza pandemic showed that vaccination of pregnant women substantially decreased the risk of

influenza diagnosis by 70% [adjusted hazard ratio, 0.30 (95% CI, 0.25 to 0.34)].[169] (Level II-2)

The retrospective multi-country PREVENT (Pregnancy Influenza Vaccine Effectiveness Network) study reported that maternal influenza vaccination was 40% (95% CI 12-59%) effective against laboratory-confirmed influenza-associated hospitalisation during pregnancy.[170] (Level II-2)

A cohort study from Denmark found that influenza vaccine efficacy against laboratory-confirmed influenza was 63.9% (95% CI 29.1–81.6%) in pregnant women and 56.8% (95% CI 25.0–75.1%) in infants aged <6 months.[171] (Level II-2) Maternal influenza vaccination in pregnancy prevented 56.8%, 63%, and 71% of influenza infections in infants <6 months of age in Denmark, Bangladesh, and England, respectively.[171] (Level II-2), 172 (Level I), 173 (Level II 2/3)

2.2.4 Vaccine Safety

Inactivated influenza vaccines (IIVs) have an excellent safety profile and are well tolerated by recipients of all ages including pregnant women.[145] Mild adverse reactions are frequent but self-limiting and can last up to 2 days. Mild injection-site-pain is common (60–80%); systemic symptoms include low-grade fever (2–10%), malaise, headache, myalgia and fatigue.[145] Allergic reactions like hives, angioedema, and anaphylaxis are very rare.[15]

An association between IIVs and Guillain-Barré syndrome,an autoimmune demyelinating disease of the peripheral nervous system, was first discovered after the 1976 influenza season, with an attributable rate of 1 additional case of Guillain-Barré syndrome per 100,000 vaccinated persons.[145] Subsequent research over several influenza seasons found variable Guillain-Barré syndrome incidence; with reported vaccine-attributable risk of 1–2 cases of Guillain-Barré syndrome per million persons vaccinated.[174,175]

According to the WHO's Global Advisory Committee on Vaccine Safety (GACVS), there is strong evidence that inactivated nonadjuvanted influenza vaccines are safe, supporting the WHO recommendation on influenza vaccination in pregnancy.[176] The safety of influenza vaccination during pregnancy has been consistently shown by numerous studies, including clinical trials, observational studies, and data from safety reporting systems.[160] According to data from the USA, the risk of serious adverse events such as spontaneous miscarriage and stillbirth following antenatal influenza vaccination is extremely low, with an adverse event rate of 12.5 per million pregnant women.[177]

The safety of Influenza vaccination is also confirmed by a recent systematic review. The review which included 40 studies, found no significant associations between influenza vaccination in pregnancy and small for gestational age (Adjusted Odds Ratio (AOR) 0.99, 95%CI 0.94–1.04), congenital abnormality (AOR 1.03, 95%CI 0.99–1.07), and stillbirth (AOR 0.84, 95%CI 0.65–1.08). Furthermore, there is evidence supporting the protective effect of the vaccines against preterm birth (AOR 0.87, 95%CI 0.78–0.96) and low birth weight (AOR 0.82, 95%CI 0.76–0.89).[178 (Level II-2)]

A meta-analysis of 16 cohort studies assessing fetal outcomes after H1N1 vaccination in pregnancy also observed a lower risk of stillbirth among women who had received antenatal influenza vaccination (adjusted hazard ratio 0.80, 95% CI 0.6–0.92). There were no statistically significant differences in the risk of spontaneous abortion, preterm delivery, and small for gestational age between the vaccinated and unvaccinated groups.[179 (Level II-2)]

2.2.5 Contraindications

A history of a severe allergic reaction (such as anaphylaxis) after a previous dose of influenza vaccine is the only contraindication to future influenza vaccination.[145,160,165] Individuals with egg allergy

(regardless of severity) may receive egg-based vaccine[165], provided they are monitored for at least 15 minutes following vaccination in a setting with access to medical care.[145]

2.2.6 Timing and Schedule

Influenza vaccines cause antibodies to develop in the body about two weeks after vaccination. Influenza vaccine should be given annually due to a decline in the immune protection from vaccination over time, and the ever-changing circulating influenza strains.[142]

Pregnant women are advised to get vaccinated annually even if they received an influenza vaccine during a previous pregnancy.[160] Any age-appropriate quadrivalent inactivated (IIV4) or recombinant (RIV4) vaccines may be given in any trimester.[165]

IIV4s and RIV4 may be administered concurrently or sequentially with other inactivated vaccines.[165] Influenza vaccine can safely be given at the same time as a pertussis vaccine and/or COVID-19 vaccine (See Section 2.5).[180]

2.2.7 Special Circumstances

For the Northern Hemisphere: Annual influenza vaccination should be offered during September or October (before the onset of influenza season). Vaccination in **July and August** can be considered for pregnant persons who are in the third trimester during these months.[165]

Regardless of when a pregnant woman presents for antenatal care, influenza vaccination should always be recommended. This also applies if the woman has been recently vaccinated for influenza in the **pre-pregnancy period**.[181]

Table 6: Recommendation for influenza immunisation from other authorities.

Authority	Gestation	Type of vaccine
WHO[145]	Any trimester	Inactivated or recombinant
ACOG[160]	Any trimester	Inactivated
CDC[165]	Any trimester	Inactivated or recombinant
Australian Department of Health[180]	Any trimester	Inactivated
NHS UK[182]	Any trimester	Inactivated
FIGO[183]	Any trimester	Inactivated

2.3 COVID-19

RECOMMENDATION 3

mRNA-based COVID-19 vaccines are recommended in pregnancy

2.3.1 Introduction

What began as an outbreak of pneumonia at the end of 2019, ended up being one of the most deadliest infection in the past century.[184 (Level III)] SARS-CoV-2, like its predecessor, enters host cells

via angiotensin-converting enzyme 2 (ACE2) receptor, which is widely expressed in various human organs, including the placenta. Genome sequencing studies have shown that SARS-CoV-2, the virus which causes COVID-19, shares 79.6% sequence identity with SARS-CoV.[185] (Level II-2)

Burden of disease

Since being declared a global pandemic by the WHO on 11th March 2020, there have been more than 770 million confirmed cases of COVID-19 and almost 7 million deaths reported at the time of writing.[186] (Level III) Sequencing of SARS-CoV-2 genome has allowed a better understanding of the predominant clades and variants of concern (VOC) which caused the various waves of infection in the country.[187] (Level II-2)

The first cases of COVID-19 were detected on 25th January 2020, prior to the declaration of a pandemic, when three foreign nationals from Wuhan entered Malaysia. This first wave included only 22 confirmed cases, involved only cases that had a history of travel to China or contact history, and ended on 15th February 2020.[188] (Level III) The second wave began in March 2020 and was triggered by a religious gathering attended by 16,000 people, of whom 1500 were foreign nationals from dozens of countries. This wave lasted for four months[188] (Level III) and was predominantly of B.6 lineage.[189] (Level II-2) The third wave began in September 2020 following a major cluster formation in Sabah and was attributable to lineage B.1.524.[189] (Level II-2) Although Alpha variant (B.1.1.7) emerged in the UK in September 2020.[190] (Level II-2) and separately, the Beta variant (B.1.351) in South Africa in October 2020,[191] (Level II-2) this wave peaked in January 2021, driven by lineages B.1.524 and AU.2 before declining in February and March 2021.[187] (Level II-2)

The massive surge of cases, however, began with the fourth wave between April and August 2021, driven by the highly transmissible Delta variant (B.1.617.2). More than 24,000 daily cases were reported as the total number of COVID-19 infections surpassed one million. The fifth wave began in February 2022 due to Omicron variant (BA.5) and recorded the highest daily infections reported, peaking at 33,406 cases per day on 5th March 2022.[187](Level II-2)

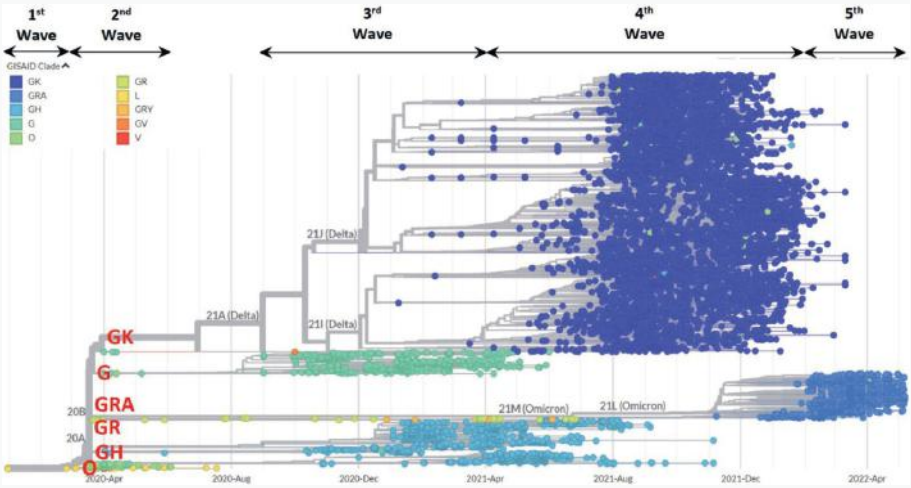


Figure 8
Timeline of COVID-19 waves in Malaysia based on phylogenetic tree analysis of SARS-CoV-2 genomic sequences. Major clades in Malaysia shown in red.[187] (Level II-2)

Periodic updates of the COVID-19 vaccine is therefore expected, due to the evolving nature of the virus highlighted above. Even as this guideline is being drafted, a new subvariant of Omicron, JN.1 has been reported in the country.[192] (Level III)

It is important to emphasise that although pregnant women are no more likely to contract SARS-CoV-2 compared to non-pregnant women, they are at risk of running a more severe course, with higher rates of intensive care unit admissions and invasive ventilation. This mirrors other viral respiratory illnesses affecting women, such as influenza.[193] (Level I), [152] (Level I) Women with COVID-19

are also at higher risk of developing hypertensive disorders in pregnancy and preeclampsia-like syndromes.[194 (Level II-2)] The human placenta has excess expression of ACE2, [195,196 (Level II-2)] which is required for viral invasion of syncytiotrophoblasts and can result in vertical transmission. Symptomatic COVID-19 infection in pregnancy is associated with preterm birth[197 (Level II-2)]. SARS-CoV-2 placentitis and stillbirths have been reported, particularly in unvaccinated women.[198 (Level II-2)]

SARS-CoV-2 virus is unlikely to be eliminated; as such, future recommendations would depend on virus evolution/emergence of virulent strains, population immunity and risk mitigation behaviours.[187 (Level II-2)] The CDC currently recommends that everyone above the age of 6 months receive the updated COVID-19 vaccine, including women who are trying to conceive, pregnant or breastfeeding.[199 (Level III)]

2.3.2 Available vaccines

183 vaccines are currently in clinical stages of development using various platforms (protein subunit, RNA, inactivated virus, viral vectors) and routes (parenteral, oral, intranasal).[200 (Level III)] The table below summarises the vaccines which have been granted emergency use listing by the WHO and were available in different countries worldwide at some point.[201 (Level III)]

Table 7: Vaccine types and recommendations in pregnancy[201 (Level III), 202 (Level III), 203 (Level III)] (Table adapted from Kalafat et al. 2022)[202 (Level III)]

Vaccine type	Examples	Recommended in pregnancy	Data on pregnancy outcomes
mRNA	BNT162b2 (Comirnaty) mRNA-1273* (Spikevax)	Yes	Available

Vaccine type	Examples	Recommended in pregnancy	Data on pregnancy outcomes
Viral vector	ChAd-Ox1/nCov-19 (Vaxzevria) Ad26.COV2-S* (Janssen COVID-19 Vaccine Suspension for Injection) Ad5-nCoV-S (Convidecia)	Not contraindicated[201]	Limited
		Limited safety data	
Inactivated	COVID-19 Vaccine (Vero Cell), Inactivated (Coronavac) COVID-19 Vaccine* (Vero Cell), Inactivated (Covilo)	Not contraindicated	Limited
Protein subunit	NVXCoV2373# (Nuvaxovid, Novavax)	No current recommendation	Not available

**The Product Registration Holder didn't renew or voluntarily terminated the registration in Malaysia at the time of writing (as of June 2024).*

#This product was never registered for use in Malaysia.

mRNA-based vaccines are recommended in pregnancy due to reassuring published data on the safety of these vaccines in pregnancy.[204] (Level II-2) mRNA encoding SARS-CoV-2 spike protein is injected via a lipid nanoparticle coat and results in spike protein production by the host cell, eliciting a protective immune response. The mRNA does not go into the nucleus of the host cell, so it remains separate from the host DNA and is broken down by the host cell within a few days.[205] (Level III)

Viral vector vaccines are modified adenovirus which contain DNA encoding the SARS-CoV-2 spike protein. The vector does not express the spike protein and has been modified so it is unable to

replicate. It merely delivers the spike protein DNA into the host cell, which produces the spike protein, eliciting a protective immune response.[205] (Level III)

Inactivated vaccines are produced through the growth of SARS-CoV-2 in the cell culture, followed by inactivation of the virus.[206] (Level III)

Protein subunit vaccines contain fragments of proteins of SARS-CoV-2 which could elicit an immune response.[207] (Level III)

The following terminology have been used by the CDC to describe the "generation" of vaccines available.[208] (Level III)

Original vaccines

Designed to protect against the original virus that caused COVID-19. According to CDC, these vaccines were no longer available as of April 2023 (BNT162b2, mRNA-1273) and May 2023 (Ad26.COV2.S).[208] (Level III)

2022-2023 Bivalent vaccines (bivalent vaccines)

Designed to protect against both the original virus and Omicron variants BA.4 and BA.5. According to CDC, as of 11th September 2023, the bivalent BNT162b2 and mRNA-1273 COVID-19 vaccines were no longer available.[208] (Level III)

2023-2024 Updated COVID-19 vaccines (updated vaccines)

The updated vaccines more closely targets the XBB lineage of the Omicron variant and could confer protection against severe COVID-19. Three updated vaccines (BNT162b2, mRNA-1273 and NVX-CoV2373) have been recommended by CDC for use.[208] (Level III)

Taking into account that most women would have had at least one prior infection, WHO recommends a simplified single-dose regime

for primary immunisation to improve acceptance and uptake.[209] (Level III)

2.3.3 Immunogenicity and effectiveness

Immunogenicity

Existing evidence demonstrate that mRNA vaccination in pregnancy leads to robust maternal antibody response and anti-SARS-CoV-2 IgG and neutralising antibodies produced are transferred transplacentally. Furthermore, vaccine mRNA products do not cross the placenta at detectable levels.[210] (Level II-2)

COVID-19 vaccine is equally effective in pregnancy compared to the general population. Available evidence suggests that pregnant women who are vaccinated experience a lower incidence of infection, severe illness, hospitalisation, ICU admission, and need for oxygen therapy prior to delivery when compared to unvaccinated pregnant women.[211] (Level II-2) A systematic review and meta-analysis also showed a reduction in stillbirths in vaccinated women [OR, 0.73; 95% CI, 0.57-0.94].[212] (Level I)

Long COVID

Women who have completed two doses of vaccination before SARS-CoV-2 infection had lower risks of persistent fatigue (OR, 0.62; 95% CI, 0.41-0.93) and pulmonary disorder (OR, 0.50; 95% CI, 0.47-0.52) compared to those who were unvaccinated.[213] (Level I) A separate meta-analysis found vaccination effective against long COVID in patients either vaccinated before SARS-CoV-2 infection/COVID-19 (RR = 0.82, 95% CI: 0.74-0.91, $p < 0.01$) or vaccinated after SARS-CoV-2 infection/COVID-19 (RR = 0.83, 95% CI: 0.74-0.92, $p < 0.01$). The risk of cognitive dysfunction/symptoms, kidney diseases/problems, myalgia, and sleeping disorders/problems were reduced compared to the unvaccinated group, although the mechanism remains uncertain.[214] (Level I)

2.3.4 Vaccine safety

There is no evidence of clinically relevant levels of transplacental transfer of mRNA vaccine products.[210 (Level II-2)]

Injection site and non-specific adverse effects

The Canadian National Vaccine Safety (CANVAS) Network found lower rates of self-reported significant adverse events in pregnant women given mRNA vaccines (BNT162b2 and mRNA-1273) compared with non-pregnant women.[215 (Level II-2)]

A significant adverse event was defined in the study as a new or worsening health event sufficient to cause work or school absenteeism, medical consultation or prevent daily health activities in the previous seven days following vaccination.[215 (Level II-2)]

Overall, 4.0% (226/5,597) of pregnant women reported a significant adverse event following immunisation (AEFI) after dose one and 7.3% (227/3,108) after dose two, compared with 6.3% (10,950/174,765) and 11.3% (10,254/91,131) in non-pregnant women of reproductive age. Malaise or myalgia were the most frequently reported significant health events within seven days of each vaccine, 2.9% (64/2183) for dose one of mRNA-1273 and 11.4% (139/1216) for dose two of mRNA-1273.[215 (Level II-2)]

Injection site reactions such as redness, pain, or swelling were reported in 75.6% (1430/1892) for dose two of BNT162b2 and 86.3% (1884/2183) for dose one of mRNA-1273 vaccine recipients.[215 (Level II-2)] In a prospective study evaluating immunogenicity and reactogenicity of BNT162b2, mRNA-1273 and ChAd-Ox1/nCoV-19, tiredness and chills were also less commonly seen in pregnant vis-a-vis non-pregnant women (p=0.043 and p=0.029 respectively) after dose one. “Feeling generally unwell” was also less commonly reported in pregnant women after dose two (p=0.046).[216 (Level II-2)] Overall, significant AEFI

were consistently lower among pregnant women across all mRNA vaccine types and doses, compared to vaccinated non-pregnant women.[215 (Level II-2)]

Obstetric adverse events

Data from CANVAS showed that compared to unvaccinated women, miscarriage or stillbirth rates were not increased after one dose of mRNA vaccine [1.5%(83/5597) vs 2.1%(7/339)].[215 (Level II-2)] Two controlled studies in pregnant women did not report any increase in spontaneous miscarriage or induced abortion, congenital malformation, small for gestational age, preterm birth, stillbirth, preeclampsia or postpartum hemorrhage.[217 (Level II-2), 218 (Level II-2)] In both studies, mRNA vaccines were used.

Myocarditis

In women of reproductive age, the potential risk of mRNA vaccine-associated myocarditis is approximately five per million vaccinations (after the second dose) for women aged 18 to 25 years and two per million vaccinations for women aged 25 to 40 years.[202 (Level III)] To put things in perspective, the risk of myocarditis or cardiac complications after SARS-CoV-2 infection is at least six to seven-fold higher than after mRNA COVID-19 vaccination.[219 (Level II-3)]

There has been no reported cases of vaccine-associated myocarditis in pregnancy to date.[220 (Level III)]

Vaccine-induced immune thrombocytopenic thrombosis

Vaccine-induced thrombosis and thrombocytopenia (VITT) is a rare, idiosyncratic reaction which has been reported with viral vector vaccines (ChAd-Ox1/nCov-19 and Ad26.COV2.S). It is not associated with traditional thromboembolism risk factors and were largely reported in younger patients occurring within the first three

weeks of vaccination.[203 (Level III)] There is no evidence that pregnant or postpartum women are at higher risk of VITT than age-matched non-pregnant women. Some authorities have, however, advised that those younger than 40 years, should be offered an alternative to viral vector vaccines.[205 (Level III), 221 (Level III)] Due to its larger existing evidence base, pregnant women are recommended to receive mRNA-based vaccines.[203 (Level III)]

Guillain-Barré Syndrome

A retrospective cohort study reported 3.29 cases per 1,000,000 doses of Ad26.COV2.S up to 21 days after vaccination.[222 (Level II-2)] In comparison, the risk of Guillain-Barré syndrome after COVID-19 infection was six-fold higher.[223 (Level II-2)] There were no increase in reported cases of Guillain-Barré syndrome with mRNA-based vaccines compared to the background incidence.[222 (Level II-2)]

Fertility

There is no evidence that COVID-19 mRNA vaccines affect male or female fertility. No reduction in sperm concentration, semen volume and sperm motility has been shown with both BNT162b2 and mRNA-1273 vaccination.[224 (Level II-1), 225 (Level II-1)] Assessment of follicular steroidogenesis and oocyte quality did not exhibit any measurable differences when compared to unvaccinated women. IVF treatment parameters such as number of oocytes and mature oocytes retrieved, fertilisation rate and ratio of top-quality embryos per fertilised oocyte did not differ between pre and post-BNT162b2 groups.[226 (Level II-3)]

Menstrual irregularities

Menstrual disorders are exceedingly common in general practice and can arise from various causes, including gynaecological, endocrinological, nutritional factors, pandemic-related stress or even COVID-19 itself.[227] (Level III)

Heavy or irregular menstrual bleeding has been reported following any BNT162b2 vaccination, although most cases were reported as self-limiting.[228] (Level III)

The exact mechanism causing menstrual irregularity is uncertain.[229] (Level II-2)

NPRA of the Ministry of Health Malaysia issued a safety alert on this on 2nd May 2023.[228] (Level III)

This particular side effect is limited to the original BNT162b2 and there are no reports of it occurring with the bivalent vaccine at the time of writing.[228] (Level III)

2.3.5 Timing and schedule

COVID-19 vaccine is safe at any gestation, although it is best administered beyond 12 weeks of gestation.[203] (Level III)

WHO recommends that pregnant women receive an additional dose of COVID-19 vaccine in each pregnancy, regardless of vaccination status. It recommends that vaccination is given during the mid-second trimester, or at any opportunity.[230] (Level III)

The Australian Technical Advisory Group on Immunization (ATAGI), however, does not recommend routine booster in pregnancy, although states that it can be considered based on an individual risk-benefit assessment.[231] (Level III)

The CDC suggests that delaying vaccination by three months after a previous infection can be considered.[208] (Level III)

Additional dose of COVID-19 vaccine should be considered in every pregnancy regardless of vaccination status, preferably beyond 12 weeks of gestation.

2.3.6 Contraindications

History of severe allergic reactions/anaphylaxis to any of the ingredients of the COVID-19 vaccine. Women with fever over 38.5°C on the day of vaccination should delay their vaccination until fever subsides.[232]

2.3.7. Special Circumstances

Moderate and severely immunocompromised persons (ICP) are not only at greater risk of severe COVID-19 but also have lower vaccine immunogenicity and effectiveness. The WHO SAGE Roadmap suggests that additional boosters be considered at intervals of six months, although this advice is not specific to ICP in pregnancy.[230] (Level III)

The CDC recommends three doses of the updated COVID-19 vaccine in unvaccinated women, two doses for those with one previous BNT162b2 or mRNA-1273 vaccine and one dose for women with two previous BNT162b2 or mRNA-1273 vaccine. There is no specific recommendation about booster doses in ICP, but women are encouraged to discuss it with their healthcare providers.[233] (Level III)

2.4 Respiratory Syncytial Virus (RSV)

RECOMMENDATION 4

Currently, there is a highly efficacious vaccine yet to be available for pregnant women in Malaysia. When available, it is recommended to be given between 32–36 weeks of pregnancy.

2.4.1 Introduction

RSV is becoming a more significant common virus and is known to infect adults and children worldwide.[234] It is a single stranded RNA virus belonging to the Paramyxoviridae family. There is only one serotype of this virus, but it is classified into 2 strains "A" and "B".".[235] The difference between the 2 strains is variation in the structure of the membrane proteins especially the attachment protein.[235]

It is widely distributed in humans and because of the lack of long-term immunity, reinfection can occur frequently.[236 (Level II-2)] It affects children mainly under 2 years of age although it does affect older children and adults.[236 (Level II-2)] The disease has an incubation period of 2–8 days and is mainly a respiratory tract infection.[236 (Level II-2)] It is usually a mild upper respiratory tract infection, but in children under 1 year of age, it can affect the lower respiratory tract, leading to bronchiolitis.[236 (Level II-2)] The disease differs in the area studied and the ability to diagnose using rapid antigen testing or PCR.[236 (Level II-2)]

In the largest multicentric trial (RESCEU) with almost 10,000 infants followed for 1 year, it was found that 57.9 % of RSV hospitalisations occurred in infants less than 3 months of age.[237 (Level II-2)] About 50% of all respiratory tract infections were associated with RSV.[238] Mortality from a birth cohort study was 6.9 per 1 million births and highest amongst premature babies less than 29 weeks gestation.[239] In adults more than 60 years of age in a retrospective study, the mortality was 5.6%.[240 (Level II-2)] In Malaysia, the largest retrospective study of 23,000

cases from different states and laboratories between 2015-2019 revealed an RSV positivity rate of 15.9 % and hospitalisation rates of 42.3% in infants less than 1 year of age and 42.2 % in children 1–2 years old.[241] (Level II-2)

2.4.2 Available vaccines

There is currently only one vaccine for maternal immunisation for RSV approved by the Food and Drug Administration (FDA) of the USA.[242] The bivalent RSV prefusion F protein–based (RSVpreF) vaccine is supplied as a vial of Lyophilized Antigen Component that is reconstituted at the time of use with a Sterile Water Diluent Component and given intramuscularly. The antigen component contains recombinant RSV preF (fusion) A and RSV preF B.[243]

The RSV preF A and RSV preF B recombinant proteins are expressed in genetically engineered Chinese Hamster Ovary cell lines grown in suspension culture using chemically defined media, without antibiotics or animal-derived components. The recombinant proteins are purified through a series of column chromatography and filtration steps followed by formulation, filling into vials, and lyophilization.[243]

After reconstitution, each dose of the vaccine is approximately 0.5 mL. The vaccine is formulated to contain 120 mcg of RSV stabilized prefusion F proteins (60 mcg RSV preF A and 60 mcg RSV preF B) per 0.5 mL. This vaccine also contains the following buffer ingredients: 0.11 mg tromethamine, 1.04 mg tromethamine hydrochloride, 11.3 mg sucrose, 22.5 mg mannitol, 0.08 mg polysorbate 80, and 1.1 mg sodium chloride per 0.5 mL. It is a sterile, clear, and colourless solution.[243]

This vaccine contains no preservatives. Each dose may also contain residual amounts of host cell proteins (≤0.1% w/w) and DNA (<0.4 ng/mg of total protein) from the manufacturing process.[243]

2.4.3 Immunogenicity and Effectiveness

The MATISSE trial is a phase 3, double-blind trial which was conducted in 18 countries in pregnant women from 24–36 weeks gestation who received a single intramuscular dose of 120 μg of a bivalent RSV preF protein-based vaccine or placebo. Overall, 3682 maternal participants received vaccine and 3676 received placebo; 3570 and 3558 infants were evaluated. The vaccine efficacy against severe lower respiratory tract illness was 81.8%; 99.5% CI 40.6–96.3 within 90 days.[244 (Level I)]

At 180 days after birth, vaccine efficacy was 69.4%; 97.5% CI 44.3-84.1. This met the statistical criterion for success up to 180 days.[244 (Level I)]

Regarding medically attended RSV- associated lower respiratory illness occurring within 90 days of birth, the vaccine efficacy results did not meet statistical success criterion.[244 (Level I)]

2.4.4 Vaccine safety

The side effects most commonly reported by pregnant mothers who have received the vaccine are similar to that of other vaccines, i.e., pain at the injection site, headache, muscle pain and nausea. [244,245 (Level I)]

In the prescribing information with this vaccine, there is a warning about an imbalance in preterm births in such recipients (5.7%) versus placebo (4.7%) mainly in participants from low- middle income countries.[243] Most of the infants who were born premature were between 34 and 37 weeks.[244 (Level I)] Furthermore, most of the preterm births discrepancy in delivery was more than 30 days from the vaccination (137 cases administered the vaccine vs 111 administered placebo).[245 (Level I)] The available data are insufficient to establish or exclude a causal relationship between vaccination and preterm birth so further study is to be conducted regarding this matter.

In the safety studies, low birth weight as well as jaundice occurred at a higher rate in infants born to vaccine recipients compared to placebo (5.4% vs 4.4% for low birth weight and 7.2% vs 6.7% for jaundice).[243]

2.4.5 Contraindications

This vaccine should not be administered to any individuals with a history of severe allergic reaction, i.e., anaphylaxis, to any of its components.[243]

2.4.6 Timing and schedule

Although the phase 3 trial (MATISSE) recruited participants to receive the vaccine between 24 and 36 weeks of gestation due to the caution on the probability of preterm labour, it is recommended to administer the vaccine between 32 to 36 weeks of gestation for pregnant women.[243, 244 (Level I)] It is not known if the vaccine is excreted in human milk, however it is known that RSV antibodies are transferred through breast milk following maternal infection and do confer protection. Therefore, breast feeding should be encouraged in vaccine recipients.[243]

2.4.7 Special Circumstances

As all women with pre-existing conditions were not included in this study there is no information available.[244 (Level I)] However, immunocompromised individuals, including those receiving immunosuppressive therapy, may have diminished immune response.[243]

2.5 Co-administration of vaccine

2.5.1 Co-administration of the Tdap vaccine with influenza vaccine

Tdap vaccine can be administered with influenza vaccine during pregnancy, at the same visit. It is important to use a separate syringe for each vaccine and each injection must be given at a different anatomical site.[246] (Level III)

In a retrospective study by Sukumaran et al., concomitant administration of Tdap and influenza vaccine during pregnancy was not associated with medically attended acute events (fever, any acute reaction) and adverse birth outcomes (preterm delivery, low birth weight, small for gestational age).[247] (Level II-2)

The FluMom Study showed that vaccinated mothers with inactivated influenza vaccine and pertussis did not have an elevated risk of an adverse birth outcome (preterm birth, low birth weight at term or small for gestational age) compared with unvaccinated mother.[248] (Level II-2)

2.5.2. Co-administration of the Tdap vaccine with COVID-19 vaccine

The CDC states that there is no contraindication in co-administration of Tdap with COVID-19 vaccines,[249] One study which looked at anti-spike IgG after administration of COVID-19 vaccine and Tdap within two weeks of each other did not find any significant differences in maternal SARS-CoV-2 antibody levels at delivery. However, it did not specifically study co-administration of both vaccines.[250] (Level II-2)

A case report of co-administration of BNT162b2 mRNA vaccine and Tdap vaccine in a non-pregnant Asian woman of reproductive age, demonstrated a delay in the development of SARS-CoV-2 Spike (S1)

antibodies. Antibody levels were absent at 6 weeks but present only 8 weeks after the second dose. The immunoassay for diphtheria and tetanus antitoxoids revealed protective post-vaccination antibody levels.[251] (Level II-3)

In the absence of additional data and outside the setting of a pandemic, an interval of 14 days between COVID-19 vaccination and Tdap is suggested.

2.5.3 Co-administration of the Tdap vaccine with RSV vaccine

The implications of co-administration on infant protection is not known. However, for Tdap the umbilical cord antibody concentrations are shown to be higher in newborns immunised between 27 and 30+6 weeks, compared to later in pregnancy. Therefore, Tdap can be given earlier followed by RSV vaccine at 32–36 weeks.[252] (Level III) Current recommendations indicate that co-administration of Tdap and RSV is safe and well-tolerated.[252] (Level III)

2.5.4 Co-administration of the influenza vaccine with COVID-19 vaccine

From a practical perspective, co-administration of COVID-19 vaccine with influenza vaccine did not result in higher systemic reactions compared to administration of COVID-19 vaccines alone.[253] (Level II-2) Immunogenicity analysis measuring IgG spike protein post-vaccination found that co-administration resulted in a slightly lower geometric mean titre of 0.84 (95% CI, 0.69-1.04) than in the COVID-19 alone group, but this was not statistically significant. Furthermore, none of the co-administration group were infected with SARS-CoV-2 up to 60 days post-follow-up.[253] (Level II-2) In this study, the Omicron BA.4/BA.5–adapted bivalent mRNA (BNT162b2) and tetravalent influenza vaccine (2022/2023) were given.[253] (Level II-2)

Co-administration of COVID-19 vaccine and influenza vaccine is acceptable.

2.5.5 Co-administration of the COVID-19 or influenza vaccine with RSV vaccine

For influenza, the data of co-administration regarding immunogenicity and reactivity is limited but supports co-administration. The 2 vaccines must be given in different limbs.[252] (Level III)

There are no data evaluating immunogenicity and reactogenicity of RSV co-administration with COVID-19 vaccines.[252] (Level III)

SECTION 3

VACCINES FOR PREGNANT WOMEN UNDER SPECIAL CIRCUMSTANCES

3.1 Breastfeeding

RECOMMENDATION 5

Except for the yellow fever vaccine, no vaccines are contraindicated in breastfeeding women due to potential risk of acute neurotropic disease in the infant.[262,263] **(Level II-3)**

Rationale

Postpartum vaccination gives women who have not received vaccines during childhood, the pre-pregnancy period and the antenatal period an opportunity to receive them after they have given birth. It enables women who are at risk of severe vaccine-preventable infections to obtain protection as soon as possible.[254] (Level II-3)

Immunology

Postpartum vaccination confers benefits to both mothers and infants. It protects mothers from vaccine-preventable infections. In terms of infant protections, there are two mechanisms. First, sIgA is produced after the administration of certain vaccines, such as Tdap

and influenza, and is transferred to the infants through breast milk.[255] (Level I), 256(Level I) Second, postpartum vaccination decreased the risk of infection in the mothers and, therefore, reduced the transmission of the pathogen to the infants.[257] (Level I) Postpartum vaccination may not be as effective as antenatal vaccination because the mothers and the infants can only gain protection and immunity 2 weeks after the vaccination.[258] (Level III) Nevertheless, as postpartum vaccinations still provide some extent of maternal and infant benefits, it should be offered to a woman during postpartum period if the vaccines are not administered during that pregnancy.

Safety

Inactivated, recombinant, subunit, polysaccharide, conjugate and toxoid vaccines are safe for breastfeeding mothers and their infants.[259] (Level III) For live vaccines, the amount of live viral particles excreted in breast milk is insignificant to cause an infection in the infants except for the yellow fever vaccine (see yellow fever vaccine in **Table 8**).[15] (Level I), 260 (Level I) Therefore, there is no need to delay post-partum vaccination in breastfeeding women who have no immunity to and have risk factors for vaccine-preventable diseases.[254] (Level II-3)

Recommendations of vaccine use in breastfeeding mothers are shown in Table 8.

Table 8: Recommendations of vaccine use in breastfeeding mothers.

Vaccine	Vaccine type	Use in breastfeeding women	Comments
Inactivated influenza	Inactivated	Yes	This vaccine is routinely recommended during each pregnancy and is preferably to be given during the antenatal period.[261] (Level I)
Tdap	Inactivated	Yes	This vaccine is routinely recommended during each pregnancy. Optimal infant protection against tetanus and pertussis is achieved by antenatal vaccination.[261] (Level I) Postpartum women can still receive it although the efficacy of infant protection is reduced.[262] (Level II-2)
Hepatitis A	Inactivated	Yes	Used for women who are at higher risk of severe outcome from hepatitis A infection, such as underlying chronic liver disease, clotting-factor disorders, traveling and working with non-human primates.[261] (Level I)
Hepatitis B	Inactivated	Yes	Used for women who have household contacts or sex partners who are hepatitis B surface antigen-positive; are intravenous drug users; have high-risk sexual behaviour; previous sexually transmitted infection; chronic liver disease; HIV infection; or have travelled to certain endemic countries.[261] (Level I) Can also be used for women who request for protection against hepatitis B.[261] (Level I)

Vaccine	Vaccine type	Use in breastfeeding women	Comments
COVID-19	Inactivated mRNA	Yes	Primary vaccination or booster can be administered if the women have not received it before or during pregnancy.[263] (Level I)
Pneumococcal	Inactivated	Yes	Used for selected women who require protection against pneumococcal infection.[261] (Level I)
Meningococcal conjugate (MenACWY) and Meningococcal serogroup B	Inactivated	Yes	Used for selected women with certain medical or immunocompromised conditions.[261] (Level I)
Human papillomavirus (HPV)	Inactivated	Yes	Used for postpartum women who have no prior HPV vaccination.[261] (Level I) Use in pregnancy is not recommended.[261] (Level I)
Measles-mumps-rubella (MMR)	Live	Yes	Used for women who have no immunity to rubella.[261] (Level I) Transmission of the rubella vaccine virus to breastfed infants through breast milk rarely happens. Even if it occurs, symptoms in the infants are either absent or mild.[264] (Level II-1), 265 (Level II-3), 266 (Level II-3)

Vaccine	Vaccine type	Use in breastfeeding women	Comments
Varicella	Live	Yes	Recommended for varicella-seronegative women.[261] (Level I) Varicella-zoster vaccine virus has not been detected in the breast milk samples of lactating women who have received varicella vaccines, and no adverse effects on breastfed infants have been reported.[267] (Level II-1)
Yellow fever	Live	No	Avoid this vaccine in lactating women due to the potential risk of acute neurotropic disease in the infants.[268] (Level II-3), [269] (Level II-3)
Monkeypox	Live	Yes	Women can receive this vaccine after a significant exposure to monkeypox virus.[270] (Level I), [271] (Level I)

3.2 Immunosuppressed

Pregnant women are considered as immunosuppressed when they have autoimmune diseases; are receiving immunosuppressive treatment such as corticosteroids or disease-modifying anti-rheumatic drugs (DMARDs); have undergone solid organ transplant or haematopoietic stem cell transplant, have functional or anatomical asplenia; have malignancy; are receiving chemotherapy or radiotherapy; and have HIV.[272] (Level I)

While inactivated vaccines are not contraindicated in immunosuppressed women, they should avoid live vaccines not only because they are contraindicated in pregnancy but also because they can cause vaccine-related infections.[272 (Level I)]

Immunocompromised women should receive the recommended vaccines before and during pregnancy as shown in Table 9.[261(Level I), 272 (Level I)] Table 9 also shows additional vaccines that are required for specific types of immunocompromised conditions.

Table 9: Recommendations of vaccine use in immunosuppressed mothers

Immunocompromised condition	Recommended vaccines before pregnancy	Recommended vaccines during pregnancy
All	HPV*, recombinant zoster^, COVID-19#	Inactivated influenza, Tdap
HIV	Pneumococcal#, meningococcal#, hepatitis B#	
Asplenia	Pneumococcal#, meningococcal#, haemophilus influenzae type b (Hib)#	
Women who receive renal dialysis	Hepatitis B#	
Liver transplant	Hepatitis A#	
Haematopoietic stem cell transplant	Meningococcal#, hepatitis B#	

*The vaccine is not recommended in pregnancy; however, inadvertent vaccination during pregnancy is not a reason to terminate pregnancy because it does not appear to have any harmful effects on foetuses.

^The vaccine could not be recommended in pregnancy as its safety data in pregnancy is not available.

#The vaccine can be given during pregnancy if the women have never received it before pregnancy or the next vaccine is due.

Pregnant women with cancer who have severe neutropenia (absolute neutrophil count <0.5 × 109/L) should not receive any vaccines, to avoid an acute febrile episode.[272] (Level I)

For pregnant women who received biologic DMARDs during pregnancy in the third trimester, live vaccines, such as BCG vaccine and rotavirus vaccine, should be deferred in their infants for 6 months.[272] (Level I) Otherwise, the infants should receive inactivated vaccines according to the recommended schedule.[272] (Level I)

3.3 Travellers

Overseas travel exposes pregnant women to the risk of acquiring vaccine preventable infectious diseases. As travel vaccines are not routinely recommended in pregnancy, pregnant women should be advised against travelling abroad. If the travel is unavoidable, discuss with the woman the risks and benefits of travel vaccines (Table 10) and other strategies to reduce the risk of acquiring infections.

Table 10: Recommendations of travel vaccine-use in pregnant mothers

Vaccine	Use in pregnancy
Meningococcal	Limited data on the vaccine safety in pregnancy.[22] (Level I) Benefits of protection outweigh risks.[22] (Level I), 273 (Level I) This vaccine is mandatory for pilgrims travelling for the Hajj in Saudi Arabia.[274]
Cholera	Not necessary if pregnant travellers can avoid contaminated food and water.[275] (Level I) Endemic area: South and Southeast Asia, and Africa.[275] (Level I)

Vaccine	Use in pregnancy
Hepatitis A	Benefits of protection outweigh risks.[273] (Level I) Endemic area: Parts of Africa and Asia, Central and South America[276] (Level I)
Japanese encephalitis (JE) - inactivated	Benefits outweigh risks.[22] (Level I), 273 (Level I) Staying at least a month in Asia, Papua New Guinea.[277] (Level I)
Rabies	Benefits of protection outweigh risks[22] (Level I), 278 (Level I) Use when the likelihood of exposure to rabid animals, such as stray dogs, stray cats, monkeys and bats, is high and access to health care to obtain post-exposure prophylaxis is difficult.[22] (Level I), 278 (Level I) Limited data suggests that the rabies vaccination during pregnancy is unlikely to cause harm to the fetus.[279] (Level II-3), 280 (Level II-3)
Tick-borne encephalitis (TBE)	Safe in pregnancy.[281] (Level II-3), 282 (Level II-3) Use in travellers who hike or camp in forests in Central and northern Europe and northern Asia.[283]
Typhoid (typhoid Vi polysaccharide vaccine)	Safe in pregnancy [22] (Level I) Endemic area: Countries with poor water quality and sanitation, including the Indian subcontinent, most Southeast Asian countries and Papua New Guinea.[284]

Vaccine	Use in pregnancy
Yellow fever	Benefits of protection outweigh risks. Although it is a live attenuated vaccine, the risk to fetus is very low.[285] (Level I) Endemic Area: Tropical and subtropical regions of Africa and South America, and where exposure to mosquitoes is unavoidable.[285] (Level I)

3.4 High-risk occupations

3.4.1 Working with non-human primates

Pregnant women working as primatologist, zoologist and related fields; or who deal with non-human primates, i.e., monkeys, apes, lemurs etc., are susceptible to Q fever, rabies and influenza.[286] (Level I)

The Q fever vaccine should be avoided in pregnancy as there are no studies of the vaccine in pregnancy.[287] (Level I) Vaccination against the rest of the infections during pregnancy may be considered for the non-immune pregnant women if the benefits outweigh the risks.[22] (Level I), 278 (Level I), 288 (Level II-1), 289 (Level II-1), 290 (Level II-2)

Recommendations for vaccines are as shown in Table 11.

Table 11: Recommendations of vaccine use in mothers who work with non-human primates

Vaccine	Use before pregnancy	Use during pregnancy
Q fever	Yes	No[22] (Level I)
Rabies	Yes	Benefits outweigh risks[22] (Level I)
Influenza	Yes	Yes*[22] (Level I), 261 (Level I)

*Influenza vaccine in an inactivated form is routinely recommended in every pregnancy.

3.4.2 Working with pathogens

Pregnant women who work in a laboratory may be exposed to specific pathogens, namely *Bacillus anthracis; Corynebacterium diphtheriae; Coxiella burnetii;* JE virus; lyssaviruses; *Neisseria meningitidis;* poliovirus*; Salmonella typhi;* and yellow fever virus.

Therefore, it is not advisable for pregnant women to work in these areas as vaccines against these pathogens are not recommended in pregnancy, except for Tdap vaccine which protects against infection by *Corynebacterium diphtheriae*.[22 (Level I), 261 (Level I)]

3.5 High-risk lifestyle

3.5.1 High risk sexual behaviour

Pregnant women who have high-risk sexual behaviour for example unprotected sex with multiple partners; high risk sexual activities (i.e. unprotected anal sex) etc. are at risk of sexually-transmitted infections (STIs). Some STIs are vaccine preventable, such as hepatitis B and HPV, and vaccination against these infections should be discussed with them (see Table 12).

Table 12: Recommendations of vaccine use in pregnant women who have high-risk sexual behaviour[22 (Level I), 261(Level I)]

Vaccine	Use before pregnancy	Use during pregnancy
Hepatitis A	Yes	Yes*
Hepatitis B	Yes	Yes*^
HPV	Yes	No#

*The vaccine can be given during pregnancy if the women have never received it before pregnancy or the next vaccine is due.

^Avoid recombinant vaccine due to the lack of safety data in pregnancy.[273 (Level I)]

#The HPV vaccine is not recommended in pregnancy; however, inadvertent vaccination during pregnancy is not a reason to terminate pregnancy because it does not appear to have any harmful effects on foetuses. Postpartum vaccination is recommended.

3.5.2 People who use drugs (PWUD) and People who inject drugs (PWID)

Pregnant women who use drugs and who inject drugs are at considerable risk of contracting Hepatitis B and C infection. Both PWUD and PWID may be engaged in risky sexual behaviour and other activities which exposes them to these infections. Additionally, PWID may acquire infections through needle sharing and other drug preparation equipment e.g. sharing cotton wool, which exposes them to bodily fluid from other infected people.[291] (Level I) While Hepatitis A can affect anyone, PWUD and PWID are at greater risk of being infected and recommended to vaccinate during pregnancy.[261] (Level I)

Recommendations of vaccine use in pregnant women who use drugs and who inject drugs are shown in Table 13.

Table 13: Recommendations of vaccine use in pregnant women who use drugs and who inject drugs[22] (Level I), [261] (Level I)

Vaccine	Use before pregnancy	Use during pregnancy
Hepatitis A	Yes	Yes*
Hepatitis B	Yes	Yes*^

*The vaccine can be given during pregnancy if the women have never received it before pregnancy or the next vaccine is due.

^Avoid recombinant vaccine due to the lack of safety data in pregnancy.[22] (Level I)

SECTION 4

VACCINES UNDER DEVELOPMENT

4.1 Group B Streptococcus (GBS)

GBS is a common bacterium found in the vagina and rectum.[292]

It is a common cause of sepsis and meningitis in babies till 89 days of age[293] (Level I). Infection can occur, from the mother during vaginal delivery, or from ascending infection from intraamniotic infection which might lead to preterm labour, uterine sepsis, and stillbirth.[294] (Level II-2)

Intrapartum antibiotics can prevent 80% of early onset disease in babies (0–6days) but not the late onset variety (7–89 days).[295, 296, 297] (Level I)

This forms the basis of developing a vaccine to prevent both varieties of the disease as well as prevent antimicrobial resistance with antibiotic use.

GBS expresses capsular polysaccharides (CPSs), which give it its virulence.[298] (Level II-2) Although 10 CPSs serotypes have been found, 6 of them are responsible for 98% of the disease.[297] (Level I)

Such a vaccine has been developed called GBS6 and its safety, in non-pregnant women and men, has been reported.[297] (Level I)

A phase-2 placebo-controlled trial involving pregnant women is currently ongoing with 3 different doses, with or without aluminium phosphate.[297] (Level I)

The results are promising, showing that the antibodies developed were transferred to the infants associated, with a reduced risk of invasive GBS.[297] (Level I)

There are no licensed vaccines to date for GBS.

4.2 Cytomegalovirus (CMV)

Infection with CMV (DNA virus of the herpes family)[299] (Level II-2) is very prevalent worldwide and can cause severe disease in immunocompromised adults and congenitally infected infants.[300] Congenital CMV is a serious disease with lifelong sequelae.[301]

CMV infection generally causes minimal or no symptoms in non-immunocompromised individuals but can cause serious illness in immunosuppressed individuals.[299] (Level II-2) There are 3 types of infection: primary; reactivation of latent virus; and contamination with a new strain.[299] (Level II-2) All 3 types of infection lead to vertical transmission (to the fetus).[299] (Level II-2)

Vaccines are currently under development for the various groups, including pregnant mothers. The first CMV vaccine tested is comprised of gB, one of the glycoproteins responsible for viral entry into cells upon infection.[302] (Level III) It has reached phase 2 trials in non-pregnant women and girls and has an efficacy of about 50%.[303] It did not progress to phase 3 trials.[302] (Level III)

Recently, a vaccine with a pentamer complex (6 mRNA -mRNA -1647) encoding 2 proteins located on the surface of CMV and one MRNA encoding the full length gB fraction has been developed. It

is still undergoing testing in women ages 18–40 years for safety and efficacy. The phase 2 trials show good efficacy.[304 (Level I)]

There is no current efficacy and safety studies done in pregnant women to date.

4.3 Malaria

Malaria is an important parasitic infection in pregnant women and globally in 2020 there were an estimated 241 million malaria cases in 85 malaria endemic countries, with 627,000 deaths due to this condition.[305 (Level III)]

Malaria during pregnancy continues to be a major cause of maternal and fetal morbidity and mortality in endemic areas.[306 (Level III)] This is the rationale for developing vaccines against malaria.

The first malaria vaccine developed is the RTS, S/AS01. It has been used in children and has been shown to have an efficacy of about 31%.[307 (Level I)]

The second vaccine, the R21/Matrix-M is more effective.[308 (Level I)] It has been approved by WHO for children because of its efficacy and safety.[309]

Neither of these vaccines has been tested in pregnant mothers.

4.4 Zika Virus

Zika virus is an RNA flavivirus transmitted mainly by the Aedes Aegypti mosquito.[310 (Level II-2)] Many of them who are infected with the virus are asymptomatic.[310 (Level II-2)]

In pregnant women, maternal-fetal transmission can occur in all trimesters, whether symptomatic or asymptomatic. Fetal infection can cause congenital microcephaly and fetal loss.[310] (Level II-2)

If the infected mother is symptomatic, treatment is supportive, with rest and hydration.[311] (Level III)

There were two randomised, placebo-controlled phase 1 trials of vaccines namely mRNA- 1325 and mRNA 1893. The mRNA -1893 vaccine was well tolerated and had a robust immune response.[312] (Level I)

There are no vaccines available to date for pregnant women.

SECTION 5

RECOMMENDED VACCINES BEFORE CONCEPTION

5.1 Vaccination for women who are planning pregnancy:

A pre-pregnancy health check provides an excellent opportunity to screen the immunisation status of women planning a pregnancy. If they are at risk of vaccine-preventable infections, vaccination is recommended before embarking on pregnancy to ensure protection against these infections.

The principles of vaccination for this group of women include assessing their previous history of vaccination and infection; arranging relevant serological testing if their vaccination history or infection is uncertain; offering vaccination if they have no immunity against any vaccine-preventable infections; and advising them to avoid pregnancy within 28 days of vaccination if they receive a live vaccine.[313,261,22,314 (Level I)]

CDC 2024 does not recommend MPOX vaccine for all adults, but only those with increased risk for or severe outcomes from disease.[315]

Table 14: Recommended vaccines for women who are planning pregnancy.

Vaccine	Vaccine type & schedule	Who should receive	Rationale	Precaution
Hepatitis B	Inactivated 3 Doses 0,1- and 6-months interval	Women with risk factors of hepatitis B infection and no immunity to hepatitis B (anti-HBs-negative).	To prevent vertical transmission of hepatitis B virus from high-risk mothers to their infants.[316] (Level I)	No precaution. If a woman is pregnant before completing the vaccine series, hepatitis B vaccination can be continued during pregnancy[314] (Level I) unless the woman receives Heplisav-B.[317] (Level I)
Measles, mumps, rubella (MMR)	Live-attenuated 2 Doses 0,1-month interval	Women who have no previous infection and with negative serology for MMR viruses.	To reduce the risk of congenital infection that can lead to fetal anomalies, miscarriage, neonatal morbidities and stillbirth.[318]	Avoid pregnancy for 28 days after receiving the vaccines.[22, 314, 273] (Level I) Routine pregnancy testing before vaccination is not recommended.[273] (Level I) Inadvertent MMR vaccination during pregnancy or a pregnancy occurs within 4 weeks after MMR vaccination should not be considered a reason to terminate pregnancy[319] (Level III) because it has not been associated with congenital rubella syndrome.[261] (Level I)

Vaccine	Vaccine type & schedule	Who should receive	Rationale	Precaution
Varicella (chickenpox)	Live-attenuated 2 doses 0, 1 to 2-months interval	Women who have no previous varicella infection and with negative serology for varicella zoster virus.	To prevent varicella infection during pregnancy which can lead to severe maternal respiratory compromise, fetal varicella syndrome (FVS) and severe neonatal varicella disease.[320] (Level III)	Avoid pregnancy for 28 days after vaccination.[22, 314] (Level I) Routine pregnancy testing before varicella vaccination is not recommended.[273] (Level I) If a pregnant woman is inadvertently vaccinated or becomes pregnant within 4 weeks after varicella vaccination, it should not be considered a reason to terminate pregnancy.[321] (Level I) The VARIVAX® Pregnancy Registry has not found any cases of FVS in women who received varicella vaccine inadvertently while pregnant.[322] (Level II)

SECTION 6

CHALLENGES & OPPORTUNITIES IN VACCINE ADVOCACY

6.1 Promoting Vaccine Acceptance and Addressing Hesitancy

6.1.1 Introduction

Maternal immunisation, particularly the ATT vaccination provided in Malaysian government health clinics, is generally well accepted among pregnant women. A survey of 394 women of childbearing age (20–45 years old) in Malaysia showed that 69.8% believe vaccination during pregnancy is safe.[323] Among respondents who have been pregnant at least once, the majority (82.4%) received vaccination during pregnancy. The most common vaccine they received was the ATT (75.7%), followed by the COVID-19 vaccination (47.9%). Nonetheless, the survey also showed that very few of them received the maternal Tdap (15.4%) and influenza vaccination (10.0%). The main reasons for not receiving maternal vaccination during pregnancy are related to complacency, i.e., don't know they need it, followed by vaccination confidence, i.e., safety to baby and convenience, i.e., availability at clinic.[323]

Vaccine hesitancy refers to delay in acceptance or refusal of vaccination despite availability of vaccination services.[324] Vaccine hesitancy exists on a continuum ranging from full acceptance and trust in vaccines on one end to complete refusal and distrust on the other end. In between, there are varying degrees of hesitancy, delay, and concerns about vaccines (see Figure 9).[325] Vaccine hesitancy and refusal pose substantial obstacles to achieving optimal vaccination coverage.

Vaccine hesitancy among pregnant individuals presents a distinct challenge because a pregnant woman may approach vaccination concerns from two perspectives: First, as a parent, worried about the vaccine's effects on the well-being of the unborn child; and secondly, as an individual, concerned about how the vaccine may affect her own health.[326] Healthcare professionals play a pivotal role in optimising maternal vaccination coverage and ensuring the health and well-being of both the expectant mother and the unborn child. This chapter provides approaches to healthcare professionals on how to address hesitancy and subsequently increase vaccine acceptance among patients.

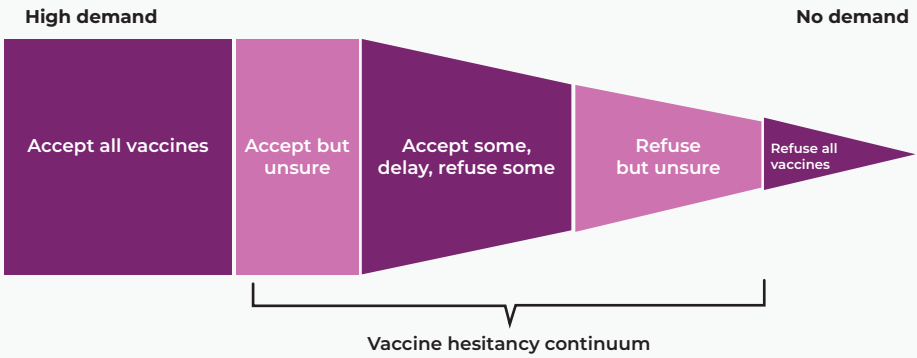


Figure 9 Vaccine Hesitancy continuum

6.1.2 Factors Contributing to Hesitancy and Refusal

Vaccine hesitancy among pregnant women can be attributed to several factors. These include concerns about potential side effects or adverse events following vaccination; a lack of confidence in the safety of vaccines; and a low perception of their risk of infection during pregnancy.[326] Additionally, issues related to the cost of vaccines; spousal hesitation for the pregnant partner to receive the vaccine; a diminished perception of the value of vaccination; and various forms of misinformation and misconceptions about vaccination contribute to hesitancy.[326]

A survey conducted on the issues of vaccine refusal by The Vaccine Policy Collaborative Initiative (VPCI), recruiting members of the American College of Obstetricians and Gynecologists (ACOG), reported that refusal of the influenza vaccine was perceived to be more common among pregnant women than the Tdap vaccine. The common reasons for vaccine refusal among pregnant patients include patients' belief that the influenza vaccine would make them ill (48%); the perception that they were unlikely to contract a vaccine-preventable disease (38%); general concerns about vaccines (32%); a desire to maintain a natural pregnancy (31%); and fears that their child could develop autism due to vaccination during pregnancy (25%).The link of autism to vaccination, with no scientific evidence backings, underscores the significant impact of vaccine safety misinformation.[327]

Addressing these concerns and misconceptions is essential to promote vaccine acceptance among pregnant women.

6.1.3 Tips for clinicians on how to communicate to improve vaccine acceptance

To effectively address vaccine hesitancy and promote vaccine acceptance, particularly concerning maternal immunisation, healthcare professionals must blend clinical knowledge, effective communication, and genuine empathy. Using an effective communication strategy (see Appendix 4) is crucial during consultations.[328]

The Ministry of Health (MOH) provides a guide, on the structured and systematic communication method during consultation regarding immunisation with patients, for healthcare professionals. This guide provides clarity, fosters trust, and facilitates informed decisions with empathy (see Appendix 5).[328]

Healthcare professionals, equipped with a thorough understanding of vaccine hesitancy, should approach consultations with preparedness. Cultivating empathy is essential to avoid making patients feel judged or insulted if they hesitate or refuse vaccines. Emotional readiness for effective communication is crucial for better outcomes and increased vaccine acceptance.[328]

At the beginning of consultations, healthcare professionals should apply the assumptive approach technique, assuming patients are ready for vaccination. Use a positive tone, avoid debates on hesitancy, and refrain from asking about negative perceptions unless raised by patients.[328]

If patients express doubts, concerns, or refuse the vaccine, healthcare professionals should proceed by identifying the reasons and degree of hesitation or refusal. People who exhibit vaccine hesitancy can fall into different categories (see Appendix 6). Understanding these different categories of vaccine hesitancy is essential for healthcare professionals to establish communication objectives and strategies, effectively address concerns and encourage vaccination among patients (see Appendix 7).[328]

To address patient concerns, healthcare professionals should communicate the importance of vaccines by highlighting the benefits of maternal immunisation and underscoring the protective effects to the mother and foetus. Reassuring patients about vaccine safety involves relying on evidence-based data; addressing common FAQs and explaining AEFI; comparing risk of AEFI to the risk of the disease itself; and providing guidance if an AEFI occurs.[328]

From a religious perspective, healthcare professionals should seek accurate information from religious sources, emphasising vaccination alignment with religious beliefs. Debunking misconceptions, ongoing education, and discussions ensure patients receive accurate information, fostering trust in maternal immunisation.[328]

6.1.4 Procedures following consultation should patients remain hesitant to vaccination.

When patients remain hesitant in accepting vaccinations, it's crucial to maintain ongoing dialogue, providing reassurance about the benefits of vaccines during subsequent appointments. Healthcare providers can educate patients about the clinical symptoms of vaccine-preventable diseases, emphasising early warning signs and potential severe complications. Many obstetric providers reported that emphasising the potential harm of the disease to the newborn was an effective approach when discussing vaccination with patients.[329] Besides, sharing relevant educational materials can help patients understand the risks and responsibilities associated with vaccine refusal.[328]

Proper documentation of vaccine refusal and the reasons behind it is essential for medical records. Importantly, healthcare professionals should leave the door open for future opportunities to discuss vaccination, allowing patients to reconsider their choices in the future. Throughout this process, it is crucial to approach these situations with empathy and understanding, respecting the autonomy of patients even when they choose to decline vaccination. Ultimately, the decision lies with the patients, but healthcare providers should continue to provide information and support for the well-being of both the mother and child.[328]

6.1.5 Conclusion

Addressing vaccine hesitancy and refusal in maternal immunisation is crucial for ensuring the health and safety of mothers and their children. Healthcare providers should engage in open and empathetic conversations with patients to understand their concerns and misconceptions, offering structured and systematic communication to provide accurate information. By emphasising the benefits of maternal immunisation and the potential risks of vaccine-preventable diseases, healthcare professionals can foster trust and confidence in vaccines.

Additionally, following up with patients who have received vaccines, gathering feedback, recording side effects or concerns, and preparing reports is essential. Continuously engaging with patients who have declined vaccinations and maintaining open lines of communication is equally important. This comprehensive approach is vital for improving vaccination rates and promoting public health. While vaccine hesitancy and refusal can be challenging, understanding the underlying reasons and addressing them with empathy and evidence can pave the way for better maternal immunisation rates.

6.2 Addressing Vaccine Failure

6.2.1 Introduction

Vaccine failure is defined as the inability of a vaccine to confer immunity or provide expected protection against a specific pathogen. This failure can manifest in various ways, from primary vaccine failure to secondary vaccine failure.[330] It is an important concern in immunisation.

Primary vaccine failure occurs when an organism's immune system does not produce enough antibodies when first vaccinated. In contrast, secondary vaccine failure occurs when enough antibodies are produced immediately after the vaccination, but the levels fall over time.[330] Recognising and delineating these types of vaccine failure is crucial for tailoring vaccination strategies and optimising the effectiveness of immunisation efforts.

6.2.2 Causes of Vaccine Failure

The causes of vaccine failure are multifaceted and can be categorised into host-related, pathogen-related, and vaccine-related factors. Host-related factors include immunodeficiency or immunosuppression and genetic variations impacting immune responses. Pathogen-related factors encompass challenges such

as antigenic variation or mutation in the infectious agent and the emergence of new strains not covered by existing vaccines. Vaccine-related factors, including issues in storage, handling, and suboptimal administration or dosing, contribute to the complexity of vaccine failure.[331]

Ensuring the correct storage and handling of vaccines is crucial in preventing and eliminating numerous vaccine-preventable diseases. Nevertheless, annually, mistakes in storage and handling lead to the need for revaccination in many individuals. Improper storage and handling can diminish vaccine potency, leading to insufficient immune responses in patients and inadequate protection against diseases. Patients may lose trust in vaccines and healthcare providers when revaccination is necessary due to potential compromise of the vaccines they initially received.[62]

6.2.3 Conclusion

The vaccine manufacturers and healthcare providers share the responsibility of ensuring the integrity of the vaccine by maintaining the cold chain from the point of manufacture to the point of use. Failing to observe this can result in vaccine failure, increasing the risk of disease and potentially impacting public health.[62] Active monitoring and participation in reporting systems contribute to a collective understanding of breakthrough infections.[331] Healthcare professionals should also embrace transparency and communicate with the patients about the possibility of vaccine failure and the importance of booster shots to ensure informed decision-making.

Staying informed about ongoing research and advocating for continued advancements will fortify the healthcare professional's capacity to manage vaccine failure effectively. Healthcare professionals, as frontline guardians of public health, are integral to recognising, investigating, and addressing instances of vaccine failure, thus contributing to the overall success of immunisation efforts.

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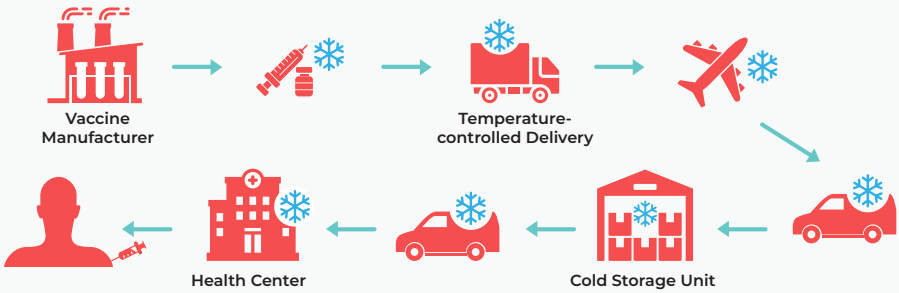
APPENDICES

Appendix 1

The cold chain: The stages of vaccine manufacture, storage, and transport



Appendix 2

Reporting of Side Effects to NPRA

In Malaysia, all new side effects or adverse effects must be reported to the National Pharmaceutical Regulatory Agency (NPRA) under the Ministry of Health Malaysia and will be investigated by the Malaysian Adverse Drug Reaction Advisory Committee (MADRAC).

Link: https://www.npra.gov.my/index.php/en/health-professionals/reporting-adr.html

QR code

Appendix 3

National Immunisation Programme Schedule

Vaksin *Vaccine*	Umur (Bulan)/*Age (Months)*												Tahun/*Year*		
	0	1	2	3	4	5	6	8	9	12	15	18	21	7	13	15
Bacille Calmette-Guerin, BCG (Tuberkulosis/*Tuberculosis*)	Dos 1															
Hepatitis B Monovalen/*Monovalent*	Dos 1															
6-Dalam-1/6-in-1 (Difteria/*Diphtheria*, Tetanus, Polio, Pertussis/Batuk kokol, Hepatitis B *Haemophilus Influenzae* B)			Dos 1	Dos 2		Dos 3						Booster				
Campak (Sabah Sahaja) *Measles (Sabah Only)*							Dos 1									
Campak/*Measles*, Beguk/*Mumps* & Rubella, MMR									Dos 1	Dos 2						
Campak/Measles & Rubella, MR														Booster		
Difteria/Diptheria & Tetanus, DT														Booster		
Human Papillomavirus, HPV (Perempuan Sahaja/*Girls Only*)															Dos 1 Dos 2	
Tetanus																Booster
Japanese Encephalitis, JE (Sarawak Sahaja/*Sarawak Only*)									Dos 1				Dos 2			
Pneumokokal/ *Pneumococcal*					Dos 1		Dos 2				Booster					

Source from Bahagian Pembangunan Kesihatan Keluarga (BPKK) Malaysia 2024.

Appendix 4

Effective Dialogue Strategies for Healthcare Professionals

- **Pay Attention**
  Give your full attention to what the patients are conveying. Identify effective communication methods.

- **Show Genuine Interest in Listening**
  Use body language to demonstrate that you are actively paying attention to them.

- **Provide Feedback**
  It's essential to ask questions to ensure the information heard is accurate. Try to understand by summarising the conversation.

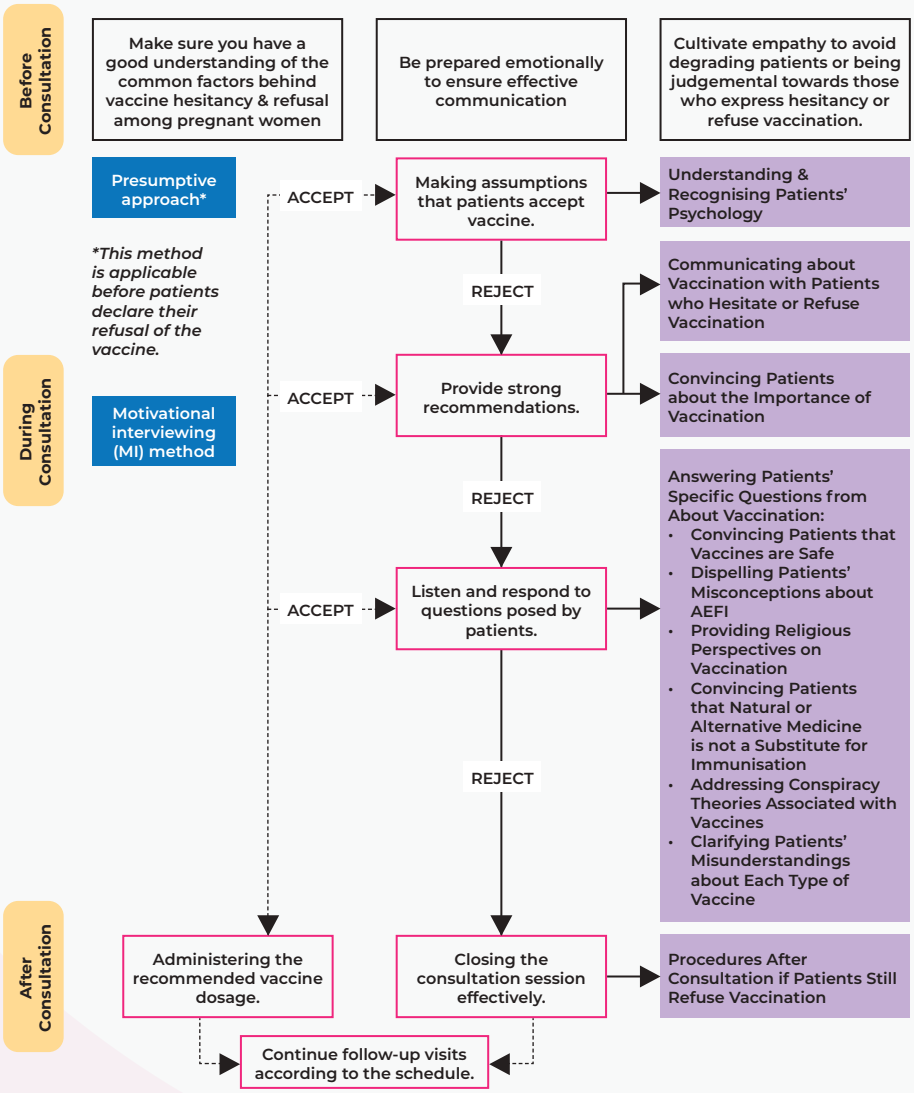
- **Avoid Being Judgmental**
  Evaluate the content of the patients' conversation to rationally understand their stance. Refrain from jumping to conclusions or being overly critical about their moral beliefs or attitudes.

  For instance, using terms like "anti-vaxxer" or labelling them as irresponsible patients should be completely avoided, as it can stir up anger and fill the conversation with negative emotions. This could result in patients becoming disappointed, and the message failing to be conveyed or understood.

- **Respond Respectfully**
  - » Provide feedback that is concise, open, and honest.
  - » Convey opinions in a respectful manner.
  - » Treat parents the way you'd want to be treated.

Appendix 5

Overview of Structured and Systematic Communication Method during Consultation Regarding Immunisation with Patients



This informative chart is adapted from the Ministry of Health (MoH) Vaccine Hesitancy and Resistance (VHR) guidebook. The VHR guidebook can be accessed here link: https://hq.moh.gov.my/bpkk/images/3.Penerbitan/2.Orang_Awam/8.Kesihatan_Kanak_Kanak/2.PDF/22_Buku_Panduan_Menangani_Ibu_Bapa_Yang_Ragu_Atau_Menolak_Vaksin.pdf

While the guidebook predominantly centres around issues and recommendations pertaining to childhood immunisation, the insights and strategies presented within the guidebook extend their relevance beyond childhood immunisation, offering valuable guidance for all healthcare providers (HCPs) interested in effectively addressing Vaccine Hesitancy and Resistance (VHR) within their respective practices.

Appendix 6

Categories of Vaccine Hesitancy

Accept all vaccines	• Eager to be vaccinated • Have faith in vaccine safety • Good relationships with healthcare providers • Limited vaccine knowledge
Accept the vaccine, but unsure of it	• Accept vaccines but have concerns • Neutral relationships with healthcare providers • Open to discussing their worries
Accept/refuse some vaccines or delay	• Have numerous doubts and concerns about benefits and safety of vaccines. • Neutral relationships with healthcare providers • Inclined to engage in discussions about vaccines
Refuse but unsure why	• Refuse vaccines without clear reasons • Seek knowledge to address concerns • Conflicted feelings about about whom to trust for information
Refuse all vaccines	• Reject various types of vaccines • Trust alternative medicine practitioners • May actively support anti-vaccine promotional activities

Appendix 7

Addressing Vaccine Hesitancy among patients.

Category of patients	Communication objective	Communication technique
Accept all the vaccines	Maintaining patients' trust and keeping them positive about their decisions.	• Regularly acknowledge and commend patients for their commitment to vaccination. • Highlight the positive impact of their actions on personal and community health. Reinforce the idea that they are contributing to disease prevention.
Accept the vaccine, but unsure of it	Strengthening their belief that vaccines are safe and effective.	• Provide clear and concise information about the safety and efficacy of vaccines. • Address specific concerns they may have by presenting evidence-based facts. • Offer success stories or testimonials from individuals who had positive vaccination experiences. • Share personal experience of getting the vaccine for yourself or your own family members, if applicable.
Accept/ refuse some vaccines or delay	• Winning hearts and minds of hesitant patients and ensuring that they receive recommended vaccinations.	• Establish a trusting relationship by understanding their specific concerns. • Provide personalised information tailored to address their doubts. • Share success stories of individuals with similar concerns but chose to vaccinate. • Share personal experience of getting the vaccine for yourself or your own family members, if applicable. • Emphasize the benefits of timely and complete immunisation.

Category of patients	Communication objective	Communication technique
Refuse but unsure why	Guiding patients toward considering immunisation.	• Engage in open and non-judgmental conversations. • Identify and address the root causes of their uncertainty. • Provide educational materials and resources to empower them with accurate information. • Offer opportunities for questions and discussions to clarify misconceptions. • Share personal experience of getting the vaccine for yourself or your own family members.

Appendix 8

Patient Education Leaflet

Kindly scan the QR code below to access the patient education leaflet:

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