SLMA GUIDELINES AND INFORMATION ON VACCINES

EIGHTH EDITION

SRI LANKA MEDICAL ASSOCIATION
COLOMBO
2023

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TABLE OF CONTENTS

ANNEXES

INTRODUCTION

We are glad to have completed the eighth edition of the SLMA Guidelines and Information on Vaccines.

The eighth edition has 40 chapters, of which three are new.

They are:

Chapter 6. COVID-19 vaccine by Dr. Rajiva de Silva and Prof. Neelika Malavige

Chapter 25. Other vaccines of interest by Prof. Enoka Corea and Dr. Geethani Galagoda

Chapter 39. Vaccine hesitancy by Dr. H. T. Wickremasinghe

All other chapters have been fully revised.

The new authors of chapters are:

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Dr. Surantha Perera, Consultant Paediatrician, Castle Street Hospital for Women, Colombo

As in all past editions, brand names of vaccines are not mentioned in the chapters, except in the case of COVID-19 vaccines. We decided on this exception, because during the COVID-19 pandemic (2019-2022), healthcare workers and the public identified the vaccines with either their brand names or the manufacturers of these vaccines and the usage of only the generic names in this book may lead to confusion.

Meetings to compose the book commenced on 2nd March 2022.

Meetings were held fortnightly and later weekly at the SLMA.

We sincerely thank the authors of the chapters and the volunteers who formed the Core Review Group. The latter enjoyed the meetings and discussed the chapters with great enthusiasm.

The President and Council and the staff of the SLMA gave us unstinted support. The Chair and members of the SLMA Expert Committee on Communicable Diseases gave us a free hand in writing this book.

We are grateful to GlaxoSmithKline (GSK) Sri Lanka for sponsoring the printing of this book for the eighth occasion.

Dr. Lucian Jayasuriya
Dr. Omala Wimalaratne
Prof. Jennifer Perera
Dr. Geethani Galagoda
Dr. Rajiva de Silva

Joint Editors

PREFACE

A new chapter in the history of medicine began in 1796, when Edward Jenner inoculated an eight-year old boy, using pus obtained from blisters on the hands of a milkmaid who had been infected with cowpox, to prevent smallpox. The above experiment of Edward Jenner led to the production of an effective vaccine which ultimately contributed to the eradication of smallpox from the world nearly two centuries later.

With regard to childhood immunization programmes, the World Health Organization (WHO) established the Expanded Programme on Immunization (EPI) in 1974. Through the 1980s, WHO and UNICEF worked together to achieve universal childhood immunization with the six EPI vaccines namely, BCG, OPV, diphtheria, tetanus, pertussis and measles.

Vaccination against smallpox was introduced in the then Ceylon as early as 1886, BCG in 1949 and DPT in 1961. This was closely followed by OPV in 1962. Sri Lanka launched the EPI in 1978 and measles vaccination was included in the National Programme of Immunization (NPI) in 1984. Since then, many other vaccines, both EPI and non-EPI, have been introduced to Sri Lanka.

During the latter part of the twentieth century, many new developments have taken place in the sphere of vaccine production. The new vaccines represent a major advance in the science of discovery as well as in production technologies.

In 2019, the world faced a major pandemic, SARS-CoV-2, with nearly seven million deaths to date.

Fortunately, research groups had developed novel vaccine platforms, especially the mRNA vaccines, which made it possible to produce new vaccines rapidly and in large quantities to meet the global demand. The effectiveness of this response can be compared with the mortality rates during the influenza pandemic in 1918-20, where over 50 million died,

when the world population was only about 1.5 billion, mainly due to the lack of a vaccine.

Sri Lanka's immunization programme is widely recognized as one of the strongest performers in the region and is among the best in the world. It has effectively controlled or eliminated most traditional childhood vaccine preventable diseases through outstanding levels of sustained infant immunization coverage.

More than two decades ago, in 2001, the Communicable Diseases Committee of the SLMA realized that it would be appropriate to introduce guidelines for the use of non-EPI vaccines. From the next edition it was expanded to cover all vaccines available in Sri Lanka with the help and participation of experts in the relevant field. I take the opportunity to appreciate the invaluable services rendered by the late Professor Anura Weerasinghe, who took the initiative in preparing these guidelines and was the Joint Editor of the first five editions.

These guidelines, which are regularly revised and published, are intended to provide assistance to medical practitioners and represent a consensus opinion arrived at, by the authors of chapters and the reviewers. As new information becomes available this edition will be revised.

I express my sincere gratitude to the Joint Editors and authors of the chapters and the core group who reviewed them, for their dedicated efforts to compile the 8th edition of these guidelines. I am grateful to Dr. Lucian Jayasuriya who spearheaded this activity on behalf of the Expert Committee on Communicable Diseases of the SLMA. I thank GlaxoSmithKline for their sponsorship during the preparation of the manuscript and for its publication.

Dr. Ranjith Perera
Chairperson,
Expert Committee on Communicable Diseases of the SLMA

FOREWORD

I am delighted to write the foreword for the 8th Edition of the SLMA Guidelines and Information on Vaccines. This edition is particularly significant as it is the first one published after the COVID-19 pandemic, which has brought about a significant shift in vaccination strategies not only in Sri Lanka but around the globe. In response to this global health crisis, this edition includes a dedicated chapter on COVID-19 vaccination.

Despite the immense challenges posed by the unprecedented crises in Sri Lanka, SLMA has been successful in developing and releasing this updated guideline. The healthcare sector in the country has been hit hard by the crisis, leading to severe shortages of essential supplies, including medicines, reagents, devices, equipment, and human resources. The impact of these shortages on the ability of the healthcare system to provide quality care is significant. It is commendable that, the Editorial Team led by SLMA Past President Dr. Lucian Jayasuriya has been able to overcome these obstacles and deliver this much-needed guideline. Their dedication and tireless efforts are truly appreciated and recognized. This updated guideline will undoubtedly serve as a valuable resource for healthcare professionals in Sri Lanka and help improve the quality of care provided to patients.

Traditionally, vaccines have been primarily focused on protecting maternal and child health. However, the COVID-19 pandemic brought about a new and unprecedented challenge in the form of a population-wide vaccine effort. This was a complex undertaking, unlike any other vaccination campaign in history. Developing and distributing a vaccine for a disease that had only recently emerged presented numerous scientific, logistical and ethical challenges. Scientists and researchers around the world worked tirelessly to develop effective vaccines against the virus. Regulatory authorities had to rapidly evaluate and approve

these vaccines, ensuring their safety and efficacy for public use. Given the challenges faced by the healthcare sector in Sri Lanka.

I believe that this updated guideline will be an invaluable resource for healthcare professionals. It offers comprehensive guidance on best practices and procedures. As such, I believe that this guideline will play a crucial role in improving the quality of care provided to patients in Sri Lanka following the SLMA Theme for this year "Towards Humane Healthcare; Excellence, Equity and Community".

I wish to express my sincere appreciation and gratitude to the Chairperson and the members of the Expert Committee on Communicable Diseases, Joint Editors and the authors of different chapters. Your dedication and attention to detail have been truly invaluable in ensuring the quality and accuracy of continuing this initiative.

Dr. Vinya Ariyaratne
President,
Sri Lanka Medical Association

ABBREVIATIONS

ABC	airway, breathing, circulation
ACIP	Advisory Committee on Immunization Practices
A&E	accident & emergency
AEFI	adverse events following immunization
AFP	acute flaccid paralysis
AIDS	Acquired Immunodeficiency Syndrome
AIIRD	autoimmune inflammatory rheumatic diseases
ALL	acute lymphocytic leukaemia
ALT	alanine aminotransferase
AMR	antimicrobial resistance
APC	antigen presenting cell
APP	American Academy of Paediatrics
ARSN	Asian Rotavirus Surveillance Network
ART	antiretroviral therapy
ARV	anti-rabies vaccine
ASO4	alum and monophosphoryl lipid
AST	aspartate aminotransferase
aTd	adult tetanus and diphtheria vaccine
BCG	Bacille Calmette- Guerin
BNF	British National Formulary
bOPV	bivalent oral polio vaccine
BP	blood pressure
BSA	bovine serum albumin
CAR-T	chimeric antigen receptor therapy
$CCID_{50}$	cell culture infective $dose_{50}$
CD4	cluster of differentiation 4
CD8	cluster of differentiation 8
CDC	Centers for Disease Control & Prevention
CGD	chronic granulomatous disease
CHD	congenital heart disease
CHDR	Child Health Development Record
CIN	cervical intraepithelial neoplasia
CIOMS	Council for International Organizations of Medical Sciences

CKD	chronic kidney disease
CLD	chronic liver disease
CMVIG	cytomegalovirus immunoglobulin
COPD	chronic obstructive pulmonary diseases
CRS	congenital rubella syndrome
CSF	cerebrospinal fluid
cVDPV	circulating vaccine derived poliovirus
CVID	common variable immunodeficiency
CYD-TDV	chimeric yellow fever tetravalent dengue vaccine
DF	dengue fever
DHF	dengue haemorrhagic fever
DNA	deoxyribonucleic acid
DSS	dengue shock syndrome
DT	diphtheria and tetanus vaccine
DTaP	diphtheria, tetanus and acellular pertussis vaccine
DTaP-HepB	diphtheria, tetanus, acellular pertussis and hepatitis B vaccine
DTaP-HepB-Hib-IPV	diphtheria, tetanus and acellular pertussis, hepatitis B, *H. influenzae* type b, injectable poliovirus
DTP	diphtheria, tetanus and pertussis vaccine
DTP-HepB	diphtheria, tetanus, pertussis and hepatitis B vaccine
DTP-HepB-Hib	diphtheria, tetanus and pertussis, hepatitis B and *H. influenzae* type b vaccine
DTP-Hib	diphtheria, tetanus and pertussis, and *H. influenzae* type b vaccine
DTwP	diphtheria, tetanus and whole cell pertussis vaccine
ELISA	enzyme linked immunosorbent assay
EPI	Expanded Programme of Immunization
ERIG	equine rabies immunoglobulin
ETEC	enterotoxigenic *Escherichia coli*
ETU	Emergency Treatment Unit
FA	fluorescent antigen
FDA	Food and Drugs Administration
FDC	follicular dendritic cells

fIPV	fractional inactivated polio vaccine
FVS	fetal varicella syndrome
fYFV	fractional yellow fever vaccine
GACVS	Global Advisory Committee on Vaccine Safety
GAVI	Global Alliance on Vaccination and Immunization
GBS	Guillain-Barré syndrome
GDP	gross domestic product
GMP	good manufacturing practices
GVHD	graft vs host disease
HAV	hepatitis A virus
HBcAb	hepatitis B core antibody
HBIG	hepatitis B immunoglobulin
HbOC	haemophilus b oligosaccharide
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCW	health care worker
HDC	human diploid cell
HDCV	human diploid cell vaccine (for rabies)
HDV	hepatitis D virus
Hep B	hepatitis B
HHE	hypotonic hyporesponsive episode
Hib	*Haemophilus influenzae* type b
Hib-MenCY-TT	*H. influenzae* type b-*N. meningitidis* serogroups C and Y-tetanus-toxoid conjugate vaccine
HibMenC	Hib & *N. meningitidis* sero group C vaccine
HIV	human immunodeficiency virus
HMSO	His Majesty's Stationery Office
HNIG	human normal immunoglobulin
HPV	human papillomavirus
HRIG	human rabies immunoglobulin
HSCT	haemopoetic stem cell transplantation
HTIG	human tetanus immunoglobulin
HTLV	human T cell lymphotropic virus
HZ	herpes zoster

ICU	intensive care unit
ICV	International Certificate of Vaccination
ID	intradermal
IDSA	Infectious Diseases Society of America
IFNγ	interferon gamma
IG	immunoglobulin
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
IGRA	interferon gamma release assay
IHR	International Health Regulations
IIV	inactivated influenza vaccine
IL	interleukin
IM	intramuscular
IMIG	intramuscular immunoglobulin
IPD	invasive pneumococcal disease
IPV	inactivated poliovirus vaccine
ITI	Industrial Technology Institute
ITP	immune mediated thrombocytopenic purpura
IU	international units
IV	intravenous
iVDPV	immunodeficiency associated vaccine derived poliovirus
IVIG	intravenous immunoglobulin
JE	Japanese encephalitis
JE-CV	Japanese encephalitis chimeric vaccine
JEV	Japanese encephalitis vaccine
LAIV	live attenuated influenza vaccine
LJEV	live attenuated Japanese encephalitis vaccine
LV	left ventricle
mAB	monoclonal antibodies
MCV4	tetravalent meningococcal conjugate vaccine
Men A	serogroup A meningococcal vaccine
Men B	serogroup B meningococcal vaccine
MenACWY	tetravalent meningococcal vaccine conjugated with diphtheria toxoid

MHC	major histocompatibility complex
mIU	milli international units
mL	millilitre
MMR	measles, mumps and rubella vaccine
MMRV	measles, mumps, rubella and varicella vaccine
MPL	monophosphoryl lipid
MPSV4	tetravalent meningococcal polysaccharide vaccine
MRI	Medical Research Institute
MSM	men who have sex with men
MSMD	Mendelian susceptibility to mycobacterial disease
Mtb	*Mycobacterium tuberculosis*
N saline	0.9 % sodium chloride
NAT	nucleic acid amplification testing
NCD	non-communicable diseases
NCP	North Central Province
NGO	non-governmental organisation
NIP	National Immunization Programme
NMRA	National Medicinal Drugs Regulatory Authority
NPI	National Policy on Immunization
NTHi	non-typable *H. influenzae*
OCV	oral cholera vaccine
OD	orally daily
OMV	outer membrane vesicle
OPV	oral polio vaccine
PCEC	purified chick embryo cell vaccine (for rabies)
PCR	polymerase chain reaction
PCU	primary care unit
PCV	pneumococcal conjugate vaccine
PCV7	7 valent pneumococcal conjugate vaccine
PCV10	10 valent pneumococcal conjugate vaccine
PCV13	13 valent pneumococcal conjugate vaccine
PET	post exposure treatment
PHK	primary hamster kidney cell culture
PHN	post herpetic neuralgia
PID	primary immunodeficiency
PLHIV	people living with HIV/AIDS
PO	per oral

PPSV23	pneumococcal polysaccharide vaccine (23 valent)
PRP	polyribosyl-ribitol-phosphate
PRP-CRM 197	with CRM protein
PRP-D	with diphtheria toxoid
PRP-OMP	with meningococcal outer membrane protein
PRP-T	with tetanus toxoid
PTB	pulmonary tuberculosis
PVRV	purified vero cell rabies vaccine
QIV	quadrivalent influenza vaccine
RIG	rabies immunoglobulin
RNA	ribonucleic acid
RRP	recurrent respiratory papillomatosis
RSV	respiratory syncytial virus
RZV	recombinant subunit zoster vaccine
SAGE	Scientific Advisory Group of Experts
SaO_2	oxygen saturation
SAPNA	South Asia Pneumococcal Network Alliance
SC	subcutaneous
SCID	severe combined immunodeficiency
SCIG	subcutaneous immunoglobulin
SEAR	South-East Asia Region
SLMA	Sri Lanka Medical Association
SLSI	Sri Lanka Standards Institute
ST	sensitivity test
STD	sexually transmitted diseases
TB	tuberculosis
TCV	tissue culture vaccine
Tdap	tetanus, reduced antigen, diphtheria and acellular pertussis vaccine
TDV	tetravalent dengue vaccine
TfH	follicular helper T cells
TIG	tetanus immunoglobulin
TIV	trivalent inactivated vaccine (influenza)
TLR	toll-like receptor
TNF	tumor necrosis factor
tOPV	trivalent oral polio vaccine

TST	tuberculin skin test
TT	tetanus toxoid
TY21a	oral typhoid vaccine
UNICEF	United Nations International Emergency Children's Fund
VAPP	vaccination associated paralytic poliomyelitis
VDP	vaccine derived poliovirus
ViPS	unconjugated Vi polysaccharide
VLP	virus-like particles
VPDs	vaccine preventable diseases
VVM	vaccine vial monitor
VZIG	varicella zoster immunoglobulin
VZV	varicella zoster vaccine
WaSH	water sanitation and hygienic practices
WC	whole cell
WHO	World Health Organization
WPV	wild polio virus
XLA	X-linked agammaglobulinaemia
YEL-AND	yellow fever associated neurologic disease
YEL-AVD	yellow fever associated viscerotropic disease
YF	yellow fever
YF-JE	yellow fever – Japanese encephalitis chimeric vaccine
YFV	yellow fever vaccine
YFVC	Yellow Fever Vaccine Centre

CHAPTER 1

THE IMPACT OF IMMUNIZATION

Introduction

The acronym GOBIFF stands for the pillars of primary health care of children; (Growth monitoring, Oral rehydration therapy, Breast feeding, Immunization, Family planning and Female education). As could be clearly seen, immunization is one of the central pillars which has contributed to a vast reduction in infant and childhood morbidity and mortality across the world. The ultimate goal of immunization is control of transmission of infection, elimination of disease and eventually, eradication of the pathogen that causes the infection and disease; the immediate goal is prevention of disease in people or groups.

In 1796, an Englishman named Edward Jenner made the landmark discovery that when cowpox material (containing the virus) was injected into a human, it provided protection against infection by the smallpox virus. Since then, vaccines have been developed against 29 infectious diseases ranging alphabetically from African trypanosomiasis (African sleeping sickness) to yellow fever[1].

The latest addition is the vaccine against COVID-19 which was introduced globally in 2020.

Global Impact of Immunization

Table 1. Milestones in global immunizations

Year	Vaccine	Year	Vaccine
1796	Smallpox	1985	Hib conjugate
1879	Chicken cholera (first live attenuated bacterial vaccine)	1992	Japanese encephalitis (inactivated)
1885	Rabies	1995	Hepatitis A (inactivated), varicella
1897	Plague	1998	Rotavirus
1914	Pertussis, typhoid	2000	Pneumococcal conjugate 7 valent
1923	BCG	2001	Combined hepatitis A & hepatitis B
1945	Inactivated influenza	2003	Nasal influenza vaccine
1947	DPT	2006	Human papilloma, Zoster vaccine
1954	Inactivated polio	2009	Pneumococcal conjugate 10 valent
1963	Trivalent oral polio, Measles	2010	Pneumococcal conjugate 13 valent
1966	Mumps	2014	Human papilloma virus 9 valent
1969	Combined MMR	2018	Dengue
1977	Pneumococcal polysaccharide 14 valent	2019	Ebola
1981	Hepatitis B, meningococcal quadrivalent	2020	COVID-19
1983	Pneumococcal polysaccharide 23 valent	2022	Malaria, Mpox

There are 300 million illnesses and five million deaths annually due to 23 infectious diseases. Vaccines prevented at least 20 million deaths between 2011 and 2020[2]. Four million deaths are prevented worldwide by childhood vaccination every year. It is predicted that 51 million deaths could be prevented through immunization between 2021and 2030[2].

About 300 million people died from smallpox in the 20th century which has a fatality rate of 30% in unvaccinated individuals. Smallpox was eradicated from the world in 1980; the last case of endemically circulating case of smallpox occurred in Somalia in 1977[3]. It is the only infectious disease in humans to be eradicated so far although its vaccine was developed 184 years prior to eradication. Rinderpest or cattle plague was eradicated in 2011; however, it does not infect humans. Poliomyelitis has been eliminated globally except for a few pockets in Pakistan and Afghanistan[4].

The return on investment for every dollar invested in vaccines was USD 51.0 from 2011 to 2020 for identified 10 diseases in 94 countries[5].

In 2018, 19.4 million infants worldwide were not reached with routine immunization. There are over 10 million deaths per year in the <5 year age group and 99% of these are in developing countries. Nearly 70% of these deaths are caused by infectious diseases such as measles, pertussis and tetanus, despite the availability of effective vaccines for many years[1].

Invasive pneumococcal disease (E.g. meningitis and septicaemia) is regarded as the world's leading vaccine preventable child killer, which is estimated to result in one million deaths in children under five years of age annually[6]. One year after the introduction of the pneumococcal conjugate vaccine (PCV) in 2000, there was a 69% decrease in the rate of invasive disease in children less than two years of age[7]. Interestingly, the rates of invasive pneumococcal disease in the elderly have also decreased since the introduction of the vaccine, due to herd immunity[8]. Numerous studies have shown the cost-effectiveness of the PCV in reducing <5-year mortality of children globally.

In the UK, Hib vaccine was introduced in 1993 which was followed by a dramatic drop in infections caused by *H. influenzae* type b[9].

Refusal of vaccination has resulted in outbreaks of measles in the recent past in the USA and Europe[10]. A 5% reduction in MMR vaccination coverage resulted in a 3-fold increase in annual cases of measles with an addition of USD 2.1 million in public sector costs[10].

Impact of Immunization in Sri Lanka

Introduction

Sri Lanka has an immunization coverage of 99% in infancy, which is among the highest rates in the world. Free health care, free education resulting in high levels of literacy combined with the virtual absence of vaccine hesitancy has contributed to this. However, the task is not yet complete as a few more vaccines, such as those against pneumococci, dengue and influenza need to be included in our NIP schedule in the foreseeable future.

Table 2. Milestones of immunization in Sri Lanka

Year	Vaccine	Year	Vaccine
1886	Smallpox	1995	Launching of National Immunization Days to eradicate poliomyelitis
1949	BCG	1996	Rubella vaccine for women of childbearing age
1961	DTP	2001	Measles and rubella (MR) vaccine
1962	Oral polio (OPV)	2001	Introduction of new immunization schedule: DTP 2, 4, 6 and 18 months, MR at 3 years, DT & OPV at 5 years, aTd at 12 years
1963	BCG for newborns	2003	Hepatitis B vaccine
1969	Tetanus toxoid for pregnant women	2008	Pentavalent vaccine including Hib vaccine
1978	Launching of the EPI by WHO	2009	Replacement of killed JE vaccine with the live attenuated vaccine

1984	Measles vaccine	2011	Inclusion of JE vaccine in NIP schedule
1988	JE vaccine in a phased basis	2011	MMR vaccine
1989	Achievement of Universal Childhood Immunization status	2017	HPV vaccine
1991	Tetanus toxoid 5 dose schedule for pregnant women	2020	COVID-19 vaccine

Poliomyelitis

Sri Lanka has eliminated poliomyelitis, the last case being reported in 1993. Under guidance from the WHO, the oral polio vaccine (OPV) is being gradually replaced by the inactivated polio vaccine (IPV). This is a welcome move because there have been few cases of vaccine associated paralytic poliomyelitis (VAPP), the incidence of which is 1 case per 2.4 million doses of OPV and appears to be higher after the first dose. In Sri Lanka, only one case of VAPP has been diagnosed since the introduction of OPV[11]. As part of the global eradication programme of poliomyelitis, a national committee of experts meets regularly to review cases of acute flaccid paralysis (AFP).

Rubella

Prior to the introduction of the rubella vaccine, congenital rubella syndrome (CRS) was a major cause of congenital heart disease (CHD) in children. It had been reported that CHD was the second commonest cause of mortality in a paediatric unit at the Lady Ridgeway Hospital, accounting for 25-33% of the deaths[12,13,14]. The last major outbreak of CRS was in 1994 (275 cases) and in the first four months of 1995 (169 cases)[15]. The monovalent rubella vaccine was introduced in the national schedule in 1996, measles-rubella (MR) vaccine in 2001, which was

replaced with the measles-mumps-rubella (MMR) vaccine in 2011. The WHO declared Sri Lanka is rubella and congenital rubella syndrome free in 2020[16].

Measles

CDC estimated that there were 9.5 million cases of measles with 128,000 deaths, in 2021 globally[17].

Many children succumbed to measles prior to the introduction of the vaccine in Sri Lanka in 1984. Protein-energy malnutrition was precipitated in many survivors and vitamin A deficiency led to ocular complications. There was an outbreak of measles in 1999-2000 (15,000 cases) and 40% gave a history of vaccination[18]. Subsequently, a second dose of measles vaccine was introduced at the age of 3 years to the NIP schedule in 2011. Another smaller outbreak of measles occurred in Sri Lanka in 2014/2015. A significant number of the cases were in the <1-year age group, prompting the Epidemiology Unit to change the age of first MMR dose to 9 months from 1 year[19].

Diphtheria

Diphtheria was rampant up to the 1970s and Lady Ridgeway Hospital had a special tracheostomy ward to care for them. Many children died due to complications of laryngeal diphtheria. At present, there are no cases of laryngeal diphtheria being reported and there have not been any fatalities for the past decades[20].

Pertussis (whooping cough)

Over 1000 cases were reported annually until the late 1970s and many children died, developed pulmonary complications or protein-energy malnutrition. A gradual decline has been observed from the 1990s and <100 cases have been reported from 2001 onwards[21]. In the mid-1990s the use of an ineffective pertussis vaccine resulted in an outbreak of pertussis[22].

Tuberculosis

Like the other vaccines in our NIP schedule, there is almost 100% BCG coverage in infancy. As a result, complicated types of TB such as tuberculous meningitis, miliary TB, bone and joint TB and renal TB are very rare in children. Occasionally, BCGitis results after vaccination, most probably due to improper technique.

Tetanus

Around 2000 cases of tetanus per year were reported until the late 1970s. A gradual decline has been observed from the 1980s and <50 cases have been reported annually from 1997. In 2009, only 18 clinically confirmed cases were reported. A few cases of tetanus are still being reported among adults who were born before the introduction of DTP vaccine in 1961. Since 2009, not a single case of maternal or neonatal tetanus has been reported[23].

Japanese encephalitis (JE)

The first major outbreak of JE occurred in the North Central Province (NCP) in 1985-6. There were 385 cases with 64 deaths. The disease occurred in epidemic proportions in the years 1986-7 and 1987-8. The latter was the largest epidemic reported so far with 812 cases and 192 deaths. It later spread to three adjoining districts outside the NCP[24]. The inactivated JE vaccine was introduced on a phased basis in the prevalent areas in 1988. Later in July 2009, it was replaced with the live attenuated JE vaccine SA 14-14-2, which is less costly and required only a single dose, compared to the former vaccine which required 3-4 doses. In 2009, it was included in the NIP schedule[25].

Influenza vaccine

The influenza vaccine is available in two formulations, one each for the northern and southern hemispheres. It is available in the private sector and is recommended for high risk children (E.g. congenital heart disease and nephrotic syndrome), pregnant women and adults over 65 years of age. It has to be given annually.

Human rabies vaccine

Human rabies is still reported in our country although it is an island. However, with the vaccination of dogs and the use of post exposure prophylaxis for humans, deaths from rabies have gradually decreased from 377 (2.9 per 100,000 population) in mid 1970s to 31 in 2021[26]. The use of intra-dermal vaccination has resulted in a significant reduction in expenditure[27].

Other vaccines

There are two vaccines in our NIP schedule that prevent malignancies; hepatitis B vaccine (HBV) prevents primary hepatoma of the liver and human papillomavirus (HPV) vaccine prevents cervical cancer. In Sri Lanka, the fourth commonest cause of malignancy in females is cervical cancer[28]. The HPV vaccine was introduced in Sri Lanka in 2017, for 10-year-old girls as a 2 dose course[29].

There are a few vaccines such as the pneumococcal conjugate vaccine (PCV 14), rotavirus, varicella and hepatitis A vaccines which are available in the private sector but not in the state sector as yet.

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CHAPTER 2
IMMUNOLOGICAL BASIS OF VACCINATION

Introduction

Immunization aims to artificially induce immunity against disease. This may be active, whereby the immune system is recruited to provide protection against the disease/ infection or passive, where exogenous protection is provided, albeit, temporarily.

Normal immune response

Cells of the immune system

The immune system provides protection against infectious agents. Classically, the system is divided into the innate immune system and the specific or acquired immune system. The innate immune system consists of cells (monocytes, macrophages, dendritic cells, neutrophils, eosinophils and natural killer cells) and molecules (complement, cytokines, chemokines etc.) while the specific immune system is composed of lymphocytes. These include B lymphocytes producing antibody and subsets of T lymphocytes including CD4+ T lymphocytes ("helper T cells") and CD8+ cytotoxic T lymphocytes. The CD4+ T lymphocytes are further divided into:

- Th1 cells- producing inflammatory cytokines such as interferon γ (IFN γ), for immunity against intracellular pathogens
- Th2 cells-producing IL 3 and IL 5, for anti-helminthic immunity
- Th17 cells-against extracellular bacteria colonising the mucosa
- Follicular helper cells (Tfh)-are present in secondary lymphoid organs, for the generation of high affinity antibodies
- Regulatory T cells-control immune responses and maintain tolerance[1,2]

Activation of the innate immune system

The innate immune system recognises the pathogen and subsequently activates the specific immune system[3], which then acts in concert against the infection. Pathogens that enter the body through skin/mucous membranes are taken up by resident antigen presenting cells (APC) in these tissues. The main APC is the dendritic cell. Blood borne pathogens are directly taken up by dendritic cells in the white pulp of the spleen. The APC and molecules of the innate immune system have pattern recognition receptors (PRR), for example, toll like receptors (TLR) that can recognize conserved foreign molecules found only on pathogens (pathogen associated molecular patterns or PAMPs). Recognition is followed by activation of these cells and molecules. Dendritic cells found in the skin and other sites are crucial in the subsequent activation of the specific immune system[1]. The dendritic cell senses potential 'danger' when recognizing PAMPs. Recognition is followed by uptake of the pathogen and activation of the dendritic cell and other APC. Activation occurs in the presence of pathogens.

This leads to

- production of cytokines and chemokines resulting in inflammation
- up-regulation of co-stimulators on the APC, essential for successful antigen presentation to T cells
- localisation of the pathogen containing APC to the draining lymph node

During this process, the dendritic cells internalise the pathogens and present peptides derived from the microorganisms, in conjunction with major histocompatibility complex (MHC) class II molecules on its surface. Viruses infecting dendritic cells produce virus coded peptides in the cytoplasm. These peptides are presented in conjunction with MHC Class I molecules.

Activation of the specific immune system

T and B cells have receptors that recognise antigen. Most circulating lymphocytes recognise non-self antigen[2]. Lymphocytes circulate in the

body between blood and peripheral lymphoid tissue (cell trafficking). Activated dendritic cells present peptides derived from pathogens, in conjunction with MHC Class II molecules to CD4+ T cells in the T cell areas of the lymph nodes and spleen. The CD4+ T cell will be activated only if second signals are provided by co-stimulatory molecules on the surface of dendritic cells. These co-stimulators are up-regulated only if PAMPs are recognized by the dendritic cells. As these patterns are only found on pathogens, the dendritic cell will only activate non-self-reacting CD4+ T cells. Depending on the pathogen and the cytokine milieu around the reaction, the CD4+ T cells become either armed effector Th1 or Th2 cells; Tfh cells or memory cells[2].

Dendritic cells which are activated by microorganisms such as *M. tuberculosis* produce cytokines that switch a naive CD4+ T cell to an activated Th1 cell, while helminths and some bacterial pathogens induce a Th2 response. Th1 cells produce cytokines (IL 2, IFN γ) that activate CD8+ cytotoxic T lymphocytes, B lymphocytes and macrophages, while Th2 cells activate B lymphocytes by producing IL 4, 5 and 13. In the germinal centers, Tfh cells activate B lymphocytes to produce T dependent antibodies.

Humoral immunity

B cells that recognise protein antigens need help from CD4+ T cells to produce antibody. The initial B cell response takes place extra-follicularly (outside the germinal centre)[2], with help from Th1 and Th2 cells, resulting in the production of low affinity IgM and a small amount of IgG. This occurs within a few days of the infection/immunization and is short lived. This is followed by a response in the germinal centre. B cells move into the germinal centre and encounter their cognate antigen found on the surface of follicular dendritic cells (FDC). The FDC and Tfh cells provide activation and survival signals to the B cell, which proliferate, producing a clone of daughter cells. These daughter cells have antigen binding receptors (immunoglobulin molecules found on the surface of the B cells) which have undergone point mutations (somatic hypermutation). These mutations are confined to the antigen binding

site of the receptor. B cells with receptors with a greater fit (affinity) would bind to the cognate antigen and survive, while those with a weaker fit would undergo apoptosis. The surviving B cells would differentiate into long lived plasma cells or memory B cells. With time, high affinity (affinity maturation) IgG, IgA and IgE antibodies are produced (isotype switching) by plasma cells, some being long lived. Memory B cells are capable of producing high affinity, class switched antibody with great rapidity, after re-exposure to the same microorganism. Affinity maturation, isotype switching and memory need T cell help and are hallmarks of antibody responses to protein antigens. T cell help is provided in germinal centers by Tfh cells. This response takes 10-14 days to appear and terminates in 3-6 weeks. Peak antibody concentrations occur 4-6 weeks after primary immunization.

Polysaccharide epitopes such as the capsules of *S. pneumoniae* and *H. influenzae*, do not activate CD4+ T cells[2]. A subset of B cells in the marginal zone of the spleen, assisted by marginal zone macrophages, produce intermediate affinity IgG (T independent antibodies). Polysaccharides are poorly immunogenic in children under 2 years, till maturation of the marginal zone. As T independent responses do not produce memory cells, subsequent re-exposure evokes a repeat primary response. In some instances, revaccination with certain bacterial polysaccharides may even induce lower antibody responses than the first immunization, a phenomenon referred to as hyporesponsiveness[4].

Antibodies provide protection against extra-cellular organisms, such as capsulate bacteria or viruses during an extra-cellular phase. IgA provides mucosal immunity, preventing infection by bacteria and viruses through the mucosa; IgM provides quick responses to blood borne pathogens while IgG protects blood and tissues.

Cell mediated immunity

Protection against intracellular microorganisms is through cell mediated immunity. Viruses infect cells and produce virus derived proteins in the cytoplasm. Peptides derived from these proteins are presented on MHC Class I molecules by all nucleated cells. These are recognised by

previously activated cytotoxic T lymphocytes and the infected cell is destroyed. Microorganisms residing in intracellular vesicles of macrophages such as *M. tuberculosis*, are dealt with by Th1 cells activating the macrophage, resulting in intracellular killing of the bacteria.

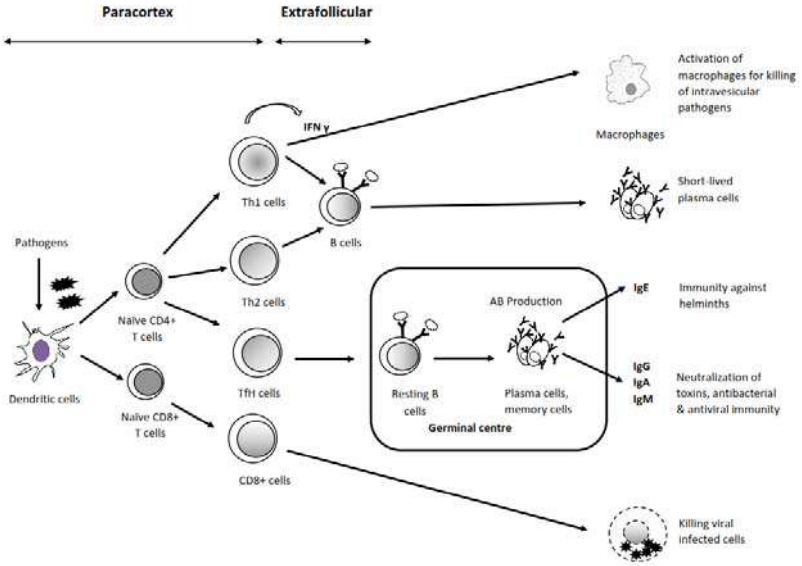

Figure: Normal immune response

(Courtesy: Dr. Dhanushka Dasanayake)

Vaccines

"A vaccine is a biological product that can be used to safely induce an immune response that confers protection against infection and/or disease on subsequent exposure to a pathogen"[5]. There are two main types of vaccines, live and non-live.

The different types of vaccines are[5].

- Live attenuated (MMR vaccine)
- Non-live
    - Killed whole organism (IPV)
    - Subunit (purified protein, recombinant protein, polysaccharide, peptide) (HPV)
    - Virus-like particle (HPV)
    - Outer membrane vesicle (Meningococcal B vaccine)
    - Viral vectored (SARS-CoV-2)
    - Nucleic acid vaccines (mRNA and DNA vaccines) (SARS-CoV-2)
    - Toxoids (Tetanus)

Live vaccines are attenuated i.e. they have a reduction in virulence due to deliberate or natural changes in the virulence genes. When given to immunocompetent hosts, they have the ability to replicate sufficiently to produce a strong immune response, without causing disease. They have a potential for uncontrolled replication leading to disease in immuno-compromised subjects (E.g. BCG). Non-live vaccines do not pose such a threat but may not produce a strong immune response in immuno-compromised individuals[5].

New vaccines

The viral vector vaccines (replicating or non-replicating) are recombinant constructs, where the vector genome has been modified with the addition of the target genetic sequence from the pathogen. After transcription and translation in the cytoplasm of the host cells, the target peptide is presented to the immune system with signals from the vector, which induces a strong immune response, both humoral and cell mediated, without the need for adjuvants[5].

mRNA vaccines have been used against SARS-CoV-2[6]. They comprise synthetic mRNA molecules formulated in a lipid nanoparticle as a delivery system. The vaccine is endocytosed and directed to the cytosol, where it is translated to produce peptides[6]. A DNA vaccine against SARS-CoV-2 is also available[7]. DNA for the S protein is enclosed in a plasmid vector, which is then translated in host cells.

Immune response to vaccines

Vaccines are administered to prevent clinical disease. However, some vaccines prevent infection or colonisation, thereby preventing transmission of the pathogen, inducing herd immunity[5].

All vaccines (except the BCG vaccine) mainly confer protection by inducing antibodies[5]. However, most vaccines induce a T cell response as well. It is probable that, while antibodies assisted by Th cells prevent infection, cytotoxic T cells (CD8 T cells) control and clear the infection[5].

The nature of the immune response depends on the type of vaccine. Live and most non-live vaccines evoke a T dependent response, producing high quality antibody and memory B cells. Polysaccharide vaccines (E.g. pneumococcal 23 valent vaccine) evoke a T independent response[4] where the IgG produced is of poor quality (affinity) and memory B cells are not produced. However, conjugation of the polysaccharide with a protein (conjugate vaccines) activates Tfh cells and thereby evokes a T dependent response.

Inactivated, subunit, conjugate vaccines will evoke antibody responses. Live viral vaccines/viral vector vaccines will, in addition, activate cytotoxic CD8+ T lymphocytes. These cytotoxic T lymphocytes limit the spread of infections by killing infected cells and secreting antiviral cytokines.

mRNA vaccines produce both humoral and cell mediated immunity[6].

The effector mechanisms of vaccine immunity are given in the table.

Table. Effector mechanisms of vaccines[8]

Immune response	Mechanism of action
Antibody	Prevents infection with extra-cellular pathogens by • Neutralization (prevent entry into cells) • Opsonophagocytosis (clearance of pathogens by neutrophils and macrophages) • Complement activation • Binding to toxins and prevent their function
CD8 T cells	• Direct killing of infected cells • Indirect killing by producing antimicrobial cytokines
CD4 T cells	Reduction, control and clearance of pathogens • Th1- intracellular pathogens • Th2- extracellular pathogens (bacteria and helminths) • Th17- mucosal pathogens • Tfh cells- provide help to B lymphocytes

Vaccine induced immunity is mainly due to IgG antibodies. The efficacy of the vaccine depends on the quality of the antibody (avidity, neutralizing ability and specificity), whereas long term protection is due to the persistence of protective levels of antibody and/or presence of memory B lymphocytes capable of rapidly producing high quality antibodies after re-infection[8]. Memory cells are important in vaccine responses[5]. In vaccinees, an infection will activate memory B cells leading to production of antibodies within 3-4 days. In infections with a short incubation period (IP) such as with *H. influenzae* type b, vaccinees whose antibody levels have waned below the protective threshold may develop infection

and clinical disease due to the delay in activation of memory B cells. However, when the IP is prolonged, as with hepatitis B infection, the vaccinee is protected even if antibody is not detected, as there is sufficient time for memory B cells to respond. For infections with a short incubation period, where the antibody responses wane, provision of booster doses may be needed to sustain antibody levels above protective levels. For certain vaccines, however, (E.g. yellow fever), the antibody levels persist above protective levels after one dose, thereby conferring lifelong immunity.

For protection against bacterial diseases that result from the production of toxins (tetanus and diphtheria) the presence of long-lasting antitoxin antibody and memory B cells are necessary, ensuring the presence of antitoxin antibody at the time of exposure to the toxin[8].

For infections which originate at mucosal sites, transudation of serum IgG will limit colonisation and invasion. This is due to pathogens being prevented from binding to cells and receptors in the mucosa. Transudation will only occur if sufficient neutralizing antibody is present in the serum. Polysaccharide vaccines and most inactivated vaccines do not provide mucosal protection and therefore do not provide sterilising immunity[8]. If the pathogens breach the mucosa, however, IgG in serum will neutralise the pathogen, activate complement and facilitate phagocytosis, thereby preventing spread within the body.

Some vaccines (E.g. oral polio, rotavirus and nasal influenza) will stimulate production of IgA antibody at mucosal surfaces, thereby limiting virus shedding.

Antibody responses are ineffective against intracellular organisms such as *M. tuberculosis.* There is evidence that a CD4+ Th1 response, with production of IFN γ leading to activation of infected macrophages is elicited following BCG vaccination[9]. IFN γ producing CD4 cells may be useful in infants who have been immunized with the measles vaccine at 6 months. Due to interference of maternal antibodies, an antibody response may not have been evoked, and they are susceptible to measles. However, the presence of IFN γ producing CD4 cells may help clear the infection[8]. The whole cell pertussis vaccine given in infancy may

provide longer efficacy due to the presence of CD4 cells, even though the antibody levels have waned[8].

Antibody alone may prevent infection, but disease attenuation and clearance of infection are mediated by T cells, even in the absence of antibody[8].

Correlates of protection[8]

The mere presence of antibody does not indicate that the patient is protected. A formal demonstration that a specific marker (antibody titre or a number of antigen specific cells) provides vaccine induced protection is needed. Such correlates of protection (i.e. antibody titres) have been identified for a number of diseases.

Determinants of primary vaccine response[8]

- Intrinsic immunogenicity of the vaccine
- Type of vaccine
    - Live viral vaccines elicit better responses than non-live vaccines. This is due to live vaccines
        - having sufficient PAMPs to efficiently activate immature dendritic cells, a key requirement for the development of specific immunity.
        - multiplying at the site of inoculation and disseminating widely, and being taken up by dendritic cells at many sites. These dendritic cells are then activated and are carried to many peripheral lymphoid organs, where activation of antigen specific B and T lymphocytes occurs. As the immune response occurs at multiple sites, live viral vaccines evoke a strong immune response persisting for decades. Due to the early and efficient dissemination of the virus, the site or route of inoculation does not matter (E.g. SC versus IM). BCG vaccine acts similarly, by multiplying at the site of inoculation and at distant sites as well.

- Non-live vaccines
  - may have enough PAMPs to activate dendritic cells but in the absence of microbial replication this activation is limited in time and is restricted to the site of inoculation[8]. As the immune response is restricted to the local lymph nodes, it is weaker than with a live vaccine. Therefore, repeated booster doses are necessary. As only the regional nodes are involved, multiple non-live vaccines can be given simultaneously, provided the inoculations are performed at different sites. Booster doses are ineffective with polysaccharide vaccines as memory B cells are not produced.
  - rarely induce high and sustained antibody responses after a single dose. Therefore, primary immunization schedules usually include at least two doses, repeated at a minimum interval of 4 weeks to generate successive waves of B cell responses. Even so, the response usually wanes with time.

- Dose – As a rule, higher doses of non-live antigens, up to a certain threshold, elicit higher primary antibody responses. This may be particularly useful when immuno-competence is limited E.g. for hepatitis B immunization of patients with end stage renal failure
- Route – The route of inoculation is important. The dermis has many dendritic cells, and for example, the rabies vaccine given intradermally at a fraction of the IM dose can evoke an equally good response. Where the vaccine is not very immunogenic (E.g. hepatitis B vaccine), IM injections are preferred over SC as muscle tissue has more dendritic cells than adipose tissue[8,10].
- Nature of the protein carrier
- Genetic composition of the individual
- Age – responses at the extremes of age are weaker and less persistent. In the elderly, this is due to the decline in immune function (immunosenescence)[5]. Provision of additional signals to the immune system, using certain adjuvants (ASO1, MF 59) may overcome this.

- The interval between 2 doses of vaccines may determine the immunogenicity of the vaccine. For example, with a mRNA vaccine against SARS-CoV-2 (BNT162b2-Pfizer BioNTech), an interval of 6-14 weeks resulted in a greater titre of neutralising antibodies, as well as a more sustained T and B cell response compared to an interval of 3-4 weeks[11].
- The immunogenicity of vaccines may be boosted and broadened by mixing and matching vaccines (heterologous prime boost), as was seen with vaccines against SARS-CoV-2[12]. For example, mixing the adeno virus vector (adeno virus 5 and adeno virus 26, in the Gam-COVID-Vac /Sputnik V) gave better results than using the same vector; priming with an adenovirus vector vaccine (ChAdOx1-S-Oxford/AstraZeneca) and boosting with an mRNA vaccine (BNT162b2) gave better cell mediated and antibody responses than giving 2 doses of the adenovirus vector vaccine, and comparable antibody responses and better cell mediated responses compared to 2 doses of the mRNA vaccine. The reason for this phenomenon is not clear.

Determinants of duration of vaccine response

Plasma cells which produce antibodies are usually short lasting, while a few plasma cells produced in the germinal centre may survive for long periods in the bone marrow. These cells are responsible for the maintenance of protective antibodies for long periods[8]. This occurs most efficiently with live vaccines, less efficiently with non-live vaccines, but not with polysaccharide vaccines[8]. Live viral vaccines are the most efficient at evoking long lasting immune responses that may persist lifelong due to the presence of viral antigens that may regularly activate the immune system. However, while live vaccines are more immunogenic than killed/subunit vaccines, they still do not confer durable protection comparable to natural infection. Therefore, most live vaccines need booster doses (E.g. varicella, measles, live JE, oral polio, etc)[13].

The interval between doses is important. Two doses given one week apart may evoke a rapid short-lived response, whereas 2 doses 4 weeks apart may be longer lasting[8].

Vaccination at extremes of age or in patients with chronic disease may evoke short lived responses.

Booster doses

The affinity maturation process in the germinal centre takes up to a few months after completion of the germinal centre reaction. It is therefore, customary to boost the immune response at 6 months (E.g. 0-1-6 months with a prime-prime-boost regime)[8]. A secondary antigen exposure (boost) will give better affinity antibodies.

Adjuvants

Adjuvants enhance the magnitude and duration of the immune response[14], including seroconversion rates, dose sparing and reduction of doses[15]. The mechanism of action of adjuvants includes activating the innate immune system, by stimulating PRR such as TLR. PRR are activated by PAMPs or by damage associated molecular patterns (DAMPs), which are signals released by the host after cell death or damage. Adjuvants contain PAMPs or cause the release of DAMPs, for example, alum causing release of uric acid. Adjuvants also prolong antigen delivery at the site of inoculation, thereby recruiting more dendritic cells[16].

Human adjuvants such as

- Alum – an aluminum salt-based adjuvant such as tetanus toxoid containing vaccines
- Oil-in-water emulsions – such as MF59 and AS03 with the influenza vaccines activate DAMPs.

A new group of adjuvants, Adjuvant System (AS) has been formulated, which are a combination of established adjuvants such as alum or emulsions, with an immune potentiator, such as monophosphoryl lipid A (MPL)[17]. MPL is a natural agonist recognized by TLR 4 on APC, with resultant activation of the specific immune system. MPL is combined with alum to formulate AS04, which is the adjuvant that is used in one of the licensed HPV vaccines[17]. TLR agonists enhance the immune

response, such that the antibody levels reached is higher with the HPV and HBV vaccines containing ASO4, compared to the vaccines containing alum. In addition, the efficacy of the HPV vaccine containing ASO4 is 100% even after 9 years, indicating the durability of the response[14]. ASO1 contains two immuno-stimulatory molecules, MPL and the saponin QS-21, formulated together in liposomes[17]. This is used in the malaria and zoster vaccines[17].

The TLR 9 agonist CpG 1018, an oligo nucleotide, is a potent T cell adjuvant and stimulates strong B cell and NK cell activation, and is included in a Hepatitis B vaccine licensed for adults[14]. An inactivated SARS-CoV-2 vaccine, "Covaxin", incorporates a new adjuvant, idazoquinoline (Algel-IMDG), which also activates TLR, in this instance TLR 7/8[18].

Summary

All vaccines produce antibodies which can neutralise extracellular pathogens. Conjugate vaccines, toxoids, inactivated vaccines and live attenuated vaccines produce high affinity antibody and memory cells unlike polysaccharide vaccines. Polysaccharide vaccines are made more immunogenic by conjugation with a protein carrier.

Live viral vaccines evoke cytotoxic T lymphocyte responses which act against intracellular pathogens. Similarly, the BCG vaccine activates Th1 cells, whose cytokines help macrophages control *M. tuberculosis.* Live viral vaccines produce long lasting, even lifelong immunity compared to non-live vaccines.

Adjuvants potentiate immune responses in some non-live vaccines.

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CHAPTER 3
GENERAL INFORMATION ON VACCINES

Introduction

Vaccines contain weakened or inactivated whole or parts of a particular organism (antigen) that trigger an immune response within the body. Some newer vaccines contain the blueprint for producing antigens rather than the antigen itself. Regardless of the type, this weakened version will not cause the disease in the person receiving the vaccine, but it will prompt their immune system to respond much as it would have, on its exposure to the actual pathogen.

Vaccines are highly complex biological products, where batch to batch variation is inevitable even when produced by the same manufacturer. By adhering to good manufacturing practices (GMP), continuous quality control procedures and maintaining cold chain at all times, the manufacturer assures safety, immunogenicity and efficacy of vaccines.

As a vaccine non-producing country, Sri Lanka maintains the quality, safety and efficacy of procured vaccines through a stringent process of registration, lot release, monitoring of adverse events following immunization (AEFI) and having access to a laboratory for quality testing when necessary.

Types of vaccines[1]

They could broadly be categorized as either live or non-live vaccines.

Live

- Live attenuated

Non live

- Killed whole organism
- Toxoid

- Subunit (purified protein, recombinant protein, polysaccharide, peptide)
- Virus-like particle
- Outer membrane vesicle
- Protein-polysaccharide conjugate

Novel vaccines

- Viral vectored
- Nucleic acid vaccine

Live attenuated vaccines

These vaccines contain whole bacteria or viruses which have been "weakened" (attenuated) so that they evoke a protective immune response but do not cause disease in healthy people.

E.g. rotavirus, MMR, varicella, BCG vaccines

Inactivated vaccines

These vaccines contain whole bacteria or viruses which have been killed or have been altered, so that they cannot replicate.

E.g. IPV (inactivated polio), inactivated flu vaccine, hepatitis A, rabies, inactivated JE

Subunit vaccines

These vaccines typically contain one or more specific antigen/s (or "flags") from the surface of the pathogen.

Subunit vaccines usually do not evoke a strong or long-lasting immune response compared to live attenuated vaccines. They usually require repeated doses initially and booster doses subsequently. Adjuvants are often added to subunit vaccines. These are substances which help to strengthen and lengthen the immune response.

E.g. hepatitis B, HPV vaccine

Recombinant protein vaccines

Recombinant vaccines are manufactured using bacterial or yeast cells. A small segment of DNA coding for the relevant antigen from the target organism is inserted into the manufacturing cells through genetic engineering. The purified peptides/protein (the antigen) produced by the host cell is used as the vaccine.

E.g. hepatitis B, HPV vaccine

Toxoid vaccines

Some vaccines are made with inactivated versions of toxins termed 'toxoids' which are non-toxic but immunogenic.

E.g. diphtheria and tetanus toxoids

Conjugate vaccine

Less immunogenic polysaccharide vaccines are conjugated to a protein to make it more immunogenic.

E.g. Hib, PCV (pneumococcal conjugate vaccine), MenACWY

Newer vaccine types

Nucleic acid vaccines

These vaccines work in a different way to other vaccines, in that these do not supply the protein antigen to the body. Instead, these provide the genetic instructions of the antigen to cells in the body to produce the antigen, which stimulates an immune response. Nucleic acid vaccines are quick and easy to develop, and provide significant promise for the development of vaccines in future.

- **RNA vaccines**

  RNA vaccines use messenger RNA (mRNA) inside a lipid membrane. This membrane protects the mRNA when it first enters the body and also helps it to enter cells by fusing with the cell membrane. Once the mRNA is inside the cell, it is translated into

the protein antigen. The mRNA typically lasts a few days, but sufficient antigen is manufactured to stimulate an immune response. It is then naturally broken down and removed by the body. RNA vaccines are not capable of combining with the human genetic code (DNA). The mRNA vaccines are highly unstable and their global use is limited by ultracold storage requirements.

E.g. Pfizer BioNTech and Moderna COVID-19 (mRNA-1273) vaccine

- **DNA vaccines**

DNA is more stable than mRNA, therefore, it does not require the same stringent storage conditions. The DNA vaccines are typically administered with a technique called electroporation. This uses low level electronic waves to allow the host cells to take up the DNA vaccine. DNA must be translated to mRNA within the cell nucleus before it could be translated to protein antigens which stimulate an immune response.

There are several DNA vaccines under development.

E.g. ZyCov-D for COVID-19 infection registered in India

Viral vectored vaccines

Viral vectored vaccines are produced utilizing a new technology. Nucleic acid coding the antigen of a target organism is incorporated into the genome of a harmless vector virus which then delivers the genetic code to the host cells to produce a protein. The proteins that are produced stimulate an immune response against the target organism.

Viral vector vaccines could be replicating or non-replicating.

- **Replicating**

Replicating viral vectors retain the ability to make new viral particles alongside delivering the vaccine antigen when used as a vaccine delivery platform. As with live attenuated vaccines, these have the

inherent advantage of a replicating virus, such that it could provide a continuous source of vaccine antigen over an extended period of time. These vaccines produce a stronger immune response compared to non-replicating vaccines, and therefore, a single dose of vaccine may be sufficient to offer protection.

E.g. Ebola vaccine - Ervebo (rVSV-ZEBOV) uses a recombinant vesicular stomatitis virus

- **Non-replicating**

  Non-replicating viral vectors do not retain the ability to make new viral particles during the process of delivering the vaccine antigen to the host cells. This is because the key viral genes that enable the virus to replicate have been removed (replication deficient). The immune response is generally weaker than with replicating viral vectors and booster doses are likely to be required.

  E.g. Oxford/AstraZeneca (ChAdOx1-S [recombinant] vaccine) – for COVID-19

Routes of administration

Different routes are used to administer different vaccines

- Oral route: administered by mouth (OPV, rotavirus vaccines)
- Subcutaneous route (SC): injected into the area just beneath the skin into the fatty, connective tissue (MMR, varicella, yellow fever)
- Intramuscular route (IM): injected into muscle tissue (tetanus containing vaccines, hepatitis, pneumococcal vaccines)
- Intradermal route (ID): injected into layers of the skin (BCG, rabies, IPV)
- Intranasal route: administered into the nose (live influenza vaccine)

Interchangeability of vaccines

Similar vaccines made by different manufacturers could differ in the number and amount of their specific antigenic components and

formulation of adjuvants and conjugating agents, thereby eliciting different immune responses. Wherever possible, effort should be made to complete a series with vaccines produced by the same manufacturer. Although data documenting the effects of interchangeability are limited, most experts have considered vaccines interchangeable when administered according to their recommended schedule and dosing regimen. According to recommendations from the American Academy of Pediatrics (AAP) or Advisory Committee on Immunization Practices (ACIP), approved vaccines that may be used interchangeably from different manufacturers, include diphtheria and tetanus toxoids, hepatitis A, hepatitis B and rabies vaccines[2].

If different brands of a particular vaccine require a different number of doses for series completion and a provider uses different brands in the primary series, then the higher number of doses is recommended for series completion[2].

Lapsed immunizations

A lapse in the immunization schedule does not usually require recommencing the entire series. If a dose of vaccine is missed, immunization should be given at the earliest possible opportunity. In the case of children whose immunizations have been missed or postponed, their immunization chart should be flagged to remind health care professionals to complete immunization schedules at the next available opportunity.

Unknown or uncertain immunization status

A physician may encounter some children with uncertain immunization status. Many young adults and some children do not have adequate documentation of immunizations and recollection by the parent or guardian may be of questionable validity. In general, these persons should be considered disease susceptible and appropriate immunizations should be administered. There is evidence that administration of measles, rubella, MMR, varicella, Hib, hepatitis B or polio vaccine to already immune recipients, is not harmful. Tdap rather than DTP should be given to those 5 years of age or older[3].

Simultaneous administration of vaccines

Most vaccines could be simultaneously administered safely and effectively. Healthy infants, children and adults have sufficient immunological capacity to respond to multiple vaccines.

- Simultaneous administration of IPV, MMR, varicella or DTP vaccines results in rates of seroconversion and adverse effects similar to those observed when the vaccines are administered at separate visits[3].
- When vaccines are administered simultaneously, separate syringes and separate sites should be used. Injections into the same extremity should be separated by at least 1 inch, so that any local reactions could be differentiated.
- Individual vaccines should never be mixed in the same syringe unless they are specifically licensed and labelled for administration in one syringe[3].
- If parenteral live vaccines are not administered concurrently, a minimum gap of 4 weeks should be kept between immunizations[3].
- There is no required interval between administration of a live vaccine and an inactivated vaccine or between inactivated vaccines.
- If an inactivated vaccine and an immunoglobulin product are indicated concurrently (e.g. hepatitis B vaccine with HBIG, rabies vaccine with RIG), they should be administered at separate anatomical sites.
- Live vaccines administered by the oral route (OPV, rotavirus vaccine, oral typhoid) do not interfere with each other if given simultaneously. These vaccines may be given at any time before or after each other.
- Live vaccines should not be given within three months of receiving immunoglobulin, blood or blood products (refer Chapter 33).

Antimicrobial therapy and vaccination

Antimicrobial therapy is not a contraindication to vaccination, with the following exceptions[3];

- Vaccination with oral typhoid vaccine (Ty21a) should be delayed for ≥72 hours and oral cholera vaccine for ≥14 days after administration of antibiotics
- Antibiotics should not be taken within 72 hours of the last dose of Ty21a vaccine
- Antiviral agents active against herpes viruses (such as acyclovir) may interfere with the response to varicella-containing vaccines
- Antiviral agents active against influenza virus (such as zanamivir and oseltamivir) may interfere with the response to live attenuated influenza vaccine

Vaccine safety

Although immunization has successfully reduced the incidence of vaccine-preventable diseases, vaccination could cause both minor and rarely, serious side effects. Public awareness and controversy about vaccine safety has increased primarily because of the increase in vaccine coverage and safety vigilance, which has resulted in an increased number of adverse events reported after vaccination. Such adverse events include both true reactions to vaccine and more often events coincidental to, but not caused by vaccination. When allergens such as gelatin or egg proteins are components of the formulation, the rate of serious allergic reactions may be higher. Nevertheless, potentially life-threatening reactions like anaphylaxis to vaccines are still a rare event. The estimated incidence of anaphylaxis was 1.3 per million vaccine doses administered for all vaccines[4].

Despite concerns about vaccine safety, vaccination is still safer than accepting the risk of diseases these vaccines would prevent. Unless a disease has been eradicated (E.g. smallpox), failure to vaccinate increases the risk to both the individual and the society[5].

Allergy to vaccine components

Vaccine components could cause allergic reactions in some recipients. These reactions could be local or systemic and could include anaphylaxis. The vaccine components responsible could include the vaccine antigen or excipients like animal proteins, antibiotics or stabilizers (such as gelatin)[5].

Allergy to egg protein

Presently available influenza and yellow fever vaccines contain egg proteins in trace amounts. Yellow fever vaccine is contraindicated in persons who have a history of anaphylaxis to egg protein[6]. The risk of an allergic reaction to influenza vaccine in patients with egg allergy is very low, probably due to the very low amount of ovalbumin in the vaccine. Any such theoretical risk is far outweighed by the risk of such patients remaining unvaccinated. Thus, persons with egg allergy of any severity including anaphylaxis, may receive influenza vaccine. Persons with a history of suspected egg allergy, should be evaluated by an immunologist to determine the status of their allergy, but this should not delay their influenza vaccination when indicated. Skin testing with the vaccine and fractionating the dose are not necessary. The vaccine should be administered in a medical setting where anaphylaxis could be recognized and treated[7].

Allergy to bovine/porcine gelatin or bovine serum albumin (BSA)

The varicella, MMR and live JE vaccines contain bovine/porcine products. A few patients allergic to cow's milk or red meat (beef/pork/mutton) may develop allergic reactions following immunization with these vaccines. While gelatin is the culprit allergen in the West and Japan, BSA is implicated in Sri Lanka[8]. Patients who develop anaphylaxis to cow's milk or red meat should consult a specialist before immunization with the MMR, live JE or varicella vaccine.

Contraindications and precautions

Contraindications and precautions to vaccination are conditions under which vaccines should not or may not be administered.

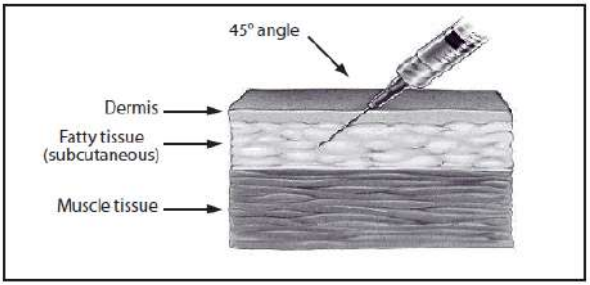
- The only contraindication applicable to all vaccines is a history of a severe allergic reaction (anaphylaxis) after a previous dose of vaccine or to a vaccine component.
- Severely immunocompromised persons should not receive live vaccines. However, there are exceptions (refer Chapter 31).
- Children who experienced encephalopathy within 7 days after administration of a previous dose of diphtheria and tetanus toxoids and whole-cell pertussis vaccine (DTP), or with acellular pertussis (DTaP or Tdap) not attributable to another identifiable cause, should not receive additional doses of a vaccine that contains pertussis.
- Because of the theoretical risk to the fetus, women known to be pregnant should not receive live attenuated vaccines[3].

Injection techniques

A vaccine recommended to be administered through the intramuscular route (such as adjuvanted vaccines), should not be administered subcutaneously.

All parenteral live viral vaccines are recommended to be administered subcutaneously.

Subcutaneous (SC) injections



Subcutaneous injections are recommended to be administered at a 45° angle.

- **Needle size:**

  Subcutaneous injections go into the fatty tissue below the skin and require a smaller, shorter needle. A needle that is ½ inch to 5/8 of an inch long with a gauge of 25 to 27 is usually recommended to administer the vaccine[9].

- **Sites recommended for subcutaneous injections:**

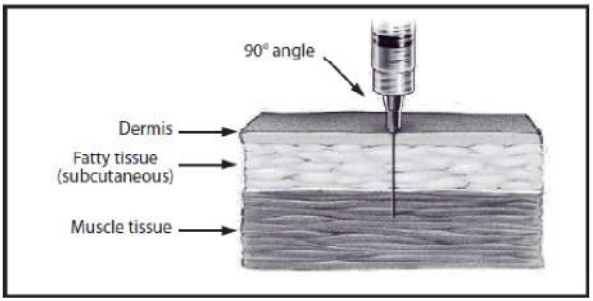
  Upper Arm: Deltoid region

  Abdomen: On either sides of the umbilicus

  Thigh: Antero-lateral region

Sites on the body where a subcutaneous injection can be given

Intramuscular (IM) injections



Intramuscular injections are recommended to be administered at a 90° angle.

All adjuvanted vaccines should be given IM.

- **Sites recommended for intramuscular injections:**

  Infants – Antero-lateral thigh

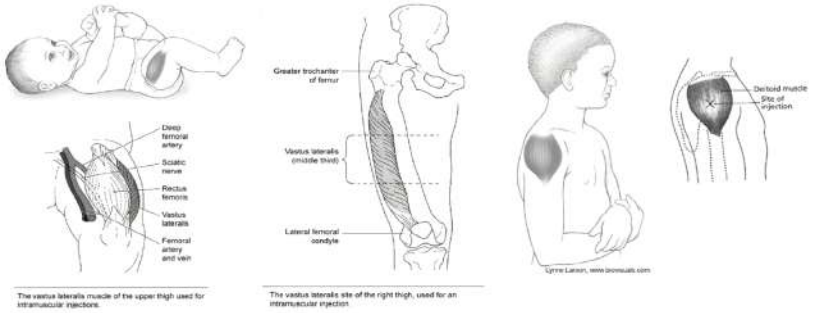
  Children over 1 year and adults – deltoid region

- **Needle size:**

  Intramuscular injections go into the muscle below the subcutaneous layer. Therefore, the needle must be thicker and longer to ensure that the vaccine is injected into the muscle.

  Pull back the plunger to make sure that you are not in a blood vessel before injecting the vaccine. Needles that are 23-25G and 1 to 1.5 inches long are usually appropriate[9].

- **Sites recommended for IM injections:**



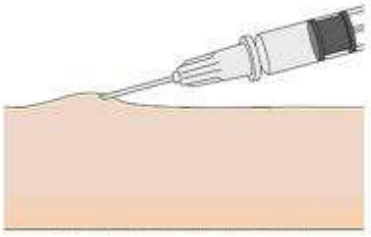
The vastus lateralis muscle of the upper thigh used for intramuscular injections.

The vastus lateralis site of the right thigh, used for an intramuscular injection

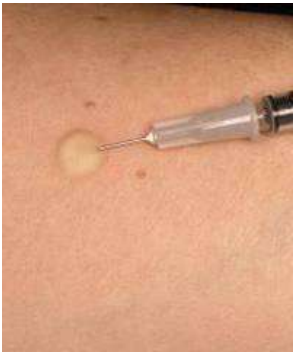
Intradermal (ID) injections

For intradermal injection, a needle of 27G and 3/8 to ¾ inch (1-2 cm) is inserted into the skin parallel to the skin surface, with the bevel of the needle facing upward.

A wheal should appear immediately after injection at the site. The same sites recommended for subcutaneous injections could be used for administering intradermal injections.



Skin wheal caused by intradermal injection



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CHAPTER 4
B C G

Introduction

Mycobacterium tuberculosis (Mtb), the aetiological agent of tuberculosis (TB) is an important cause of disease and death, particularly in developing countries. In 2020 an estimated 10 million people worldwide were infected with tuberculosis out of which 1.1 million were children. Over 95% of cases and deaths from tuberculosis are from developing countries[1]. In most developing countries the existing strategies for the control of TB are inadequate due to the rising number of drug resistant strains, the high cost of drugs and other socioeconomic conditions.

Primary infection often goes undetected clinically in the majority of those infected and may progress to pulmonary tuberculosis, extra-pulmonary tuberculosis, disseminated tuberculosis, or meningitis. During the pandemic, superinfection of tuberculosis with COVID-19 significantly increased morbidity and mortality due to tuberculosis. At the same time, there have been significant interruptions to tuberculosis surveillance activities during the COVID-19 pandemic, making it even more important to strictly adhere to tuberculosis preventive measures[2,3].

Sri Lanka is a low prevalence country for tuberculosis, with an estimated incidence of 64 cases per 100 000 population in 2018[3].

The only vaccine currently available for the prevention of tuberculosis is BCG (Bacille Calmette-Guérin), which was developed by two French bacteriologists named Albert Calmette and Camille Guérin and first used in humans in 1921. BCG vaccine is effective in protecting against meningitis and disseminated TB in children. A review also found that BCG-vaccinated children exposed to persons with open pulmonary TB (PTB) had 19% less infection than unvaccinated children (95% CI: 8-29) indicating protection against primary disease[4]. However, there is

no evidence to show that it prevents the reactivation of latent pulmonary infection, which is the principal source of bacillary spread in the community.

A cross sectional analysis of data from adult contacts with tuberculosis has revealed that the prevalence of latent TB infection is lower in individuals vaccinated with BCG. The same study revealed the effectiveness of the vaccine to be 30% which wanes off with time[15]. Therefore, the impact of BCG vaccination on the transmission of *Mtb* is limited. However, BCG vaccination is considered a life-saving and important component of standard TB control measures in most endemic countries[4].

BCG has a protective effect against leprosy in the range of 26-41% based on controlled trials[4,6]. However, it is not used specifically to control leprosy[4,6]. BCG has also shown effectiveness in preventing Buruli ulcers due to *M. ulcerans*[4]. A specific formulation of BCG is used in the treatment of superficial forms of bladder cancer. It mounts a local immune reaction against the tumour[7].

BCG vaccination was introduced to Sri Lanka in 1949 and has a coverage of 99%, which is one of the highest in the world[8].

Type of vaccine

BCG is a freeze-dried vaccine containing a live attenuated *M. bovis* strain that Calmette and Guérin passaged through numerous cycles. Several BCG vaccine strains are available. All vaccine sub-strains in use stem from one source, strain Bacille Calmette-Guérin. In terms of efficacy, no BCG strain is demonstrably better than another, and there is no global consensus as to which strain of BCG is optimal for general use[4].

Efficacy

BCG shows efficacy in the range of 60-80% in non-endemic countries but shows a much lower efficacy in endemic countries. However, the average protection against TB meningitis and disseminated disease is 86%[4].

Due to this, childhood immunization with BCG has caused a remarkable reduction in the incidence of miliary tuberculosis and tuberculous meningitis in children[9].

Among those vaccinated as neonates, protection against PTB was 59%.

Indications

In endemic countries such as Sri Lanka, the BCG vaccine should be given soon after birth or as soon as possible before discharge from the hospital including for low birth weight and premature babies.

BCG scar

A local reaction is normal after BCG vaccination. It takes around 8 to 14 weeks for the BCG scar to develop. A few days after vaccination, an induration develops at the point of injection, gradually changing to a small papule and then an ulcer in 2-4 weeks. The local reaction usually regresses in 2-5 months, leaving a superficial scar[10,11].

The presence of a scar is used as a marker of previous BCG vaccination but does not indicate protection against TB and approximately 10% of vaccine recipients do not develop a scar[4].

Vaccination of older age groups

BCG vaccination of older age groups should be considered in:

- Unvaccinated older children, adolescents and adults living in high incidence settings of TB and/or leprosy
- Unvaccinated older children, adolescents and adults moving from low incidence to high incidence TB and/or leprosy settings
- Unvaccinated/tuberculin skin test (TST) negative or interferon gamma release assay (IGRA) negative persons at risk of occupational exposure in both low and high TB incidence areas (E.g. health care workers, laboratory workers, medical students, prison workers)

There are data on the protection afforded by the BCG vaccine when it is given to adults (aged 16 years or over), and virtually no data for persons aged 35 years or over.

BCG is not usually recommended for people aged over 16 years unless the risk of exposure is high (E.g. healthcare or laboratory workers at occupational risk through direct clinical contact with patients diagnosed with TB or contact with infectious TB materials).

Dosage and administration

BCG is a freeze-dried vaccine. One vial contains 20 infant doses. It is dissolved in 1 mL of diluent.

The dose is 0.05 mL for infants and 0.1 mL for children over 1 year and adults.

The vaccine should be injected by a trained person, strictly via the intradermal route to the **left upper deltoid region** using a fine needle (gauge 27G) of 1 cm in length. Administration of BCG to any other site is not recommended.

Antiseptics should not be applied over the site prior to injection. Normal saline or distilled water could be used to clean the area.

BCG vaccine could be safely co-administered with other routine childhood vaccines.

Revaccination

Studies have shown minimal or no evidence of any additional benefit of repeat BCG vaccination against TB or leprosy. Therefore, revaccination is not recommended even if the TST reaction or an IGRA is negative. The absence of a BCG scar after vaccination is not indicative of a lack of protection[4].

However, the National Immunization Programme (NIP) recommends that children between 6 months to 5 years of age who do not show a BCG scar after vaccination, be revaccinated without doing a TST[10].

Contraindications

- Hypersensitivity to any component of the vaccine
- Symptomatic or asymptomatic HIV disease

  However, if HIV infected individuals are

  - started on anti-retroviral therapy (ART)
  - clinically well and immunologically stable
  - CD4 T lymphocyte percentage is >25% in children under 5 years or CD4 T lymphocyte count ≥ 200 cells/μL if aged >5 years

BCG administration could be considered, especially for those living in high incidence TB settings[1]

- Inborn errors of immunity (Primary immune deficiency disorders)
- Malignant disease
- Persons under immunosuppressive treatment
- Infants born to a mother who received immunosuppressive biological therapy during pregnancy

Precautions

- Asymptomatic neonates born to mothers with TB should first receive preventive therapy with 6 months of prophylactic isoniazid which should be followed by BCG vaccination
- In cases where infants have been exposed to smear-positive pulmonary TB shortly after birth, BCG vaccination should be delayed until the completion of 6 months of prophylactic isoniazid treatment
- Neonates with a family history of immune deficiency disease should be investigated prior to vaccination; if they are inadvertently vaccinated, an infectious disease specialist should be consulted, and anti-tuberculous therapy administered if clinically indicated[12]

- If there is a history of unexplained sibling death in infancy, the baby should be investigated for immunodeficiency prior to administration of BCG[13]

Vaccination need not be postponed in children with common illnesses such as common cold, asthma or eczema, and in children taking antibiotics if they are not seriously ill.

Adverse effects

In rare cases, an abscess may appear at the point of inoculation. Axillary or cervical adenitis (BCGitis) may lead to suppuration in exceptional cases. Faulty injection technique is the most frequent cause of severe injection site reactions.

There is no consensus about the management of BCGitis. Treatment is usually not necessary for local reactions and there is no clear benefit of active treatment (pharmacological treatment, needle aspiration or surgical excision)[14].

Storage

Store between 2-8°C, protect from light.

Vaccine diluents should be stored as recommended by the manufacturer. Accidentally frozen BCG vaccine or diluents should not be used[15].

After reconstitution, a vaccine can be kept at 2-8°C for up to six hours. Unused reconstituted vaccines should be discarded[15].

New vaccines in the pipeline

Advances in areas such as mycobacterial immunology and genomics have stimulated research on several new experimental vaccines. The main targets of vaccination are the prevention of infection in naive individuals, prevention of reactivation of latent infection and therapeutic vaccines to prevent relapses in TB patients. Currently, the most favoured research strategies include the development of recombinant modified BCG vaccines, attenuated strains of *Mtb*, subunit vaccines and DNA

vaccines using viral vectors. Some of these are currently at the evaluation stages of either phase 2 or phase 3 trials[16].

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CHAPTER 5
CHOLERA VACCINE

Introduction

Cholera is an acute intestinal infection caused by the toxigenic Gram-negative bacterium, *Vibrio cholerae*. The incubation period of cholera is 2-3 days in a majority of patients (range – few hours to 5 days). The infection is often asymptomatic or mild and self-limited. In severe illness, the patient develops profuse, painless, watery diarrhoea with characteristic 'rice water stools' associated with sudden onset of effortless vomiting, thirst and muscle cramps. This leads to rapid volume depletion, sometimes resulting in circulatory collapse. Death may occur in severely dehydrated patients within a few hours after onset of symptoms. The case fatality rate can exceed 50% among untreated severe cases but is less than 1% with proper and timely treatment.

Humans are the only natural host for the pathogen. Cholera is a non-invasive and essentially toxin-mediated disease. Once adherent to intestinal mucosa, bacteria produce cholera enterotoxin, which consists of a single A and five B subunits. While there are more than 200 serogroups of *V. cholerae*, only two toxigenic serogroups, O1 and O139, are known to cause outbreaks[1]. *V. cholerae* O1 has caused all recent outbreaks. *V. cholerae* O139, first identified in Bangladesh in 1992, caused outbreaks in the past, but recently has only been identified in sporadic cases. It has never been identified outside Asia. There is no difference in the illness caused by the two serogroups. Serogroup O1 has two biotypes (classical and El Tor) and these are further divided on the basis of their O antigen into subtypes, Ogawa and Inaba. Some strains possess determinants of both these subtypes and are named as subtype Hikojima.

To date, toxigenic *V. cholerae* (O1 serogroup) has caused seven pandemics, six of which were due to the classical biotype and the seventh pandemic caused by El Tor[3].

A new strain has been identified as 'atypical El Tor', which has traits of both classical and El Tor. This strain is of the El Tor biotype but produces cholera toxin formerly produced only by classical strains. These variant strains which appear to be the predominant strains globally, are more virulent and cause more severe illness than the original El Tor strains[2].

There is no known cross-protection between the O1 and O139 serogroups.

The natural habitat of *V. cholerae* is semi-saline (brackish) waters where it is associated with biofilms of zooplankton and chitinous surfaces of shellfish.

Infection is acquired primarily by ingesting faecally contaminated water, shellfish or other foods. Person-to-person spread may occur through the faeco-oral route.

In travellers from non-endemic countries, cholera is a very rare disease, with a risk of 0.01-0.001% per month of stay in a developing country[3].

Cholera outbreaks could occur periodically in any part of the world where water supplies, sanitation, food safety and hygiene practices are inadequate. Continued occurrence of outbreaks, emergence of new, more virulent strains of *V. cholerae* O1 (original El Tor has been replaced by new and more virulent strains in parts of Africa and Asia) and emergence and spread of antibiotic-resistant strains have raised serious concerns regarding control of the disease. Since 2010, Haiti has been fighting the largest cholera epidemic in the world in five decades. Although, cholera has not been reported in Sri Lanka since 2003, it is a notifiable disease and is under surveillance.

Typical at-risk areas include peri-urban slums, and camps for internally displaced persons or refugees, where minimum requirements of clean water and sanitation are not met.

Main strategies of cholera prevention include appropriate case management, water sanitation and hygienic practices (WaSH interventions), surveillance and community mobilization. Vaccination is synergistic with these activities.

Types of vaccine

Currently, there are three WHO pre-qualified oral cholera vaccines (OCV): All three vaccines require two doses for full protection.

Oral cholera vaccines

- Inactivated oral cholera vaccines
    - WC-rBS: A monovalent vaccine containing inactivated whole cell (WC) of *V. cholerae* O1 (biotypes classical and El Tor, serotypes Inaba and Ogawa) with recombinant B subunit of cholera toxin (rBS)[3]
    - WC, killed modified whole cell bivalent (O1 and O139) vaccines without the B subunit[3,4]
- Oral live attenuated vaccine
    - Live attenuated oral single-dose vaccine (lyophilized CVD 103-HgR)[4]. It protects against toxigenic strains of *V. cholerae* O1 but not against serogroup O139. It is approved in the USA for adult travellers[1,5,6].

Cholera vaccines are currently not available in Sri Lanka.

Efficacy

All currently available vaccines are safe and offer protection of >50% for at least two years among endemic populations. The cumulative efficacy of the 2 vaccine doses over 3 years is 51% (95% CI: 40-60%) against El Tor and classical cholera combined, and slightly lower against El Tor than classical cholera[3,4]. The OCV are reported to be effective against these El Tor variants[7].

Oral live attenuated vaccine may be less effective in partially immune individuals in cholera endemic areas as pre-existing antibodies may inhibit live organisms and decrease colonization of the gut[7,8,9].

Duration of protection

- WC-rBS – 2 years in adults but only 6 months in children aged 2-5 years. It is cross-protective against entero-toxigenic *Escherichia coli* (ETEC)[3].
- Modified bivalent killed whole-cell vaccine (WC) – protection has been demonstrated up to 5 years after vaccination. However, differences were observed in different age groups[5].

Since immunization does not provide complete protection against cholera, all travellers to endemic countries should be cautioned that the best protection is to avoid contaminated water and food. The vaccines should always be used in conjunction with other cholera preventive and control strategies.

Vaccine safety

Both WC-rBS and modified WC inactivated vaccines have a good safety profile, including when used in pregnancy and in HIV-infected or other immunocompromised individuals.

Indications

Currently, there is no mandatory requirement for cholera vaccination as a prerequisite for entry into any country. These vaccines should be used in areas with endemic cholera, in humanitarian crises with high risk of cholera and during cholera outbreaks. Use of vaccine in areas with endemic cholera should be guided by risk assessment and targeting cholera hotspots rather than the entire population.

The live attenuated oral cholera vaccine has been licensed in the United States for adult travellers to endemic or epidemic areas[2]. Immunization should be completed at least one week before potential exposure.

Dosage and administration

- WC-rBS – A single dose vaccine is available as a 3 mL whitish suspension. The vaccine is given with bicarbonate buffer mixed

with water to protect the toxin B subunit from being denatured by gastric acid. Once the buffer is added, the solution becomes colourless.

- Modified killed whole-cell vaccines (WC) – single dose vials or 5-dose vials.

Cholera vaccine could be given at the same time with other vaccines.

Food and drink should be avoided for 1 hour before and 1 hour after receiving the inactivated cholera vaccine, because the vaccine is acid-labile.

Table: Vaccination schedule

Product	Age group	Primary Immunization	Booster for individuals with continuing risk of infection or before re-exposure[3]
WC-rBS	Adults & children ≥ 6 years of age	2 doses, at least 1-6 weeks apart. If the 2nd dose is delayed for >6 weeks after the first, primary immunization should be restarted.	Since the previous vaccination • If <2 years – a single dose • If >2 years – full vaccination (2 doses)
	Children 2-5 years of age	3 doses, at least 1 to 6 weeks apart. The interval between each dose is 1-6 weeks. If the subsequent dose is delayed for more than	Since the previous vaccination • If <6 months – a single dose • If >6 months – full vaccination

		6 weeks, the primary course should be restarted.	
Modified killed WC	Adults and children ≥1 year of age	2 doses, 14 days apart	No manufacturers' recommendations on re-vaccination
Oral live attenuated[5,6,9]	Adult travellers (aged 2-64 years)	A single-dose for persons travelling to areas endemic for toxigenic *V. cholerae* O1[1,5]	

Special populations

- HIV infected individuals – Data on HIV infection and its influence on susceptibility to cholera infection as well as immune response to cholera vaccines are limited[3].
- Pregnancy – Data from well-controlled studies on OCV use in pregnancy are limited. A recent study has shown that OCVs are safe for use in pregnancy[3]. Overall, the decision to administer the vaccine should depend on the epidemiological context and after weighing the potential risks and benefits. On the basis of current understanding of the vaccine and evidence from different studies, pregnant women should not be excluded from oral cholera vaccines during vaccination campaigns[10]. No data exist on use of CVD 103-HgR in pregnant or breastfeeding women[6].

Adverse effects

Headache, diarrhoea, abdominal pain, and rarely nausea, vomiting, loss of appetite, dizziness, fever, respiratory symptoms.

Contraindications

General contraindications for vaccines are applicable.

Storage

2-8°C. Do not freeze.

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CHAPTER 6
COVID-19 VACCINE

Introduction

Coronavirus disease of 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This disease was first detected in Wuhan, China in late 2019, which spread throughout the world, resulting in a global pandemic[1]. As of 1st May 2023, there have been 764,474,387 confirmed cases and 6,915,286 deaths, world-wide[2].

SARS-CoV-2 is an enveloped, positive-stranded RNA virus belonging to the *Coronaviridae* family. It enters the body by binding to the angiotensin-converting enzyme 2 (ACE2) receptor found on human cells, including epithelial cells, using the spike proteins S1 and S2.

Viral particles are present in respiratory droplets, aerosols, blood, ocular secretions, urine and stool. The virus is primarily spread through direct person-to-person respiratory transmission. It is spread from the mouth and nose as droplets and smaller aerosolized particles which may become airborne[3]. It may be spread by asymptomatic individuals. In those with symptoms, viral shedding may occur up to 3 days before the onset of symptoms. The incubation period is 1-14 days (typically 4-5 days).

Clinical features

Patients may be asymptomatic or symptomatic. During the initial stages of the pandemic, over 80% of patients had mild disease[3]. Patients over 75 years, those with co-morbidities (obesity, hypertension, diabetes, renal, cardiovascular or pulmonary disease, cancer, transplant patients, those on immunosuppressives[1,3,4]) had a worse prognosis. However, with widespread immunization, the severity has decreased, even in those with co-morbidities[5].

Most patients present with fever, changes in taste and/or smell, myalgia and respiratory tract symptoms[1]. However, with new variants appearing,

there are differences in presenting features. Viral pneumonia, hypoxaemic respiratory failure and acute respiratory distress syndrome (ARDS) are the most common reasons for ICU admission[1]. In addition to respiratory symptoms, patients may develop symptoms and signs pertaining to other organs. These include cardiovascular (acute coronary syndrome (ACS), heart failure and myocarditis), CNS (mild illness to severe manifestations such as stroke), gastrointestinal and haematological disorders[1].

Some patients may develop persistent neurological, respiratory or cardiovascular symptoms. These are termed "post-acute COVID-19 syndrome" or "long COVID-19"[6].

SARS-CoV-2 variants

Mutations in the spike proteins lead to variants. A number of variants identified during the pandemic are classified into four categories: variants of concern (VOC), variants of interest (VOI), variants being monitored (VBM) and variants of high consequence (VOHC). This classification is based on their transmissibility, virulence and ability to cause severe disease. In addition, impact on diagnostics and efficacy of vaccines and immunotherapies are also considered[7]. A variant is designated a VOC if it is known to spread more easily, cause more severe disease, escape the body's immune response, change clinical presentation or decrease effectiveness of known tools – such as public health measures, diagnostics, treatments and vaccines[8]. Previous VOC included Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.1.529); As of February 2023, the only VOC is Omicron. This includes BA.1, BA.2, BA.3, BA.4, BA.5 and descendent lineages and also BA.1/BA.2 recombinant forms such as XE[9].

Types of vaccines

Monovalent vaccines

Many COVID-19 vaccines were developed and some of them were used in Sri Lanka including the traditional inactivated vaccines (BBIBP-CorV- Sinopharm manufactured by Beijing Institute of Biological

Products Co., Limited (BIBP)), non-replicating adenovirus vector vaccines (AZD1222/Chadox1 ncov-19 "Vaxzevria/Covishield" – manufactured by AstraZeneca/Oxford and Gam-COVID-Vac "Sputnik V" manufactured by Gamaleya Institute) and mRNA vaccines (mRNA-1273 "Spikevax" manufactured by Moderna and BNT162b2 "Tozinameran"/"Comirnaty" manufactured by Pfizer-BioNTech)[10].

All vaccines were produced against the Wuhan strain and had good efficacy following a primary series but had reduced neutralizing antibody titres against subsequent variants including Omicron[11]. A primary series of the inactivated vaccine BBIBP-CorV had no neutralizing activity against Omicron for the majority of recipients. However, 9/10 individuals given a heterologous regime (a primary series with an inactivated vaccine followed by an mRNA booster) achieved neutralizing activity[11].

Vaccine efficacy (VE) against the Omicron variant was reduced compared to the Delta variant, with all vaccines, including a booster dose[12].

Inactivated vaccine

BBIBP-CorV (Manufactured by Sinopharm Beijing)

BBIBP-CorV is an aluminium-hydroxide-adjuvanted, Vero-cell derived inactivated whole-virus vaccine. It was shown to induce overall seroconversion rates of 95%, with lower seroconversion rates in individuals >60 years of age (93%)[13] after the primary series (2 doses). However, the overall antibody levels to the virus and antibodies to the receptor binding domain of the virus waned by 3 months, especially in older individuals[14]. A phase 3 trial with 2 doses, administered at an interval of 21 days, showed a VE of 79% (95% confidence interval (CI): 66-87%) against symptomatic SARS-CoV-2 infection, 14 or more days after the second dose. Vaccine efficacy against hospitalization was 79% (95% CI: 26-94%)[15]. Data on people over 60 years was limited.

Post introduction data from Argentina showed a vaccine effectiveness of 84% (95% CI: 80-88%) against COVID-19-related mortality in those aged 60 years and older, whereas in Hungary, the vaccine effectiveness in a large cohort aged ≥16 years was 69% (95% CI: 67-70%) against

SARS-CoV-2 infection; and 88% (95% CI: 86-89%) against COVID-19-related mortality[16].

The duration of protection seems to wane with time; VE against symptomatic disease in those vaccinated with 2 doses declined from 70% (95% CI: 57-79%) at 60 days post primary series vaccination, to 57% (95% CI: 50-63%) at 240 days[16]. In addition, VE against hospitalization also declines; hospitalization with severe or critical COVID-19 was 88% (95% CI: 84-91%) at 1-30 days after the primary vaccine series; 61% (95% CI: 54-67%) at 121-150 days; and 64% (95% CI: 59-69%) at ≥150 days.

Administration

- **Primary series**

  Two doses (0.5 mL) IM to deltoid, 21-28 days apart.

  SAGE recommends a third dose for people over 60 years and immunocompromised persons, 1-3 months after the 2nd dose[16].

- **Booster doses**

  4-6 months after primary series. Evidence suggests that immunogenicity and vaccine effectiveness is superior with a heterologous booster (mRNA/viral vector vaccine) following a primary vaccine series with BBIBP, compared to a homologous booster.

  For immunocompromised persons, a booster should be given, 4-6 months after completion of the primary series. However, as a 4th homologous dose did not boost immunity in health care workers, a heterologous boost is recommended[16].

Indications

All individuals ≥18 years. WHO recommends use in pregnant women when the benefits of vaccination outweigh the potential risks[16]. It may be given during lactation.

Safety data are limited for persons above 60 years of age (due to the small number of participants in clinical trials).

Contraindications

Individuals with a history of anaphylaxis to any component of the vaccine. People who have an anaphylactic reaction following the first dose of this vaccine should not receive a second dose of the same vaccine.

Precautions

People with fever of >38.5°C should postpone vaccination.

Adverse effects

- Local: Injection site pain.
- Systemic: Dizziness, fatigue, headache, nausea, vomiting, fever and allergic dermatitis.

Safety data are limited for persons above 60 years of age (due to the small number of participants in clinical trials).

Storage

2-8°C

Viral vector vaccines

AZD1222/ChAdOx1 nCoV-19 (Vaxzevria/Covishield – manufactured by AstraZeneca)

AZD1222 is a non-replicating, chimpanzee adenovirus-vectored vaccine containing the gene of the spike protein of SARS-CoV-2. It was found to be highly immunogenic, even in the elderly. More robust immune responses were observed when the gap between the two doses of the vaccine was increased[17]. VE against symptomatic SARS-CoV-2 infection was 74% (95% confidence interval [CI]: 65.3-80.5%) in participants 18 to 64 years of age and 83.5% (95% CI: 54.2-94.1%) in trial participants aged 65 years or older[18]. Studies of antibodies following immunization with this vaccine against Beta (B.1.351), Gamma (P.1), and Delta (B.1.617.2) show that neutralizing activity is variably lower than against the ancestral strain[19]. Among those who had received

2 doses of AZD1222, there was no effect against Omicron from 20 weeks after the second dose[20].

Vaccine effectiveness against symptomatic illness waned 20 weeks after the primary series, but less so against hospitalization during the Delta epidemic[19].

Administration

- **Primary series**

  Two doses (0.5 mL) IM to deltoid at a 4-12 week interval.

  As the efficacy and immunogenicity increases with a longer inter-dose interval, WHO recommends an interval of 8-12 weeks between the 2 doses.

  WHO/SAGE recommends that severe and moderately immuno-compromised persons should be offered an additional dose of vaccine 1-3 months after the 2nd dose[19].

  Immune responses after a dose of AZD1222 followed by a dose of mRNA vaccine gives higher neutralizing antibody and T cell responses compared to two doses of AZD1222, and is comparable to two doses of mRNA vaccine. WHO recommends that either of the mRNA vaccines can be used as a second dose following a first dose with AZD1222. The vaccine can be used as a second dose following any WHO recommended inactivated vaccines (BBIBP-CorV, Sinovac or Bharat) dependent on product availability[19].

- **Booster doses**

  Mixing and matching:

  A heterologous booster with an mRNA vaccine (BNT162b2, mRNA 1273), 4-6 months after completion of the primary series with the AZD1222 resulted in superior immunogenicity and vaccine effectiveness compared to a homologous booster with AZD1222. Therefore, SAGE considers using a different type of vaccine for a third/booster dose a more favourable option. However, maintaining a homologous schedule is still acceptable.

Indications

- All individuals ≥18 years.
- WHO recommends the use of AZD1222 in pregnant women only when the benefits of vaccination outweigh the potential risk. It may be given during lactation.

Contraindications

- Individuals with a history of anaphylaxis to any component of the vaccine.
- A patient who develops vaccine-induced immune thrombotic thrombocytopenia (VITT) following the first dose of this vaccine should not receive a second dose of the same vaccine.

Precautions

Persons with immediate, non-anaphylactic allergic reactions to the first dose (i.e. urticaria/ angioedema without respiratory signs or symptoms that occurs within 4 hours of administration) should not receive additional doses, unless recommended after review by a healthcare professional with specialist expertise.

Adverse effects

- Local: Pain and stiffness at the injection site.
- Systemic: Headache, fatigue, muscle aches, lethargy, chills, fever, joint pain, and nausea.

Vaccine-induced immune thrombotic thrombocytopenia (VITT): It is an autoimmune disease with anti-platelet antibodies (against platelet factor 4), leading to a consumptive coagulopathy with thrombocytopenia, hypofibrinogenaemia and elevated D-dimer levels. Clinical features include thrombosis with thrombocytopaenia. Venous thrombosis is present at multiple sites and sometimes at unusual sites. They include cerebral venous sinus thrombosis, splanchnic vein thrombosis and pulmonary

embolism. It occurs 5-30 days after vaccination and occurs mainly with the first dose. The Medicines and Healthcare Products Regulatory Agency (MHRA), UK, gives the risk of VITT after the first dose as one in 100,000 for people older than 50 years and one in 50,000 for those aged 49 years or younger. Mortality ranges from 23-60%[21].

Storage

2-8°C

Gam-COVID-Vac (Sputnik V – manufactured by Gamaleya)

Gam-COVID-Vac has two different adenovirus vectors in the two doses. The first dose has Ad26 vector and the second dose Ad5, both containing the genetic material for the spike protein of SARS-CoV-2. It was found to have similar immunogenicity levels as AZD1222 in individuals aged 18-60 years[22,23]. A phase 3 clinical trial estimated an efficacy of 91% against symptomatic disease with non-VOC[22]. An observational study in Hungary during the Alpha variant outbreak reported effectiveness of 98% against mortality and 88% against any infection[24]. As there is limited data in individuals over 60 years of age, the vaccine is not recommended in this age group.

Administration

Two doses (0.5 mL) IM to deltoid 21 days apart. First dose rAd26, second dose rAd5.

Indications

Persons 18 to 60 years of age.

Contraindications

- Dose 1 – Hypersensitivity to any constituents of the vaccine, severe allergic reactions in the past, pregnant women, individuals below 18 years.

- Dose 2 – Severe post-vaccination complications for dose 1 (anaphylactic shock, severe generalized allergic reactions, convulsive syndrome).

Precautions

Chronic liver and kidney disease, endocrine disorders (apparent thyroid function abnormalities and diabetes mellitus in decompensation stage), serious diseases of the hematopoietic system, epilepsy and other CNS diseases, acute coronary syndrome and acute cerebrovascular event, myocarditis, endocarditis, pericarditis.

Adverse effects

- Local: Pain, swelling, and redness at the injection site.
- Systemic: Mild flu-like condition with symptoms such as fever, chills, muscle and joint pain, sore throat, nasal congestion, weakness, malaise, and headache.

Storage

Store in a light-proof place at a temperature of -18°C or below. Store in a thawed state at room temperature (15-25°C) for no more than 2 hours.

mRNA vaccines

mRNA-1273 and BNT162b2 are the two widely-used mRNA vaccines for primary immunization and booster doses in many countries. A bivalent vaccine has also been developed to be given as a booster (see below). mRNA vaccines contain the mRNA that codes for the spike protein of the SARS-CoV-2 virus. mRNA vaccines are safe as they are non-infectious, have no risk of mutations and are degraded by normal cellular responses. mRNA vaccines induce potent innate and adaptive immune responses and this technology is one of the most immunogenic vaccine platforms[25].

BNT162b2 (Tozinameran/ Comirnaty – manufactured by Pfizer-BioNTech)

In a phase 3 clinical trial, a two-dose regimen of BNT162b2 given 21 days apart conferred 91% protection (95% confidence interval (CI): 89 to 93%) 7 days' post dose 2 against symptomatic SARS-CoV-2-infection with the ancestral strain in persons aged 16 years and above, based on a median follow up of 6 months[26]. VE was significantly higher against both infection and hospitalization with a longer 7-8-week interval between doses versus the manufacturer-specified 3-4-week interval.

There was waning of immunity against infection and mild disease, less so against severe disease, with time after primary vaccination[27]. Vaccine effectiveness is also reduced with VOC (Delta and Omicron).

A booster ≥5 months after the primary series increased effectiveness against hospitalization among adults without immunocompromising conditions from 82% (95% CI = 77%-86%) for 2 doses to 97% (95% CI = 95%-99%) for 3 doses ($p<0.001$) during the Delta variant outbreak. Vaccine effectiveness against hospitalization among adults with immunocompromising conditions was 69% (95% CI = 57%-78%) for 2 doses and 88% (95% CI = 81%-93%) for 3 doses[28]. A second booster can enhance vaccine effectiveness[29]. However, in a study from Israel during the Omicron BA 1 period, protection against confirmed infection after a 4th dose appeared short-lived whereas protection against severe illness did not wane during the study period[30].

Administration

- **Primary series**

  IM to deltoid

  - 6 months-4 years – three doses of 3µg, 0.2 mL
    A schedule of two doses 3 weeks apart followed by a third dose at least 8 weeks after the second dose is recommended by the manufacturer. However, countries could consider extending the interval between the first and second doses up to 8 weeks[29].

- 5-11 years – 2 doses of 10µg, 0.2 mL
- ≥12 years – 2 doses of 30µg, 0.3 mL

  Vaccine effectiveness was significantly higher against both infection and hospitalization with a longer 7-8-week interval between doses versus the manufacturer-specified 3-4-week interval. WHO recommends that the second dose should be provided 4-8 weeks after the first dose, preferentially 8 weeks, as a longer interval between doses is associated with higher vaccine effectiveness and potentially lower risk of myocarditis/ pericarditis[29].

- Immunocompromised persons.

  A 3rd dose (30µg) for those aged 12 years and above, and 10µg for those aged 5 to 11 years, 1-3 months after 2nd dose.

- **Booster doses**

  For persons ≥12 years, one dose (30µg) 4-6 months after primary series. BNT162b2 can also be used as a booster after primary series using any other vaccine. A first and second booster dose (fourth and fifth doses) given 4-6 months after the previous dose is recommended for all immunocompromised persons. No boosters are recommended for persons below 12 years, except in the immunocompromised[29].

Indications

All individuals ≥6 months.

Contraindications

Severe allergic reactions to any component of the vaccine.

Precautions

A person with an immediate non-anaphylactic allergic reaction to the first dose (i.e. urticaria/angioedema without respiratory signs or symptoms that occurs within 4 hours of administration) should not receive additional doses, unless recommended after review by a healthcare professional with specialist expertise.

Adverse effects

- Local: Mild to moderate pain at site of injection, more in younger patients.
- Systemic: Fatigue, headaches, myalgia, arthralgia and fever (≥38°C), more common with the second dose and in younger participants. Lymphadenopathy in the axillary, supraclavicular or cervical nodes on the same side as the injection was reported in less than 1%[30]. Severe systemic effects, defined as those that interfere with daily activity, included fatigue in 4% and headache in 2%[30].

Anaphylaxis was increasingly reported initially, but later studies have shown that the rate to be lower, at 5 per million doses. While allergy to polyethylene glycol (PEG) was implicated initially, this concern has diminished. However, the CDC recommends consultation with an allergist for patients with PEG allergy before administration of the vaccine[31].

During post marketing surveillance, a number of cases of myocarditis and pericarditis were reported after BNT162b2, typically a few days after the second dose and mainly in young males. Vaccine Adverse Event Reporting System (VAERS) of the US indicated that the incidence peaks in young males of 15-17 years with 105.9 cases per million doses administered and identified the second dose as the highest risk compared to the first dose. The outcomes are generally favourable. The risk of myocarditis after COVID-19 is greater than after vaccination[32]. Vaccination is recommended with an increased gap of >30 days between the two doses, to reduce the incidence of myocarditis.

Storage

Store between – 60°C - 90°C.

mRNA-1273 (Spikevax – manufactured by Moderna)

The phase 3 study, in participants aged ≥18 years, showed a VE of 94% in preventing COVID-19 of any severity[33]. After a median follow-up of 5.3 months at the end of the blinded phase of the trial, VE in

preventing COVID-19 was 93% (95% confidence interval [CI]: 91-95%); in preventing severe disease, efficacy was 98% (95% CI: 93-100%); and in preventing asymptomatic infection, 63% (95% CI: 57-69%)[34].

Effectiveness against any PCR-confirmed infection declined from 90% (95% CI: 89-91%) at 0-2 months, to 65% (95% CI: 63-67%) at 7-8 months after the second dose. Vaccine effectiveness against hospital admissions and deaths declined at significantly lower rates: at around 15% and 10% respectively during the first 6-8 months after the second dose. The administration of a booster dose returned protection to a rate equal to, or above, the effectiveness in the first 2 months after dose 2[35].

Administration

- **Primary series**

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  - 6 months - 5 years - 2 doses of 25µg 0.25 mL, 4 weeks apart
  - 6-11 years - 2 doses of 50µg in 0.25 mL, 4 weeks apart
  - ≥12 years - 2 doses of 100µg, 0.5 mL, 4 weeks apart

WHO recommends that the second dose should be administered 4-8 weeks after the first dose; an interval of 8 weeks between doses is preferred as this interval is associated with higher vaccine effectiveness and lower risk of myocarditis.

WHO recommends an additional (third) full 100µg dose for the immunocompromised.

- **Booster dose**: For persons ≥12 years, one dose (50µg) of 0.25 mL 4-6 months after completion of primary series. For persons aged 12 and above, a 50µg dose of mRNA-1273 vaccine may be used as a booster dose following a completed primary series using any other WHO recommended vaccine.

A first and second booster dose (fourth and fifth doses) given 4-6 months after the previous dose is recommended for the immunocompromised. No boosters are recommended for persons below 12 years, except in the immunocompromised.

Indications

WHO recommends the vaccine for all individuals 6 months and above, with an adjustment in dosage up to 11 years. WHO recommends use in pregnancy and lactation.

Contraindications

Individuals with a history of severe allergic reaction to any component of the vaccine should not take this or any other mRNA vaccine[36].

Precautions

A person with an immediate non-anaphylactic allergic reaction to the first dose (i.e. urticaria/ angioedema without respiratory signs or symptoms that occurs within 4 hours of administration) should not receive additional doses, unless recommended after review by a healthcare professional with specialist expertise.

Individuals who developed myocarditis or pericarditis following the first dose of mRNA-1273 vaccine should not receive additional doses of any COVID vaccine unless with the recommendation of their doctor or a healthcare professional[36].

Adverse effects

- Local: Pain, erythema, swelling and lymphadenopathy
- Systemic: Fever, headache, fatigue, myalgia, arthralgia, nausea/ vomiting and chills

Myocarditis is a rare adverse event that has been reported after mRNA COVID-19 vaccines. The observed risk is highest in males aged 18-39 years (with the highest risk in males aged 18-24 years), and highest within a few days after dose 2. The CDC estimates 32.2 excess cases per 1 million second doses in those ≥18 years. Most resolve without treatment.

Storage

Store between – 15°C-50°C.

COVID-19 bivalent vaccines

Bivalent vaccines for prevention of COVID-19 were only developed using the mRNA platform (mRNA-1273.214 and BNT162b2 bivalent). These are currently not available in Sri Lanka and many other countries. These vaccines contain the genetic material of the ancestral strain of SARS-CoV-2 and the Omicron subvariants, BA.4 and BA.5[37]. The added protection against these variants was only moderate and would probably be short lived. The probable reason for lower protection against BA.4 or BA.5 is due to imprinting, where the initial vaccination against the ancestral strain primed them to respond to antigens found in both ancestral and BA.4 /BA.5 and not to unique antigens in the new strains[38].

Comparison of vaccines

The COVID-19 vaccines vary widely in their ability to induce neutralizing antibodies (Nab), especially in older age groups, with the mRNA vaccines inducing the highest Nab levels, followed by adenovirus vector vaccines and then inactivated vaccines[10]. The mRNA vaccines were shown to be significantly more effective in older age groups and mortality rates were shown to be lower in those who received mRNA vaccines than inactivated vaccines[39].

However, the Nab levels following an mRNA booster dose was similar in those who had their primary vaccine series with an adenovirus vector vaccine or an inactivated vaccine[40]. The Nab responses were also significantly higher in individuals with natural infection who received any of these vaccines or who had natural infection following vaccination[10]. Three doses of inactivated vaccines, mRNA vaccines or a combination of both were equally effective in preventing deaths[39].

Special populations

- **Pregnancy**

  Pregnant women are more likely to develop severe COVID-19 and complications. Complications such as intra-uterine death, fetal distress and congenital infection are significantly higher with COVID-19. Therefore, two doses of either AZD1222, BBIBP-

CorV, mRNA-1273 or BNT162b2 are recommended and have been shown to be safe in pregnancy[41,42].

- **Children between 12 to 18 years of age**

  Only mRNA vaccines are recommended in children. Two doses of mRNA-1273 or BNT162b2 is recommended, with a gap of 12 weeks between the doses, which is different to the vaccination schedule in adults. This is to minimize the risk of possible myocarditis. Children <12 years of age are given different vaccine doses and the vaccine formulations for adults should not be used to vaccinate children <12 years of age.

- **Immunocompromised individuals**

  Individuals who are immunocompromised are at a higher risk of developing severe COVID-19 and associated complications[43]. Immunocompromised individuals had lower seroconversion rates and virus specific T cell responses with many of the COVID-19 vaccines following two doses[44,45]. Seroconversion rates were lowest in transplant recipients[45]. Therefore, in all immunocompromised individuals three vaccine doses, 4 weeks apart, are recommended as the primary vaccination series. The third vaccine dose in such individuals, which should be given 4 weeks after the second dose, is not considered as a booster dose, but the third dose of the primary vaccine series[46].

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CHAPTER 7
DENGUE VACCINE

Introduction

Dengue is an acute febrile illness caused by any one of four related flaviviruses known as dengue serotypes 1, 2, 3 and 4. Infection with one serotype is generally believed to confer long-term immunity to that virus (homologous protection) and roughly up to two years of heterotypic cross-immunity[1]. Therefore, after waning of cross protection, secondary heterotypic infection can give rise to clinical illness. Further, as the gap between first and second dengue virus infection widens, the rate and severity of secondary and more severe disease rises[2]. It is this attribute of dengue immunity which has affected the outcomes of dengue vaccines.

While the majority of dengue virus infections are asymptomatic, dengue fever (DF) is the most commonly diagnosed clinical illness. DF is characterized by the sudden onset of fever lasting between two to seven days, accompanied by severe headache, gastrointestinal symptoms such as nausea and vomiting, with muscle, joint and bone pain and a rash. DF is self-limited and usually results in complete recovery.

The more severe form of dengue infection is dengue haemorrhagic fever (DHF), and it represents a small proportion (typically <5%) of all dengue illnesses. DHF is characterized in its early stages by the signs and symptoms of DF described above, followed by increased vascular permeability and/or bleeding. This increased vascular permeability may lead to vascular collapse (also known as dengue shock syndrome, DSS) and death. Multiple epidemiological studies have shown that a second heterologous dengue virus infection is associated with a higher risk of developing DHF[3].

Types of vaccine

All are chimeric vaccines.

- CYD-TDV
- TAK-003

At present there is no dengue vaccine registered in Sri Lanka.

CYD-TDV

The first dengue vaccine is a tetravalent dengue vaccine (TDV), also known as chimeric yellow fever dengue vaccine (CYD-TDV). Each of the four live attenuated recombinant dengue viruses are contained in CYD-TDV by replacing the prM and E genes of the attenuated yellow fever 17D vaccine virus genome individually, with the corresponding genes of the dengue viruses. CYD-TDV was licensed in Mexico in December 2015 followed by the Philippines and Brazil. Subsequently, it was registered in several countries in Asia and Latin America[4].

In November 2017, the manufacturer of CYD-TDV proposed a label update (i.e. change in prescribing information) based on new analysis, which indicated that prior dengue infection in an individual must be assessed before vaccination. It further stated that vaccination should only be considered for individuals who have been previously infected by dengue virus[5].

Two other chimeric tetravalent candidates are in advanced stages of clinical development[6].

- Tetravalent dengue vaccine TAK-003, Phase 3 efficacy trial is ongoing both in Asia and Latin America where the disease is endemic.
- Tetravalent dengue vaccine candidate developed by US National Institutes of Health – TV003/TV005 vaccine Phase 3 study is progressing in multiple sites in Brazil.

Efficacy

CYD-TDV efficacy against virologically confirmed symptomatic dengue illness of any serotype assessed at 25 months post-enrolment was 56.5% and 60.8% in Asian (CYD14) and Latin American (CYD15) children aged 2-14 and 9-16 years respectively. In both trials, efficacy was lower against serotype 1 (50.2%) and 2 (39.6%) than against serotype 3 (74.9%) and 4 (76.6%)[7].

During the active phase of surveillance, pooled vaccine efficacies against hospitalized dengue illness were 72.7% and 80.8% among participants of all ages and those ≥9 years, respectively[5].

Vaccine efficacy varied according to baseline serostatus. It was higher in individuals who were seropositive at baseline compared to those who were seronegative at baseline, with pooled vaccine efficacy of 78.2% and 38.1%, respectively.

In a subset of only 13% of all trial participants, baseline serostatus was assessed subsequently. In trial participants ≥9 years, efficacy against symptomatic virologically confirmed dengue illness (VCD) of any severity was 81.9% (95% CI: 67.2 - 90.0%) in those seropositive at baseline and 52.5% (95% CI: 5.9-76.1%) in those seronegative at baseline[8].

Indications

Regulators have sought to restrict access to CYD-TDV following post-marketing research by the manufacturer which showed that, while the vaccine may offer protection for individuals who have already had one previous infection of dengue, it increases the risk of severe infection in children who were dengue-naive at the time of vaccination.

Therefore, CYD-TDV can only be used in individuals aged 9-16 years who have had one previous laboratory-confirmed dengue infection[9].

CYD-TDV has not been studied as an intervention for dengue outbreak control. Furthermore, the vaccine is not expected to have a significant impact on the course of an ongoing outbreak.

Revised WHO position

Based on retrospective analysis of data by the manufacturer in November 2017, the Scientific Advisory Group of Experts (SAGE) on Immunization of the WHO provided new recommendations in April 2018. Thereafter, the WHO issued a revised position paper in September 2018 replacing the 2016 position paper[10,11].

Accordingly, for countries considering vaccination as part of their dengue control programme, pre-vaccination screening is the recommended strategy. With this, only persons with evidence of a past dengue infection (based on an antibody test, or on a documented laboratory confirmed dengue infection in the past) would be vaccinated. Screening tests must be specific to avoid vaccinating true negative individuals and must be sensitive to ensure only vaccinating seropositive individuals. Currently available laboratory-based serological and point-of-care screening tests have not been specifically validated or licensed for the detection of past dengue infection for pre-vaccination screening.

If pre-vaccination screening is not feasible, prior infection with dengue virus of any serotype, as measured by seroprevalence, should be at least 80% or greater by age 9 years in a given area to consider vaccination.

Decisions about introduction of CYD-TDV require careful assessment at the country level, including consideration of local priorities, national and sub-national dengue epidemiology, predicted impact and cost-effectiveness with country specific inputs.

Dosage and administration

CYD-TDV should be administered as a 3-dose regime, given as a 0, 6- and 12-month schedule. Vaccine is available in a single-dose or in a multi-dose (5-dose) vial. It is a freeze-dried product to be reconstituted before injection with the provided diluent. CYD-TDV dengue vaccine contains no adjuvant or preservatives.

0.5 mL dose to be administered by the subcutaneous route.

Contraindications

WHO Global Advisory Committee on Vaccine Safety (GACVS) has concluded that individuals who have not been infected with wild dengue virus (i.e. those who are seronegative) should not be vaccinated with CYD-TDV because of the increased risk of hospitalization and severe disease identified among seronegative trial participants who became infected after vaccination.

Considering the safety signal of increased risk of hospitalization and severe disease identified in the 2-5-year age group, CYD-TDV is not recommended for use in children under 9 years of age.

CYD-TDV vaccination is contraindicated in:

- Individuals with a history of severe allergic reaction to any component of the dengue vaccine or after prior administration of the dengue vaccine or a vaccine containing the same components.
- A person with severe immunodeficiency or immunosuppression due to underlying disease or therapy, including persons with symptomatic HIV infection or CD4+ T-lymphocyte count of <200/mm^3.
- Pregnant or breastfeeding women.
- Individuals with moderate or severe febrile or acute disease (vaccination should be postponed).

Adverse effects

The outcome of CYD-TDV vaccination differs in seropositive and seronegative individuals. In seronegative individuals, the vaccine confers a low level of protection against dengue during the first 2 years, followed by an increased risk of hospitalization and severe disease following infection. This increased risk is apparent from 30 months after the first dose. Therefore, even in a high transmission setting, there may be an increased risk among seronegative persons despite a reduction in dengue illness at the population level[12].

Before considering introduction of CYD-TDV to the national schedule, it is essential to have a functional pharmacovigilance system with at

least minimal capacity to monitor and manage adverse events following immunization[7].

Local and systemic adverse reactions following CYD-TDV are comparable to those recorded for other live attenuated vaccines. Although there was a theoretical risk of acute viscerotropic and neurotropic disease due to the yellow fever backbone, no cases have been detected.

At present CYD-TDV is not recommended in pregnant and lactating women due to lack of sufficient data in this population. However, limited data from clinical trials on inadvertent immunization of pregnant women have yielded no evidence of harm to the fetus or pregnant woman. Pregnancy testing is not indicated prior to vaccinating women of childbearing age.

Storage

At 2-8°C

TAK-003

In January 2018, the manufacturer announced completion of a phase 3 trial in 8 dengue endemic countries in Asia and Latin America, including Sri Lanka[13].

The cumulative efficacy for symptomatic dengue regardless of serostatus over two years was 72.7% (95% CI: 67.1-77.3). Overall vaccine efficacy (VE) declined from 80.2% in year 1 to 56.2% (42.3-66.8) in year 2. The largest decline to 24.5% (-34.2-57.5) was in the 4-5-year-old children. In the 6-11-year age group the VE was 60.6% in year 2 (43.8 -72.4), while it was 71.2% (41.0-85.9) in the 12-16-year age group. Prevention of hospitalization over 2 years remained high, at 89.2% (82.4 -93.3). Serotype vaccine efficacy, regardless of serostatus was 69% for DENV 1, 90.8% for DENV 2, 51.4% for DENV 3. There were insufficient number of patients to measure efficacy against DENV 4. Because TAK-003 efficacy varies by serotype, observed changes in serotype dominance in vaccine study sites may contribute to year-to-year efficacy differences[14].

During the period of observation, TAK-003 did not enhance dengue disease in seronegative vaccine recipients. However, in baseline seronegative children, Rivera et al[15] reported modest efficacy for serotype 1 (43.5%), high efficacy for serotype 2 (92%) and no efficacy for serotypes 3 (-23%) and 4 (-105%) over the first 36 months of the trial. By year 3 (months 24-36), the vaccine was only efficacious against serotype 2 (85%). Therefore, TAK-003's low level of protection in young children to DENV 1, 3 and 4 needs further evaluation.

At the time of this publication TAK003 is registered in Indonesia and Brazil and approved by the European Medicines Agency (EMA) and the Medicines and Healthcare Products Regulatory Agency (MHRA) of the UK.

The WHO SAGE on Immunization has established a Working Group (WG) on Dengue Vaccines in November 2022 to review evidence and to develop policy recommendations of current and future vaccine products.

Dengue vaccines in clinical development

TV003/TV005

This is a live attenuated tetravalent formulation developed by the U.S. National Institutes of Health (NIH) and is currently in phase 3 trials in Brazil. It was also licensed to several vaccine manufacturers for further development outside Brazil, including India.

This replication deficient vaccine contains all 4 DENV serotypes with three full length DENV-1, 3 and 4 serotypes. Dengue 2 is chimeric, with a DENV-4 backbone in which the prM and E genes were replaced by the corresponding DENV-2 genes[16]. A single dose induced robust tetravalent response with 100% circulating neutralizing antibodies to all four DENV[17]. According to the results of phase 1 and 2 trials this vaccine performed well and was found to be safe[18].

Novel concepts (mRNA vaccine candidates):

The innovative mRNA vaccine platform is an important element for possible development of new dengue vaccines using this technology[19].

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CHAPTER 8

DIPHTHERIA, TETANUS, PERTUSSIS VACCINE

Introduction

Diphtheria is an acute communicable disease caused by strains of *Corynebacterium diphtheriae* and rarely by other corynebacteria (E.g. *C. ulcerans*) that produce diphtheria toxin. Diphtheria is characterized by a greyish adherent membrane in the pharynx, larynx, palate and nasal mucosa that can obstruct the airway. Toxin-mediated cardiac and neurologic complications can lead to death. The first diphtheria vaccine was introduced in 1926 using diphtheria toxoid. As all the clinical features result from a common toxin, any strain of *Corynebacterium* causing the disease could be prevented through vaccination with diphtheria toxoid.

Tetanus vaccine is unique as it is the first vaccine routinely recommended for a non-communicable disease. Tetanus is caused by *Clostridium tetani* and its spores are ubiquitous in the environment and enter the body through damaged skin. When inoculated into oxygen-poor sites, such as necrotic tissue that can result from trauma or deep puncture wounds, *C. tetani* spores germinate to vegetative bacilli that multiply and release tetanospasmin, a potent neurotoxin. Generalized tetanus typically presents with trismus, followed by rigidity caused by painful contractions of the skeletal muscles that can impair respiratory function. Glottic spasm, respiratory failure and autonomic instability can result in death. Localized tetanus is a rare form of disease occurring in adults with partial immunity. It could progress to generalized tetanus. Tetanus toxoid containing vaccine was made available for clinical use in 1938.

Pertussis is a very contagious respiratory infection found only in humans, caused by *Bordetella pertussis*, a Gram-negative coccobacillus. The organism releases toxins that damage respiratory epithelial tissue. Other species of the genus Bordetella, including *B. parapertussis* and less commonly, *B. bronchiseptica* are associated with cough like illness

resembling classical pertussis. Neither natural infection nor any pertussis vaccine confers life-long immunity. The first whole cell pertussis vaccine was introduced in 1914. A less reactogenic acellular vaccine was first introduced in 1981 in Japan. Disease caused by species of Bordetellae other than *B. pertussis* is not preventable by whole cell or acellular pertussis vaccine.

Diphtheria, tetanus and pertussis (DTP) vaccines were combined in 1948 to produce the first combined vaccine in the world. With the introduction of DTP in the universal immunization programme, it was observed that repeated vaccination with pertussis and diphtheria toxoid containing vaccines have resulted in significant reactogenic symptoms. In order to avoid such adverse reactions, a reduced dose of diphtheria toxoid is used for repeated vaccination following primary vaccination, particularly for children over 7 years. Therefore, there are two types of combined vaccines; for children less than 7 years and for children 7 years and older and adults.

Types of vaccine

Vaccines for children less than 7 years

- DTwP – Diphtheria and tetanus toxoids, and whole-cell pertussis
- DTaP – Diphtheria and tetanus toxoids, and acellular pertussis
- DT – Diphtheria and tetanus toxoids; also called paediatric DT

Vaccines for children 7 years and older and adults

- Tdap – Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis
- Td – Tetanus toxoid, reduced diphtheria toxoid; also called adult Td, aTd, and adult dT

("d" – reduced dose of diphtheria toxoid, "ap" – acellular pertussis)

DTP vaccine is now combined with other vaccines to form extended combined vaccines. There are two such combination vaccines in Sri Lanka.

- DTwP+HepB+Hib (pentavalent) used in the NIP
- DTaP+IPV+HepB+Hib (hexavalent) used mainly in the private sector (IPV – Inactivated polio vaccine)

Phase 3 trials of a hexavalent vaccine (DTwP+HepB+HiB+IPV) shows promise.

Table 1. WHO requirements for potency of each component per single human dose of diphtheria-tetanus-pertussis vaccine formulations[1]

Vaccine formula	Composition	Diphtheria toxoid	Tetanus toxoid		Pertussis	Aluminium compound (Alum adjuvant)
			Assayed in guinea pigs	Assayed in mice		
DTwP	Purified diphtheria and tetanus toxoid, suspension of *B. pertussis* inactivated usually by heating and heating and treated with formalin[3]	≥30 IU	≥40 IU	≥60 IU	≥4 IU	≤1.25 µg
DTaP	Purified diphtheria and tetanus toxoid, inactivated pertussis toxin either alone or in combination with other *B. pertussis* components such as filamentous haemagglutinin, fimbrial antigens 2 & 3 and pertactin	≥30 IU	≥40 IU	≥60 IU	≥4 IU	≤1.25 µg
DT	Purified diphtheria and tetanus toxoid	≥30 IU	≥40 IU	≥60 IU		≤1.25 µg
aTd	Purified diphtheria and tetanus toxoid	≥2 IU	≥40 IU	≥60 IU		≤1.25 µg
Tdap	Purified diphtheria and tetanus toxoid, pertussis toxin either alone or in combination with other *B. pertussis* components such as filamentous haemagglutinin, fimbrial antigens 2 & 3 and pertactin	≥2 IU	≥20 IU	≥30 IU	≥4 IU	≤1.25 µg

DTP vaccination schedule

In Sri Lanka, primary vaccination is at 2, 4 and 6 months and a booster dose is given at 18 months. However, the 3-dose vaccination series could be started at 6 weeks with a minimal interval of 4 weeks between doses, followed by a booster dose at age 15-18 months.

- **DTwP-HepB-Hib (pentavalent vaccine)**

  Primary course of immunization against diphtheria, tetanus, pertussis, hepatitis B and *H. influenzae* type b is recommended for all infants at 2, 4 and 6 months of age, unless there is a contraindication.

- **DTaP-HepB-IPV-Hib (hexavalent vaccine)**

  Primary course of immunization against diphtheria, tetanus, pertussis, hepatitis B, polio and *H. influenzae* type b; recommended for infants at 2, 4 and 6 months of age. This vaccine is used for primary immunization and the 18 months booster.

- **Diphtheria, tetanus and pertussis vaccine (DTwP, DTaP)**

  In countries where pentavalent or hexavalent is not in use for primary vaccination, these vaccines could be given instead, followed by a booster at 18 months. In Sri Lanka, following the primary course of immunization with pentavalent, DTwP is used as a booster at 18 months.

  There is no contraindication to use the same schedule of vaccination of unimmunized older children up to the age of 7 years[2].

- **Diphtheria and tetanus vaccine (DT)**

  It is recommended for children immediately before school entry at 5 years of age, preferably after 3 years from the last dose of the primary course or booster dose.

  DT can be used for primary immunization when immunization with pertussis antigen containing vaccine (DTP) is contraindicated.

- **Diphtheria and tetanus vaccine for adults and adolescents (aTd / Td)**

  It is used for primary vaccination and re-vaccination of adults and adolescents. aTd is given at the age of 10-12 years in the NIP of Sri Lanka.

- **Reduced tetanus, diphtheria antigens and acellular pertussis vaccine (Tdap)**

  For booster vaccination against diphtheria, tetanus and pertussis of individuals from age five years onwards and for those children who received DTaP containing vaccines as primary vaccination[1]. New CDC guidelines advise the use of Tdap at 11-12 years, 19 years, thereafter every 10 years[3] and for pregnant mothers at 27-36 weeks of gestation.

Dosage and administration

For all DTP or DTP containing vaccines, the standard dose is 0.5 mL. DTP vaccine should be administered deep intramuscularly in the anterolateral thigh in infants or in the deltoid muscle in older age groups.

Immunogenicity

Diphtheria and tetanus toxoids – After a series of three primary vaccines at 2, 4 and 6 months of age followed by a booster dose at 15 to18 months, approximately 95% of children achieve protective levels of diphtheria antitoxin (>0.1 IU/mL), and virtually all children achieve protective levels of tetanus antitoxin (>0.1 IU/mL)[2].

Pertussis vaccine – induces a complex immune response to many antigens, including the production of antibodies against many virulence factors. As such, there is no measurable serological correlate of disease protection.

Efficacy

Diphtheria and tetanus

The estimated efficacy of diphtheria toxoid in the prevention of diphtheria is 97%[2]. The clinical efficacy of tetanus toxoid has not been studied in vaccine trials, but it appears to be almost 100%[2].

Pertussis

- **whole cell pertussis vaccine** – A systematic review of the efficacy and effectiveness of pertussis vaccines which included 49 randomized controlled trials and 3 cohort studies, revealed that the pooled efficacy of wP vaccine against pertussis in children was 78%[4].

- **acellular pertussis vaccine** – In systematic reviews of randomized trials, the efficacy of acellular pertussis vaccines containing ≥3 pertussis antigens was variable, ranging from 71-85% in preventing typical pertussis[5]. Acellular pertussis vaccines also may provide cross-protection against *Bordetella parapertussis*[6].

Effectiveness

The effectiveness of diphtheria, tetanus and pertussis immunization is demonstrated by the sharp decline of these diseases after the introduction of DTP to the routine immunization schedule in the world since 1940[2,7].

In a prospective cohort of 469,982 children who received DTaP, the risk of pertussis was approximately 13 times greater in unvaccinated than in fully vaccinated children and approximately two times greater in incompletely vaccinated than fully vaccinated children[8].

A meta-analysis of available RCTs comparing aP vaccine (3- and 5-component formulations) and wP vaccine from 3 different manufacturers yielded overall vaccine effectiveness of 84% (95% CI: 81-87%) and 94% (95% CI: 88-97%), respectively[9].

Despite the effectiveness of pertussis vaccines, sporadic cases of pertussis occur in children who had been fully vaccinated with either DTwP or DTaP. In addition, outbreaks of pertussis in adolescents and

adults have surfaced globally after the introduction of DTaP[10]. Proliferation of strains of *B. pertussis* that have diverged from vaccine reference strains such as strains that are deficient in pertactin, may be a contributory factor[11].

Observational studies have consistently shown around 50% protection against severe pertussis in infancy following a single dose of either wP or aP pertussis vaccine, and 2 doses offer at least 80% protection. However, as the evidence is consistent with incremental protection after each additional dose, it is essential to complete the primary series to obtain the full protective effects conferred by pertussis vaccine[12]. Subsequent boosters have been shown to extend the duration of protection against pertussis.

Duration of immunity

The protection provided by diphtheria, tetanus and whooping cough vaccines decreases over time, necessitating booster doses in childhood, adolescence, and adulthood. A study in Sri Lanka had shown that the lowest median anti pertussis IgG titre, 1.43 IU/mL (minimum protective titre – 5 IU/mL), were seen between 8-11 years. However, after 11 to 24 years, 8.57% of individuals showed significantly high anti pertussis IgG levels, suggesting recent *Bordetella* infections among them[13]. This illustrates that there is a very high risk for infants less than six months to contract the disease from infected adults. However, due to increased reactogenicity with repeated wP vaccine, only DT is given at five years of age after primary vaccination followed by aTd at 10 years in countries, where DTwP is used in their NIP as in Sri Lanka. They do not receive any pertussis vaccine after 18 months of age. In contrast, in countries where DTaP is used, additional booster doses are given with DTaP at five years and Tdap at 10 years.

The effectiveness of the vaccine appears to decrease by between 2-10% per year after vaccination with wP. There is slightly faster decrease with the acellular vaccines[2].

There is increasing evidence that protection following booster doses of aP vaccines in individuals primed with wP vaccines is stronger and long

lasting than those primed with aP vaccines[14]. Despite waning immunity, vaccination continues to be the most effective strategy to reduce pertussis morbidity and mortality[15].

Contraindications

- Anaphylaxis to diphtheria, tetanus, or pertussis containing vaccine or vaccine constituents.

  Defer vaccination with diphtheria toxoid, tetanus toxoid and pertussis antigens because of uncertainty about which one was responsible, even though anaphylaxis to diphtheria toxoid is not reported. Severe allergic reactions to tetanus toxoid are extremely rare. Whole cell pertussis component is the offending agent in most cases.

  Still, it is advisable to refer to an immunologist to evaluate the component responsible for the allergic reaction.

- Encephalopathy within seven days of the administration of a previous dose of the vaccine without another identifiable cause is a contraindication to subsequent doses of wP containing vaccines. Children <7 years of age who have encephalopathy following DTwP could be given DTaP or DT instead.

Precautions

Decisions regarding administering diphtheria toxoid, tetanus toxoid and pertussis-containing vaccines to children with the following conditions should be individualized according to the benefits and risks and reassessed at subsequent visits[16].

Precautions for administration of **DTP** or **DT** include:

- Guillain-Barré syndrome (GBS) within 6 weeks of a previous dose of tetanus toxoid-containing vaccine.

  Although there have been case reports of GBS following tetanus toxoid-containing vaccines in adolescents and adults, an increased risk of GBS following diphtheria, tetanus, and pertussis immunization has not been observed in children.

- History of Arthus-type reaction after a previous dose of tetanus or diphtheria toxoid-containing vaccines; an Arthus-type reaction is a specific type of immune complex-mediated hypersensitivity reaction characterized by severe pain, induration, oedema, haemorrhage and occasionally necrosis at the injection site[16].

  Defer vaccination until ≥10 years after the last dose of the tetanus toxoid-containing vaccine.
- Moderate or severe illness with or without fever (immunization should be administered after recovery)
- In children with progressive or unstable neurologic disorders, including infantile spasms, uncontrolled seizures, or progressive encephalopathy; DTP should be deferred only until the neurologic status is clarified and stabilized[16].

Conditions incorrectly perceived as contraindications or precautions

The vaccine could be administered in the following instances[16]

- Fever <40.5°C (105°F), irritability or mild drowsiness after a previous dose of DTaP or DTwP (fever ≥40.5°C is considered to be a severe adverse reaction).
- Family history of seizures.
- Family history of sudden infant death syndrome.
- Family history of an adverse event after DTaP or DTwP administration.
- Stable neurologic conditions (E.g. cerebral palsy, well-controlled seizures, developmental delay).
- History of collapse or shock-like state i.e. hypotonic-hyporesponsive episode (HHE) within 48 hours after receiving a previous dose of DTaP or DTwP[17].
- History of seizure with or without fever within three days after receiving a previous dose of DTaP or DTwP.
- History of persistent, inconsolable crying lasting >3 hours within 48 hours after a previous dose of DTaP or DTwP.

Administration with other vaccines

Diphtheria, tetanus, and pertussis containing vaccines could be administered at the same visit as other recommended vaccines[18,19,20]. DTP vaccine should not be mixed in the same syringe with another vaccine unless the specific combination is approved by the WHO E.g. pentavalent or hexavalent vaccines[21].

Adverse effects

Mild adverse effects

Local reactions and fever ≥38°C, irritability, drowsiness, loss of appetite and vomiting.

The whole-cell component of pertussis is largely, but not solely, responsible for reactions occurring after administration of combined DTwP vaccines as demonstrated by studies that have compared the rates of adverse events after DTwP vs. DT and also DTwP vs. DTaP immunization[22,23]. A prospective study of adverse events 48 hours following DTP compared to DT vaccine in children 0-6 years showed that the reactions associated with DTwP vaccine were local redness, local swelling, pain, fever, drowsiness, irritability, vomiting, anorexia and persistent crying. These were five times more than with the DT vaccine[22].

The frequency of local reactions tends to increase with the number of doses administered, while systemic reactions with the exception of fever, may diminish with subsequent doses[22]. Local reactions are also more likely when adsorbed vaccines are given subcutaneously rather than intramuscularly[24].

Mild adverse events are similar but less frequent following vaccines containing acellular pertussis antigens compared to vaccines containing whole-cell pertussis.

Severe adverse events

- **Extensive local reactions and entire limb swelling**

  Extensive local reactions (>46 mm) of erythema or swelling are more common among children who receive four or five consecutive doses of DTaP than those who receive a mixture of DTaP and DTwP[25].

  Swelling of the entire limb has been reported in 2-6% of children after receipt of the fourth or fifth dose of DTaP[26]. Limb swelling may be accompanied by erythema, pain and fever. It may interfere with walking, but most children have no limitation of activity. When DTwP had been used in the past for booster doses, extensive local reactions, including entire limb swelling was a known occurrence.

- **High fever**

  Temperature in excess of 40.5°C may occur as a severe systemic reaction to any DTP vaccine but is four times higher with DTwP than with DTaP.

- **Persistent crying**

  Some infants develop continuous crying which may be inconsolable and last for a number of hours. It is suggested that localized reaction may be a cause of persistent crying. Persistent crying (>1 hour) occurred in children after both DTwP and DT vaccination but was 4 times more common after DTwP vaccination[22]. Persistent crying is more frequent with the initial dose and less frequent thereafter.

- **Seizures**

  The rate of febrile seizures occurring within 3 days of DTwP vaccination has been shown to be reasonably consistent in clinical studies averaging 60/100,000 doses[22]. Febrile seizures after a DTwP vaccine are more common in those individuals with a personal history or a family history of seizures. Febrile seizures, are considered benign and do not result in epilepsy. There is no increased risk of having febrile seizures following DTaP vaccination.

- **Hypotonic-hyporesponsive episode (HHE)**

  HHE is the sudden onset of limpness, reduced responsiveness and pallor or cyanosis[27]. Although, HHE occurs most frequently after whole-cell pertussis vaccine, the reaction has also been documented to occur after other vaccines, including diphtheria, tetanus, *Haemophilus influenzae* type b and hepatitis B[22]. The reported rates following a whole cell pertussis vaccine ranges from 0-291 per 100,000 doses[22]. The cause is not known but recovery occurs spontaneously and no long-term sequelae including neurological damage have been documented. The majority of these infants can be safely re-vaccinated without a recurrence of the HHE[28]. Further, the advent of acellular pertussis vaccines has markedly decreased the frequency of episodes of HHE[29].

- **Encephalopathy**

  The occurrence of encephalopathy within seven days after whole-cell pertussis vaccination has been an issue of intense debate. However, it is still considered as a contraindication for subsequent DTwP vaccination.

- **Dravet syndrome**

  Dravet syndrome, otherwise known as severe myoclonic epilepsy of infancy (SMEI), is a genetically determined epileptic encephalopathy presenting in the first year of life. Seizures following vaccinations have been the presenting feature in 27% of cases with Dravet syndrome, out of which the majority of seizures occurred after DTwP vaccination. Some of the cases of alleged encephalopathy reported following DTwP had been Dravet syndrome[30].

- **Anaphylaxis**

  Anaphylaxis is rare following DTP vaccines.

Special circumstances

- **Natural diphtheria or tetanus infection**

  Natural infection with diphtheria or tetanus does not protect against reinfection. Children with diphtheria or tetanus should receive a diphtheria and tetanus toxoid-containing vaccine (E.g. DTaP, DTwP, DT) during their convalescence (even if they were completely immunized before their illness)[1].

- **Natural pertussis infection**

  Well-documented pertussis disease (E.g. positive culture, polymerase chain reaction, or epidemiologic linkage to a culture-proven case) confers short-term immunity[20]. However, the duration of protection is unknown. DTP should be used to complete childhood immunization (if the child is younger than seven years).

Life-course approach to vaccination

In many countries DTaP vaccine is used for primary vaccination followed by DTaP booster at 18 months, Tdap at 5 years and 10-12 years or later and during pregnancy. This appears to provide robust long-lasting immunity to all three diseases at least until adulthood. Vaccination of pregnant mothers with Tdap at 27-36 weeks of gestation has shown to prevent tetanus in the newborn and pertussis in early infancy. US, Canada and Austria routinely recommend Tdap every 10 years for adults over 18 years.

The risk of infection with pertussis is substantially higher in late childhood and adolescence in Sri Lanka, as we do not use pertussis booster at 5 years and at 10 years.

Storage

2-8°C. Do not freeze.

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CHAPTER 9

HAEMOPHILUS INFLUENZAE TYPE B VACCINE

Introduction

Haemophilus influenzae type b (Hib) is a common cause of bacterial meningitis, pneumonia and sepsis in children[1]. The incidence of meningitis due to Hib in children in Sri Lanka prior to introduction of the Hib vaccine was estimated to be one of the highest in Asia[2]. With the growing antibiotic resistance, immunization has become an increasingly effective means of preventing Hib disease. By the end of 2020, WHO reported that 192 countries had Hib vaccine in their National Immunization Programmes (NIP)[3]. In 2020, the global immunization coverage with 3 doses of Hib vaccine was estimated to be 70%. There is a great variation in immunization coverage between WHO regions and the South East Asia Region (SEAR) was estimated to have a coverage of 83% with 3 doses of Hib vaccine[3]. Sri Lanka uses the pentavalent vaccine in the NIP and in 2020, a coverage of 96% was reported for all three doses of the Hib vaccine[4].

Types of vaccine

All currently licensed Hib vaccines are conjugated. In conjugated Hib vaccines, the capsular polysaccharide, polyribosylribitol (PRP) is conjugated to a variety of protein carriers. The conjugated protein carrier induces a long-lasting T cell dependent B cell immune response to the PRP polysaccharide and induces immunological memory[5]. The currently available conjugated vaccines differ in terms of the type of protein carriers conjugated to the Hib capsular-PRP polysaccharide, method of chemical conjugation, polysaccharide size and their adjuvant[6,7].

- Non-toxic mutant diphtheria toxin CRM 197 (PRP-CRM197)
- Tetanus toxoid (PRP-T)
- Outer membrane protein of *N. meningitidis* (PRP-OMP)

- Diphtheria toxoid (PRP-D) (less immunogenic in children <18 months of age than the other conjugates and has been withdrawn from the market).

  The protein conjugates used in Hib vaccines are themselves not immunogenic and do not give protection against *N. meningitidis*, diphtheria or tetanus[7].

  Hib vaccine, either monovalent or in combination with different antigens, is available in both liquid and lyophilized (freeze dried) preparations.

Available Hib vaccines in combination are as follows[6,7].

- with diphtheria, tetanus and whole cell pertussis and hepatitis B vaccine (DTwP-HepB-Hib) – pentavalent
- with diphtheria, tetanus, acellular pertussis, hepatitis B and inactivated polio vaccine (DTaP-HepB-IPV-Hib) – hexavalent
- with diphtheria, tetanus and whole cell pertussis vaccine (DTwP-Hib)
- with meningococcal vaccine

Efficacy

Hib conjugated vaccines are efficacious from early infancy. Though there is evidence of a decrease in antibody levels over time, in most instances the immunity following the primary series is protective during the years of the highest susceptibility to invasive Hib disease. All conjugate Hib vaccines have demonstrated remarkably high, consistent efficacy and effectiveness against invasive disease following a primary series consisting of two or three doses. Disease following a full course of Hib-PRP vaccine is rare[6,7].

All Hib conjugated vaccines induce a strong response when given as a booster dose in the second year of life. This schedule provides sufficient antibody levels to protect against invasive Hib disease to at least the age of 5 years[7]. There is no difference in the immune response to monovalent or combined Hib vaccines[6]. However, Hib conjugate

vaccines in combination with acellular pertussis antigen induce a lower antibody response than Hib conjugate vaccines in combination with whole cell pertussis antigen or Hib conjugate vaccines separately administered with the DTP containing acellular pertussis antigen[5].

The high efficacy and effectiveness of the Hib conjugate vaccine have been clearly demonstrated by the virtual elimination of Hib invasive disease in countries where the vaccine was introduced. Nasopharyngeal colonization has been drastically reduced in populations with high Hib vaccine coverage. This has resulted in greater reduction in the Hib disease incidence than can be directly attributed to the effects of the vaccine, suggesting that herd immunity (reduced incidence in un-immunized people) is induced by the widespread use of the Hib vaccine[6]. These vaccines do not protect against infection caused by *H. influenzae* strains without capsules, termed non-typeable *H. influenzae* (NTHi), and therefore, do not prevent the majority of cases of otitis media, recurrent upper respiratory tract infections, sinusitis or bronchitis[7].

Indications

- Infants and children under 5 years of age
- Special groups for vaccination:
    - Because of an increased risk of infection, it is recommended to administer Hib vaccine as early as possible to the following groups of children, irrespective of the age[7]
- Anatomical or functional asplenia
- Sickle cell disease
- Less severe immunoglobulin deficiency (refer Chapter 30)
- Hodgkin's disease (in remission)
- Following chemotherapy
- Nephrotic syndrome (in remission)
- HIV infection

- There is no strong evidence of an increased risk of invasive Hib disease in asplenic older children and adults. In spite of the above, many authorities recommend Hib immunization for these individuals. Therefore, national authorities have to define policies for vaccinating older children and adults with asplenia.

The response to the vaccine in children with partial immunoglobulin deficiency, Hodgkin's disease and following chemotherapy is likely to be sub-optimal[7].

Children under two years of age, who have had invasive Hib disease, should get the complete course of immunization as natural infection does not reliably produce protective immunity. Immunization should be commenced approximately one month after the onset of disease. The number of doses required will depend on the age at which the first dose after illness is given, (3 doses up to 12 months: 1 dose for those between 1 to 2 years) ignoring doses given before the illness[6].

Dosage and administration

All conjugate Hib vaccines should be injected intramuscularly. The standard dose is 0.5 mL.

Available evidence suggests that at least 3 doses are needed to achieve high vaccine efficacy and effectiveness. These can be administered as

- 3 primary doses without a booster (3p+0)
- 3 primary doses with a booster (3p+1) OR
- 2 primary doses with a booster (2p+1)

WHO recommends that in countries where the peak burden of severe Hib disease occurs in young infants, providing 3 doses of vaccine early in life may confer a greater benefit. Thus, in general, a three dose primary series is given at the same time with the primary series of DTP.

In settings where the greatest disease morbidity and mortality tend to occur later months of childhood, or where rate reductions of disease are not fully sustained after the routine use of Hib vaccine, WHO recommends that it may be advantageous to give a booster dose following

either a 2p+1 or 3p+1 schedule. It is recommended that this booster dose is best given from 12-15 months of age[8,9].

As per WHO recommendations, the age at first dose and the number of primary doses should be set after considering the local epidemiology, vaccine presentation (Hib conjugate monovalent vaccine or Hib conjugate vaccine in combination with other antigens) and feasibility with the overall routine immunization schedule of the country.

Because serious Hib disease occurs most commonly in children aged between 4 and 18 months, immunization should start from 6 weeks of age, or as early as possible thereafter. Sri Lanka administers first dose at 8 weeks. The first dose may be given as early as 6 weeks of age and the second and third doses may be given at 4th week (if three primary doses are given) or 8th week (if 2 primary doses are given) intervals along with DTP and hepatitis B.

If a booster dose is required, it should be given at least 6 months after the completion of the primary series.

Sri Lanka National Immunization Programme recommends administration of Hib vaccine at 2, 4 and 6 months of life[10]. For children aged 1-5 years who have not received a primary series of Hib vaccine, one dose is sufficient. Hib vaccine is not required for healthy children after 5 years of age[6].

If the vaccination course has been interrupted, the schedule should be resumed without repeating the previous doses[6].

Limited evidence suggests that HIV-infected children would benefit from receiving a booster dose regardless of the number of primary doses received and regardless of anti-retroviral therapy[6]. Individuals with immunosuppression caused by aetiologies other than HIV are at greater risk of infection with non-typeable *H. influenzae* (NTHi). However, there is insufficient evidence to indicate a significant risk of developing Hib disease. Therefore, there is no reason to promote a booster dose in such populations[6].

An immunization series commenced with one type of conjugate Hib vaccine may be completed with another formulation.

Hib vaccine, as a separate vaccine, can be given at the same time as other routine vaccines at a different site. However, it should not be mixed in the vial or syringe with any other vaccine[6].

Contraindications

- Hypersensitivity or anaphylaxis to any component of the vaccine
- History of hypersensitivity to a previous dose of Hib vaccine

Adverse effects

Serious adverse events following immunization with Hib vaccine are uncommon. A meta-analysis of trials of Hib-PRP vaccinations from 1990 to 1997 has confirmed it[11]. However, some local and systemic reactions have been reported. In general, these reactions appear within 24-72 hours after vaccination and are mild, transient and resolve spontaneously[6,7].

- Local reactions – redness, pain and swelling at the injection site.
- Systemic reactions – fever, loss of appetite, restlessness, irritability, vomiting, diarrhoea and unusual crying.

Though there have been rare reports of transverse myelitis, thrombocytopenia and Guillain-Barré syndrome (GBS), they are not proven to be causally related to Hib vaccine[12].

Storage

2-8°C

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CHAPTER 10
HEPATITIS A VACCINE

Introduction

Hepatitis A virus (HAV) produces an acute hepatitis after an average incubation period of 28 days (range 15-50 days). It is transmitted by the faeco-oral route, usually through person-to-person spread or contaminated food and drink. About 70% of the infections are asymptomatic in children <16 years, compared to 10-25% of adults. A person is most infectious from 14-21 days before and through 1 week after the onset of symptoms.

Complications of hepatitis A include relapsing hepatitis, cholestatic hepatitis and fulminant hepatitis. Fulminant hepatitis leading to acute liver failure and death occurs in less than 0.5% but this increases up to 2% in adults over 50 years. Acute liver failure is more common in pregnancy and in alcoholics with liver disease. HAV does not cause a chronic infection and there are no carriers of the virus. HAV has been transmitted by transfusion of blood and blood products collected from donors during their viraemic phase of infection. Sexual transmission can occur, especially among men who have sex with men (MSM).

Globally, an estimated 1.5 million clinical cases of hepatitis A occur each year. Majority of cases occur among children in highly endemic areas like Asia and Africa[1]. The anti-HAV seroprevalence is decreasing in many parts of the world including Asia, with a shift of infection towards adolescents and adults[2]. Studies in Sri Lanka, from 1976 to 2009 have shown a similar trend with a shift towards a lower seroprevalence rate[3]. Occasional cases of hepatitis due to HAV continue to occur in Sri Lanka.

Travellers to Sri Lanka are advised to be immunized against hepatitis A before travel. Accelerated schedules are available for such travellers.

Types of vaccine

Two types of vaccines are available worldwide.

- Inactivated vaccines (formaldehyde inactivated)
- Live, attenuated vaccines (available only in China and India)[1]

The preparations of inactivated vaccines available in Sri Lanka include

- Monovalent hepatitis A vaccines (formaldehyde inactivated)
- Combined vaccines with hepatitis B (hepatitis A – inactivated, hepatitis B – recombinant)

A combined vaccine with typhoid vaccine is available in countries like Britain and Australia for travellers[4,5].

Efficacy

- Pre-exposure – 94% to 95% (The duration of protection is estimated to be as long as 25 years[6])
- Post exposure – 96%[6]

Indications

- For individuals over 12 months of age

Recommended for

- Food handlers
- Children, adolescents and high-risk persons during hepatitis A outbreaks
- Persons with occupational risk
    - Armed forces, persons working in natural disaster or war affected areas, day care staff, hospital workers, laundry and cleaning staff, sewage workers
- Persons at high risk due to lifestyle
    - Intravenous drug users, MSM
- Persons at high risk due to medical conditions
    - Contacts of patients with hepatitis A, patients needing repeated transfusions of blood and blood products, persons with chronic liver disease, persons with developmental disabilities
- Travellers to high endemic areas

Post-exposure prophylaxis

Passive or active immunization or a combination of the two methods can be used for post-exposure prophylaxis.

Human normal immunoglobulin (HNIG)[7]

HNIG has limited use at present. It is recommended with the hepatitis A vaccine for post exposure prophylaxis of close contacts of patients. HNIG is recommended in addition to vaccine for contacts who are less able to respond to vaccine (those aged 60 or over, those with immunosuppression and those with HIV infection (with a CD4 count <200 cell per μL) and those at risk of severe complications (those with chronic liver disease, including chronic hepatitis B or C infection).

When administered IM within 2 weeks after exposure to HAV, HNIG has shown 47-100% efficacy in preventing infection[8]. It is not available in Sri Lanka at present.

If HNIG is administered to persons for whom hepatitis A vaccine is also recommended, a dose of vaccine should be administered simultaneously with HNIG at a different site. A second dose should be administered 6-12 months after the first dose to complete the series[5].

Hepatitis A vaccine

It is recommended for healthy persons over the age of 1 year who have been exposed to hepatitis A infection within the last 14 days[1]. The vaccine is preferred over HNIG as it gives long term protection[6]. Vaccine recipients should complete the second dose 6-12 months after the first dose to protect against infections from future exposures. Monovalent vaccines are preferred over combination vaccines for post exposure prophylaxis[5].

Dosage and Administration

- **Monovalent vaccine**

  Two doses given at 6-12 month intervals, IM to the deltoid muscle
  - 1-15 years - 0.5 mL
  - ≥16 years - 0.5 or 1.0 mL (depending on the type of vaccine)

Different vaccine brands could be interchanged.

- **Combined vaccine:** A combination vaccine containing inactivated hepatitis A and recombinant hepatitis B vaccine is available for use in persons over 16 years. The combination vaccine is given IM as a 3-dose series, at 0, 1 and 6 months. The dose is 1.0 mL.

It is recommended that the full series should be continued with the combination vaccine, and not interchanged with the monovalent vaccines. However, combined hepatitis vaccines produced by different manufacturers, are interchangeable.

Current evidence suggests that a single-dose of inactivated hepatitis A vaccines seems to be comparable in terms of effectiveness, is less expensive and easier to implement than the classical 2-dose schedule. However, the double dose schedule is still recommended. A 2-dose schedule is preferred for high risk patients and immunocompromised individuals[1].

Hepatitis A vaccines (both the monovalent and the combined) could be administered simultaneously with other vaccines. This can be safely administered to immunocompromised including patients with HIV[1]. Hepatitis A vaccines are not routinely recommended for pregnant or breastfeeding women. However, they can receive the vaccines if necessary[6]. Immunocompromised individuals and elderly patients show a reduced immune response to hepatitis A vaccination[1].

Contraindications

- Acute febrile illness
- Hypersensitivity to previous dose or any component of the vaccine

Adverse effects

- Local – transient erythema, soreness and induration at injection site.
- Systemic – headache, malaise, fever, vomiting, nausea. These usually occur 3-5 days after vaccination and lasts for 1-2 days.

Serious adverse events attributed to hepatitis A vaccine are rarely reported[9].

Storage

2-8°C. Do not freeze.

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CHAPTER 11
HEPATITIS B VACCINE

Introduction

Hepatitis B is caused by hepatitis B virus (HBV), which produces an illness that is clinically indistinguishable from other forms of infectious hepatitis. It is a significant cause of acute and chronic hepatitis in the world. Acute infection is frequently symptomatic in adults, and usually asymptomatic in young children, particularly infants.

The sequelae of chronic HBV infection vary from an asymptomatic chronic carrier state, to the development of chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC). Acute hepatitis B, characterised by acute inflammation and hepatocellular necrosis, occurs in approximately 1% of perinatal infections, 10% of early childhood infections (in children aged 1-5 years) and 30% of late infections (in persons aged >5 years). Fulminant disease develops very rarely in infants and children, but occurs in 0.5-1% of adult cases of acute hepatitis B, with a case-fatality rate of 20-33%[1]. In 2019, hepatitis B resulted in an estimated 820,000 deaths, mostly from cirrhosis and hepatocellular carcinoma[2].

The rate of progression from acute to chronic hepatitis B is primarily determined by the age of infection, and infections acquired during infancy and early childhood leads to chronic hepatitis in about 95% of cases. The risk of chronic infection remains high up to 5 years of age after which the rate stabilises at around 5%[1]. Immune tolerance to viral antigens acquired at birth is believed to play an important role in neonatal HBV persistence.

Carrier prevalence of HBV varies in different parts of the world and may be quite variable within countries. A study conducted in Sri Lanka prior to introduction of the HBV vaccine into the NIP in 2003, showed that the HBV prevalence in the community to be 0.46%[3].

HBV, though similar to HIV in its primary routes of transmission, is hundred times more infectious. It is transmitted parenterally, sexually, vertically and horizontally. However, in a significant proportion of patients, the route of transmission cannot be determined. HBV is relatively heat stable and remains infectious for at least one week in the environment and could be a source of infection[4].

Hepatitis B vaccine for infants had been introduced nationwide in 190 countries by the end of 2020. Global coverage with 3 doses of hepatitis B vaccine is estimated at 83%. In addition, 113 countries have introduced the WHO recommended birth dose to newborns within the first 24 hours of life and global coverage is 42%[5]. According to latest WHO estimates, the proportion of children under five years of age chronically infected with HBV dropped to just under 1% in 2019, down from around 5% in the pre-vaccine era[2]. Despite recombinant hepatitis B vaccine being available since 1986, it is estimated by the WHO that, 296 million people were living with chronic hepatitis B infection in 2019, with 1.5 million new infections each year[2].

Types of vaccine

It is a recombinant vaccine and contains hepatitis B virus surface antigen (HBsAg) with alum as an adjuvant. In certain preparations, thimerosal is present as a preservative. The vaccine is available as monovalent formulations for birth doses or for vaccination of adults. It is also available in combination with other vaccines:

- DTwP-HepB-Hib (pentavalent vaccine)
- DTaP-HepB-IPV-Hib (hexavalent vaccine)
- Hepatitis B-hepatitis A

A specific recombinant hepatitis B vaccine that is intended for adult patients with renal insufficiency uses aluminum phosphate and lipid A as potent adjuvants. These potentiate the immune response and thereby elicit a long-standing antibody response after vaccination[1,6]. This elicits a higher and a long-standing antibody response compared to use of 4 double doses (40ug/dose) of the standard hepatitis B vaccine[6].

Efficacy

Protective efficacy is determined by the presence of anti-HBs antibodies. Protective efficacy is higher in infants compared to adults[1]. An anti-HBs concentration of 10 mIU/mL measured 1-2 months after administration of the last dose of the primary vaccination series is considered a reliable marker of protection against future infection. Those who have seroconverted are protected even though the antibodies may not be detectable later in life.

Protective efficacy is higher in infants compared to adults. The antibody response rate reduces primarily with ageing, in chronic disease, HIV infection, smoking and obesity[1].

Ninety percent of vaccinated persons remain protected for at least 30 years[1]. Currently, the evidence does not provide a basis for a booster dose of hepatitis B vaccine after completion of the primary vaccination series for persons with normal immune status[1]. However, additional longer-term studies should be conducted to explore lifelong protection conferred by hepatitis B vaccine and the need for booster doses in different subgroups of the population.

Efficacy of vaccination in immunocompromised individuals

Some infants born prematurely with low-birth-weight (<2000 g) may not respond well to vaccination at birth and should receive 3 additional doses of the vaccine. Immunosuppressive illnesses, including advanced HIV infection, chronic renal failure, chronic liver disease and diabetes, are associated with reduced immunogenicity following vaccine administration. They should be vaccinated early in the disease with the special vaccine adjuvanted with aluminum phosphate and 3-O-desacyl-4 -monophosphoryl lipid A (ASO4)[1]. As an alternative, double dose of the vaccine could be administered (refer Chapter 32 for further details).

Indications for assessing post vaccination antibody response

Post vaccination antibody response should be tested in:

- people at risk of occupationally acquired infection e.g. health care workers (HCW)
- vaccinated infants born to HBsAg positive mothers
- patients with chronic renal disease undergoing haemodialysis
- persons with HIV and other immunocompromised conditions
- patients undergoing multiple transfusions with blood/blood products
- sex partners or needle-sharing partners of people who are HBsAg positive

In the above situations testing should be performed 1-2 months after administration of the last dose of the vaccine series and an anti-HBs titre of ≥10 mIU/mL is considered protective. Those found to have an anti-HBs antibody titre of <10 mIU/mL after the primary vaccination series should be revaccinated with a full three dose course of vaccines, followed by anti-HBs antibody testing 1-2 months after the third dose. If the titre is <10 mIU/ml after the second series they are known as non-responders. Alternatively, a dose of vaccine is administered and anti-HBs titre is tested one month later and if found to be adequate, no further doses are indicated. If the antibodies are inadequate, the full course of vaccine should be administered. Anyone who does not respond to revaccination should be tested for HBsAg[7]. The healthcare workers who are non-responders need to be evaluated after all high-risk exposures.

For healthcare personnel who wish to enter the UK for employment, it is preferable to achieve anti-HBs levels above 100 mIU/ml, although levels of 10 mIU/ml or more are generally accepted as sufficient to protect against infection[8].

By preventing HBV infection, hepatitis B vaccine also protects against hepatitis D virus (HDV) infection.

Indications

- All newborn babies, within 24 hours of birth[1] in all countries will high prevalence
- All children, adolescents and adults if not vaccinated during infancy
- Persons at high risk of contracting HBV infection including
    - persons with high-risk sexual behaviour
    - partners and household contacts of chronic HBsAg-positive persons
    - injecting drug users and men who have sex with men
    - prisoners
    - persons with chronic liver diseases
    - patients on dialysis
    - patients with diabetes
    - patients with HIV
    - persons who frequently require blood or blood products
    - recipients of solid organ transplants / haematopoietic stem cell transplants
    - those at occupational risk e.g. healthcare and emergency care staff
    - international travellers to HBV endemic countries
- Post exposure vaccination following needle stick injuries (refer PEP for additional information).

Dosage and administration

The recommended dose varies by product and with the age of the recipient. Therefore, manufacturer's recommendation for dosage should be followed. In most cases, infants and children (<15 years) receive 50% of the adult dose. The standard paediatric dose contains 5-10 μg HBsAg, and the standard adult dose is 10-20 μg depending on the product.

The vaccine is administered by IM route. The anterolateral aspect of the thigh is the preferred site of injection for infants and children aged

below 2 years; the deltoid muscle is preferred for older children and adults. Administration into the buttock (gluteal muscle) is not recommended as this is associated with decreased protective antibody levels and injury to the sciatic nerve.

A higher vaccine dose (40 μg) is required to induce a protective antibody response in immunocompromised and haemodialysis patients[1].

For vaccination schedules beyond infancy, 3 doses are recommended, with the second dose administered at least 1 month later and the third dose 6 months after the first dose. There is no evidence to support the need for a booster dose following 3 (or 4) doses if the hepatitis B vaccine in routine immunization programmes.

Vaccination schedules

Newborns

The WHO recommends that all newborns including low birth weight and premature infants should be vaccinated ideally within 24 hours of birth or as soon as possible with the monovalent HBV vaccine. The monovalent birth dose should be followed by 2 doses of hepatitis B containing combination vaccines administered during the same visits as the first and third doses of DTP containing vaccines. Alternatively, 4 doses of hepatitis B vaccine may be given for programmatic reasons (E.g. one monovalent birth dose followed by three hepatitis B containing vaccine doses)[1]. The additional dose does not cause any harm. The birth dose of the hepatitis B vaccine can be co-administered with BCG vaccine and should be given at different injection sites[7]. However, currently the NIP administers three doses of the vaccine to all infants at 2, 4 and 6 months of age and no birth dose is included.

All pregnant women should be tested for HBsAg during the early prenatal visit (E.g. first trimester) in each pregnancy, even if they have been vaccinated or tested previously[8]. Transmission from mother to infant during birth is one of the most efficient modes of HBV transmission. If the mother is positive for both HBsAg and HBeAg, about 80-90% of infants will become infected and among those 90% become carriers.

Newborns of mothers who are HBsAg positive should receive both the monovalent HBV vaccine and hepatitis B specific immunoglobulin (HBIG) within the first 12 hours simultaneously with the BCG vaccine at different injection sites as there is no immune interference. Post vaccination serological testing for anti-HBs and HBsAg should be performed after the completion of vaccine series at age 9-12 months. If anti-HBs is <10 mIU/mL they should be given a single dose of the vaccine and retested. Infants whose anti-HBs remains <10 mIU/mL following the single dose vaccination should receive 2 additional doses of hepatitis B vaccine to complete the second series, followed by post vaccination serologic testing 1-2 months after the final dose[9].

Children and adults

3 doses of vaccine can be given at any age, at 0, 1 and 6 month schedule.

Travellers and high-risk groups

WHO recommends 0, 7, 21 days and booster at 12 months for travellers[1].

Chronic kidney diseases

A vaccine dose of 40 µg/mL should be administered at 0, 1, 2, and 6 or 12 months[9]. The antibody titres against hepatitis B surface antigen (anti-HBs) should be assessed at 2 to 3 months after the primary course is completed and annually thereafter and protection may persist only as long as anti-HBs levels remain above 10 mIU/mL. Antibody levels should, therefore, be monitored annually and if they fall below 10 mIU/mL, a booster dose of vaccine should be given to patients who have previously responded to the vaccine[8].

Contraindications

- Hypersensitivity to any of the vaccine components
- Anaphylactic reaction to a previous dose of hepatitis B vaccine
- Allergy to common baker's yeast

Neither pregnancy nor lactation is a contraindication for use of the vaccine.

Adverse effects

The vaccine has a proven safety record. Adverse effects, when they occur, are transient and minor. These include local soreness, redness, nausea, diarrhoea, malaise and fever[1].

Storage

2-8°C. Do not freeze as it causes dissociation of the antigen from the alum adjuvant, resulting in loss of potency.

Post-exposure prophylaxis (PEP)

Prophylactic treatment to prevent infection after exposure to HBV should be considered in the following situations:

- Percutaneous or permucosal exposure to HBsAg-positive blood or body fluids
- Perinatal exposure of an infant born to an HBsAg-positive mother.
- Sexual exposure to a HBsAg- positive person
- Household exposure

Perinatal exposure[11]

For an infant with perinatal exposure to an HBsAg positive mother, a regimen combining one dose of hepatitis B immunoglobulin (HBIG) with the first dose of hepatitis B vaccine should be administered within 12 hrs of birth. This is 85-95% effective in preventing development of the HBV carrier state. HBIG is not required by the baby if the mother is positive for Anti HBeAb in spite of being an HBsAg positive carrier.

The following schedules of vaccination are recommended in the order of preference

- HBIG + HBV vaccine at 0, 2, 4, 6 months as per national immunization programme or
- HBIG + HBV vaccine at 0, 1, 6 months or
- If HBIG is not available HBV vaccine accelerated schedule at 0, 1, 2 and 12 months

Simultaneous administration of HBIG and vaccine should be at two different sites.

Sexual partners of persons with acute hepatitis B virus infection[11]

All susceptible persons whose sexual partners have acute hepatitis B infection should receive a single dose of HBIG and hepatitis B vaccination simultaneously at 0, 1 and 6 months after screening for HBV infection.

Household contacts of persons with acute hepatitis B virus infection[11]

Prophylaxis of an infant less than 12 months of age with HBIG and hepatitis B vaccine at 0, 1 and 6 months is indicated if the mother or primary care-giver has acute HBV infection. Prophylaxis for other household contacts of persons with acute HBV infection is recommended. If the index patient becomes an HBV carrier, all household contacts should receive hepatitis B vaccine after screening for HBV infection.

Sexual partners and household contacts of chronic carriers[11]

This group should be tested for HBV markers (HBsAg, HBsAb and total HBcAb) prior to vaccination as the contacts may have become carriers already or protected after exposure. If the markers are negative they should be vaccinated using the 0, 1 and 6 month schedule.

Percutaneous or permucosal exposure to HBsAg positive blood[11]

Wounds and skin sites that have been in contact with blood or body fluids should be washed with soap and water; mucous membranes should be flushed with water. Antiseptic can be used in addition and is optional.

Specific management is as in table 1.

Table 1. Post-exposure management of health-care personnel after occupational percutaneous and mucosal exposure to blood and body fluids[12]

	Post-exposure testing		Post-exposure prophylaxis		Postvaccination serologic testing†
	Source patient (HBsAg)	HCP testing (anti-HBs)	HBIG*	Vaccination	
Documented responder § after complete series (≥3 doses)	**No action needed**				
Documented non-responder¶ after 6 doses	Positive/unknown	No**	HBIG x2 separated by 1 month	No	No
	Negative	**No action needed**			
Response unknown after 3 doses	Positive / unknown***	<10 mIU/mL**	HBIG x1	Initiate revaccination	Yes
	Negative	<10 mIU/mL	None		
	Any result	≥10 mIU/mL	**No action needed**		
Unvaccinated / incompletely vaccinated	Positive/unknown	No**	HBIG x1	Complete vaccination	Yes
	Negative	No	None	Complete vaccination	Yes

Abbreviations: HCP = health-care personnel; HBsAg = hepatitis B surface antigen; anti-HBs = antibody to hepatitis B surface antigen; HBIG = hepatitis B immune globulin.

* HBIG should be administered intramuscularly as soon as possible after exposure when indicated. The effectiveness of HBIG when administered >7 days after percutaneous, mucosal, or nonintact skin exposures is unknown. HBIG dosage is 0.06 mL/kg.

† Should be performed 1-2 months after the last dose of the HepB vaccine series (and 6 months after administration of HBIG to avoid detection of passively administered anti-HBs) using a quantitative method that allows detection of the protective concentration of anti-HBs (≥10 mIU/mL).

§ A responder is defined as a person with anti-HBs ≥10 mIU/mL after ≥3 doses of HepB vaccine.

¶ A non-responder is defined as a person with anti-HBs <10 mIU/mL after ≥6 doses of HepB vaccine.

** HCP who have anti-HBs <10mIU/mL, or who are unvaccinated or incompletely vaccinated, and sustain an exposure to a source patient who is HBsAg-positive or has unknown HBsAg status, should undergo baseline testing for HBV infection as soon as possible after exposure, and follow-up testing approximately 6 months later. Initial baseline tests consist of total anti-HBc; testing at approximately 6 months consists of HBsAg and total anti-HBc.

*** When a source patient is unknown (e.g., as occurs from a puncture with a needle in the trash), the exposed HCP should be managed as if the source patient were HBsAg-positive.

New vaccines for hepatitis B

A two-dose recombinant, adjuvanted vaccine, given one month apart was approved by the FDA in 2017 and recommended by ACIP in 2018 for use in those above 18 years of age[13].

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CHAPTER 12
HUMAN PAPILLOMAVIRUS VACCINE

Introduction

Human papillomaviruses (HPV) are widespread throughout the general population and is known to produce epithelial tumours of the skin and mucous membranes. HPV genital infection is usually asymptomatic and subclinical. Most HPV infections are transient but persistent genital infection with certain oncogenic viral genotypes could lead to the development of anogenital precancers and cancers. Diseases caused by HPV include cancers of the cervix, vagina, vulva, penis and anus; a subset of head and neck cancers; anogenital warts; and recurrent respiratory papillomatosis.

Low risk (non-oncogenic) HPV genotypes 6 and 11 are associated with 90% of genital warts (condylomata accuminata) and majority of recurrent respiratory papillomatosis (RRP). High risk (oncogenic) HPV genotypes 16 and 18 are associated with 70% of cervical cancers and >80% of other anogenital cancers[1,2].

Prophylactic HPV vaccines are available to immunize HPV unexposed adolescents in prevention of HPV genital infection. Currently, 3 types of HPV vaccines (bivalent, quadrivalent and 9-valent) are available, of which 2 vaccine types (bivalent and quadrivalent) are available in Sri Lanka. These vaccines are prepared using recombinant technology. Both are prepared from purified L1 structural proteins that self-assemble to form HPV type-specific empty shells or virus-like particles (VLP). Neither vaccine contains live biological products or viral DNA. HPV vaccines are designed for prophylactic use with the primary target group of females aged 9-14 years and do not clear existing HPV infection and are not recommended for the treatment of HPV-related diseases[1,2]. Therapeutic HPV vaccines are under consideration for development in the future.

Bivalent vaccines: 2 types of vaccines are available.

- The WHO prequalified vaccine which includes L1 VLP of HPV genotypes 16 and 18. This is produced using a baculovirus technology that uses insect cells with an adjuvant, ASO4 that contains aluminium hydroxide plus mono phosphoryl lipids (alum and MPL). This vaccine is indicated for use in females and males from 9 years of age with the primary target group females aged 9-14 years[1,3]. The manufacturer recommends administering this vaccine to females aged 9-45 years (Cervarix product monograph revision: February 25, 2019).
- Recombinant HPV bivalent vaccine, recently received the WHO pre-qualification to be used for priority age group 9-14 years and could be used from 9-45 years. This product is presently not available in Sri Lanka.

Quadrivalent vaccine: it consists of a mixture of HPV genotype specific L1 VLPs of four genotypes, 6,11,16 and 18. The substrate of the vaccine is based on recombinant yeast technology (*Saccharomyces cerevisiae*). It contains aluminum hydroxyphosphate sulphate as an adjuvant.

This vaccine has been licensed for use in females and males from 9 years of age with the primary target group of females aged 9 to 14 years[1,3]. The manufacturer recommends administering this vaccine to females and males aged 9-26 years.

Nonavalent vaccine: includes L1 VLP of HPV genotypes for 9 genotypes, 6, 11, 16, 18, 31, 33, 45, 52 and 58. The substrate of the vaccine is based on recombinant yeast technology (*Saccharomyces cerevisiae*). It contains aluminum hydroxyphosphate sulphate as an adjuvant.

This vaccine has been globally licensed for use in females and males from 9-26 years of age[1]. This product is presently not available in Sri Lanka.

Efficacy

Both vaccines available in Sri Lanka are generally safe, well tolerated and with high efficacy and immunogenicity. Overall seroconversion observed is 99-100% for both vaccines. Long lasting immunity after vaccination has been observed for at least 10 years, which includes 100% efficacy against HPV type 16 and18 related persistent HPV infection and cervical intraepithelial neoplasia (CIN) 2 and 3.

Lower seroconversion and lower vaccine efficacy have been observed among immunocompromised individuals who are identified as a risk category for HPV induced cancers.

Indications

Bivalent vaccine for the prevention of:

- cervical precancers and cancers
- vulvar and vaginal precancers and cancers
- anal cancers

Quadrivalent vaccine for the prevention of:

- cervical precancers and cancers
- vulvar and vaginal precancers and cancers
- anal and penile cancers
- anogenital warts (condylomata acuminata)

Benefits are observed especially among sexually unexposed individuals.

Dosage and administration

Two schedules are recommended for different age categories

0.5 mL is administered IM as

- 2 doses for children 9-14 years of age: at 0 and 6 months
- 3 doses for 15 years and older:
    - At 0, 1 month and 6 months for bivalent HPV vaccine
    - At 0, 2 months and 6 months for quadrivalent HPV vaccine

All HPV vaccines are non-live and non-infectious and could be co-administered with other vaccines using separate syringes and different injection sites.

Prophylactic vaccination of sexually active women

Prophylactic vaccination of sexually active women is not recommended by WHO but is not considered a contraindication. However, there is no evidence that such vaccination prevents vaccine preventable HPV genotype associated pre-cancers and cancers among women with previous HPV exposures.

Cervical cytology screening

Cervical cytology screening, diagnosis and treatment of pre-cancerous lesions and cancers will remain as recommended and HPV vaccination should be considered as part of a coordinated and comprehensive strategy to prevent cervical cancers.

Immunocompromised persons

Immunocompromised persons and / or HIV-infected females above 9 years of age can be vaccinated with HPV vaccines. At least 2 doses or ideally 3 doses of HPV vaccines are recommended until further evidence is available. The recommendation of 3-dose schedule is considered due to the lower immunogenicity for immunocompromised individuals[1,3].

Contraindications

- Severe allergic reactions after a previous dose or to a component of the vaccine
- Severe acute illnesses

Use in pregnancy

HPV vaccine is not recommended to be given during pregnancy even though teratogenicity has not been observed in animal studies. Vaccines could be administered to lactating mothers as antigen or antibody excretion in breast milk has not been observed[1,5].

Adverse effects

Mild and transient local reactions at the site of injection (erythema, pain or swelling) were reported following HPV vaccination which usually resolves within 3-4 days. Systemic adverse events (fatigue, headache and myalgia) are other symptoms observed[1,5].

Preventing syncope after vaccination

Syncope may occur after vaccination among adolescents and young adults. This is described as a preventable event after injection among adolescents and the vaccinee should be advised to sit down during vaccination.

Storage

2-8°C protected from light. Do not freeze.

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CHAPTER 13
INFLUENZA VACCINE

Introduction

Influenza A and B viruses are important human respiratory pathogens. They are transmitted mainly by droplets and aerosols originating from the respiratory secretions of infected people and occasionally via contact with virus-contaminated fomites. Both type A and B viruses cause seasonal influenza epidemics, outbreaks and sporadic cases. Disease can range from asymptomatic to severe illness and death. Seasonal influenza occurs globally and is estimated to infect (symptomatically or asymptomatically) 1 in 5 unvaccinated children and 1 in 10 unvaccinated adults[1].

In temperate climates, seasonal epidemics are experienced mainly during the winter; in subtropical and tropical regions, influenza may occur throughout the year, with irregular outbreaks[2]. Each year, there are an estimated 1 billion cases of influenza, of which 3-5 million are severe, and between 290,000 and 650,000 influenza-related respiratory deaths (case-fatality rate, 0.1-0.2%). Morbidity and mortality from influenza in the tropics and subtropics are likely to be underestimated[3,4]. During the last decade in Sri Lanka, there has been an increased incidence of influenza, generally observed during April to June and November to January. Vaccination is currently the only effective means of reducing the burden of influenza in the community[5].

Inactivated (IIV) and live attenuated seasonal influenza vaccines (LAIV) are available as either trivalent (TIV) or quadrivalent (QIV) formulations. The trivalent formulation includes 2 influenza A subtypes (H1 and H3) and 1 influenza B virus (Yamagata or Victoria lineage), while the quadrivalent has 2 influenza A and 2 influenza B viruses (1 from each lineage). Currently available influenza vaccines are produced using either eggs, cell lines or recombinant based methods. While the egg-based and cell-based approaches use candidate vaccine viruses produced in eggs or cell culture, the recombinant-based approach

uses purified influenza antigens i.e. haemagglutinin produced using recombinant DNA technology. Inactivated egg-based vaccines are still most commonly used[1].

The virus strains in the vaccines change each year, based on global surveillance and scientists' estimations regarding which types and strains of virus are likely to circulate during the next season.

There are two types of vaccine formulations for the northern and southern hemispheres to be used in the respective winter seasons. For countries in equatorial regions, epidemiological considerations influence the choice of the vaccine[1]. Currently, the southern hemisphere vaccine is registered in Sri Lanka.

Types of vaccine

- Inactivated trivalent and quadrivalent vaccines* derived from strains cultured in cells or eggs – These injectable vaccines are approved for use in individuals older than 6 months

  * whole virus/split virus/subunit

- Intranasal live attenuated influenza vaccine** (LAIV) – This vaccine is recommended for individuals 2-50 years of age and is not recommended during pregnancy

  ** cold adapted/genetically re-assorted

Recombinant vaccines are produced in insect cell culture using a baculovirus expression system and contains no preservatives or egg protein. Quadrivalent formulations are available and, like the trivalent vaccines, have acceptable efficacy and safety profiles. It is registered for use in persons over 18 years.

These vaccines are not widely available.

Effectiveness

The effectiveness varies every year and depends on a patient's characteristics, such as age, health status and the similarity or match of the vaccine to the circulating strains in the community. When the vaccine

matches the viruses in circulation, the risk is reduced by 40-60% in the overall population, with better results against influenza B and influenza A (H1N1) viruses than influenza A (H3N2)[6].

The pooled efficacy of TIV formulations against clinical disease in adults aged 18-65 years across 12 seasons, in randomized controlled trials, was 59% (95% CI: 51-67%). IIVs reduced the risk of laboratory-confirmed influenza from 2.3% among those who were unvaccinated to 0.9% (RR 0.41, 95% CI 0.36-0.47)[7].

There have been few randomized controlled trials in children (aged 6 months to 17 years), though data are available comparing IIVs formulated with or without an adjuvant and comparing IIVs with LAIVs. The trials generally reported vaccine efficacy in the range of 45-91%[3]. A 2018 Cochrane review to assess the use of influenza vaccines in the elderly concluded that the effectiveness of TIV in this group was modest, irrespective of setting, outcome, population and study design. This review found that IIV had a VE of 58% (95% CI 34-73%) in people over 65 years of age[8].

Influenza vaccination prevents infection in pregnant women, as well as in their newborns through transfer of maternal antibodies. The pooled estimate from 3 randomized clinical trials (RR 0.5, 95% CI 0.3-0.7) conducted in low-income countries and 2 case-control studies (OR 0.4, 95% CI 0.2-0.6) showed that the seasonal vaccine was protective against laboratory-confirmed influenza in pregnant women[9].

Protective immunity generated by the vaccine typically takes up to two weeks to develop, with moderate effectiveness lasting about 6 months. Annual vaccination prevents severe and fatal influenza, especially in the elderly, highlighting its importance.

Indications

- General population
  - Any person who wishes to be protected from influenza
  - International travellers

- People at high risk for complications
  - All individuals over 65 years of age
  - Residents and care givers of institutions for the elderly and the differently abled.
  - Individuals with chronic conditions e.g. chronic cardiovascular, pulmonary, metabolic or renal disease or who are immuno-compromised.
- Pregnant women

  Pregnant and postpartum women are at higher risk of severe illness and complications. Influenza vaccine containing the killed virus is safe and is recommended for all pregnant women. It is safe in all trimesters of pregnancy[10].
- Special groups
  - Healthcare workers
  - Household members who are in close contact with high-risk persons
  - Essential services

Dosage and administration

Vaccine is recommended to be administered annually.

Inactivated vaccine

- Previously not vaccinated.
  - 6 months – 3 years of age – two doses one month apart. Half adult dose (0.25 mL) IM anterolateral aspect of thigh/deltoid.
  - 3-8 years of age – two doses one month apart. adult dose (0.5 mL) IM deltoid muscle.
  - >9 years – single dose (0.5 mL) IM deltoid muscle.
- Previously vaccinated – single dose.
  - 6 months – 3 years of age – half adult dose (0.25 mL) IM anterolateral aspect of thigh/deltoid.
  - >3 years of age – adult dose (0.5 mL) IM deltoid muscle.

Live attenuated vaccine (LAIV) – given as a nasal spray

- Children aged 2-8 years who have not received seasonal influenza vaccine during the previous influenza season – 2 doses, at least 4 weeks apart
- 9-50 years – single dose

Contraindications

Inactivated vaccines

- Infants under 6 months of age
- Previous adverse reaction to influenza vaccine
- Hypersensitivity to any component of influenza vaccine

LAIV

- Children <2 years of age
- Adults ≥50 years of age
- Individuals with a history of severe allergic reaction to any component of the vaccine or to a previous dose of any influenza vaccine.
- Children 2-7 years of age receiving aspirin or other salicylates (because of the association of Reye syndrome with wild-type influenza virus infection).
- Pregnant women
- Individuals with known or suspected immunodeficiency diseases or immunosuppressed states (including HIV).
- Children with an acute episode of asthma at the time of vaccination and in children with severe asthma.

Egg allergy

Published studies involving a large number of individuals allergic to egg protein revealed that influenza vaccine could be administered without any serious reactions. This is due to very low amount of egg protein in the vaccine. There is strong evidence that individuals with egg allergy

can safely receive an influenza vaccine without any additional precautions beyond those recommended for any vaccine[11].

Adverse effects

Inactivated vaccines

- Local reactions at the site of the injection – pain, erythema or induration.
- Systemic effects – low grade fever and body aches lasting for 1-2 days.
- Guillain-Barré syndrome – very rare[12].

LAIV

- Mild-rhinorrhoea, nasal congestion, fever, sore throat

Co-administration

IIVs do not appear to interfere with concomitantly administered vaccines of the routine childhood immunization programme, although febrile seizures may be more likely in infants.

Additionally, IIVs do not appear to interfere with concomitantly administered current vaccines for COVID-19. LAIV does not interfere with the immune response to measles, mumps and rubella or varicella vaccines administered at the same visit[13].

Storage

2-8°C. Protect from light. Should not be frozen.

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CHAPTER 14
JAPANESE ENCEPHALITIS VACCINE

Introduction

Japanese encephalitis (JE) is a disease of public health importance in many Asian countries. An estimated 3 billion people in 24 countries, mainly in the WHO South - East Asian and Western Pacific regions are considered at risk of JE, with an estimated 68,000 clinical cases every year[1,2]. It is caused by a flavivirus transmitted to man through mosquitoes and five genotypes of JE virus (JEV) have been identified[3]. This disease primarily occurs in children and most infections are asymptomatic. The ratio of infection to symptomatic illness has been estimated to vary between 25:1 and 300:1. The incubation period is 4-14 days. It is an infection of the central nervous system characterized by coma, seizures, paralysis, abnormal movements etc. Death occurs in one third of cases and serious sequelae in 40% of survivors[4].

The virus is transmitted in an enzootic cycle among mosquitoes and vertebrate amplifying hosts, mainly domestic pigs and aquatic birds. The principal vectors are *Culex tritaeniorhynchus* and *Culex gelidus*. In most temperate countries of Asia, JEV is transmitted mainly during the warm season when large epidemics could occur. In the tropics and subtropics, transmission could occur throughout the year, but often intensifies during the rainy season and pre-harvest period in rice cultivating regions[2]. JE cases have been identified from various parts of Sri Lanka throughout the year. It shows a comparative increase with the North-East monsoonal rains (November-February) as a result of increased mosquito breeding, due to water logging of rice fields and collections of water.

There is little evidence to support a reduction in JE disease burden from intervention other than the vaccination of humans. Thus, vaccination of humans should be prioritized over vaccination of pigs and mosquito control measures[2]. WHO recommends that JE vaccination be integrated into

national immunization programmes in all areas where JE disease is recognized as a public health problem[2].

JEV is not spread from person to person through direct contact. A small number of cases of transplacental transmission of JEV has been reported and transmission through blood transfusion has been documented in a JE endemic area[3]. In a laboratory setting, JEV might be transmitted through accidental percutaneous, mucosal or inhalation exposures[3].

Management consists of supportive care and management of complications. No antiviral agent or specific medication is available to mitigate the effects of JEV infection. Infection with one JEV genotype is thought to produce lifelong immunity against all genotypes[3].

Types of vaccine

There are four classes of JE vaccines

- Inactivated mouse brain derived vaccines
- Inactivated Vero cell derived vaccines
- Live attenuated vaccines
- Live recombinant (chimeric)vaccines

WHO recommends that mouse brain derived vaccines should be gradually replaced by new generation JE vaccines, given their advantageous safety profile[1].

Inactivated mouse brain derived vaccine

This vaccine is prepared from a suspension of mouse brain infected with JEV and is of two types.

- Nakayama strain – Freeze dried or liquid
- Beijing strain – Liquid

Both strains of vaccines are presently not available in Sri Lanka.

Inactivated Vero cell derived SA-14-14-2 strain vaccine

Formalin inactivated alum adjuvanted vaccine (SA 14-14-2 strain)

This vaccine is licensed in several Asian countries including Sri Lanka. It does not contain any preservatives or stabilizers. This is a WHO pre-qualified vaccine.

Live attenuated vaccine (LJEV) SA-14-14-2 strain

This vaccine is prepared in primary hamster kidney cell culture (BHK). It is based on the genetically stable, neuro-attenuated SA 14-14-2 strain of the JE virus, which elicits broad immunity against heterologous JE viruses[5,6]. It is a freeze dried preparation. This vaccine is WHO pre-qualified.

In the National Immunization Programme, all children are immunized with the live JE attenuated vaccine on completion of 12 months.

Live recombinant yellow fever-Japanese encephalitis chimeric vaccine (JE-CV)

This JE vaccine has been developed, based on the attenuated 17D YF virus genome. The YF-JE chimera virus, is grown in Vero cells. It showed good safety and immunogenicity with 94% of the vaccinees developing protective neutralizing antibodies after a single dose[7].

This freeze dried vaccine is licensed for use in 15 countries which include, Sri Lanka, Australia, Thailand, Philippines, Singapore, Malaysia, Bangladesh, Indonesia and Taiwan. This vaccine is WHO pre-qualified.

Efficacy

Inactivated Vero cell derived SA-14-14-2 strain vaccine

Vaccination is not recommended for children below the age of six months, due to the possible interference by passively acquired maternal antibodies.

Among children aged 1-2 years in endemic settings, seroprotection was 95.7% one month following the second dose of vaccine[8].

Live attenuated vaccine (LJEV)

In children aged 1-10 years, high protection rates of >98% were seen after one year following a single dose of vaccine. Case control studies

of a large vaccine trial in Nepal showed rapid onset of protection followed by a 5 year efficacy of 96% after a single dose of vaccine[4]. Based on this study, the National Advisory Committee on Communicable Diseases has recommended a single dose schedule for Sri Lanka at present[6].

Live recombinant yellow fever-Japanese encephalitis chimeric vaccine (JE-CV)

In endemic countries a high seroprotection rate of 99.3% was reported in children of 9-18 months age group, one month after administration of a single dose[9]. In a multicentre randomized control trial involving previously primed 2-5 year olds and naive 12-24 month olds were seroprotected 100% and 96% respectively 28 days after JE-CV vaccine administration. One year later, seroprotection rates in the two age groups were 97% and 84% respectively[10].

Vaccine safety

The WHO Global Advisory Committee on Vaccine Safety (GACVS) reviewed data on inactivated Vero cell derived, live attenuated and live recombinant vaccines and all were found to have acceptable safety profiles[1].

Indications

Children above 12 months of age and adults.

Dosage and administration

Inactivated Vero cell derived vaccine

- Residents in JE endemic countries – Primary immunization consists of two doses, 0.5mL each administered intramuscularly 4weeks apart. For children <3yrs dose is 0.25mL.
- Immunization for travellers visiting JE endemic countries (refer chapter 29).

Live attenuated vaccine

Primary immunization of 0.5mL is administered SC. A booster dose after one year is recommended by the manufacturer.

Single dose vaccine is reconstituted with the sterile diluent provided and should be used immediately after reconstitution. Multi dose vaccine should be used within 6 hours after reconstitution.

The National Advisory Committee on Communicable Diseases approved the use of the live JE vaccine in children who had previously received an incomplete course of the mouse brain derived inactivated JEvaccine[11].

Live recombinant yellow fever-Japanese encephalitis chimeric vaccine

One dose of 0.5mL is administered SC.

In children and adolescents up to 18 years of age, if long term protection is required, a booster dose should be given preferably one year after the primary vaccination even up to 2 years.

In adults, a booster dose, if required could be given after 05 years.

Contraindications

Inactivated JE vaccine

- Hypersensitivity to any component of the vaccine
- History of convulsions during the past 1 year
- Progressive neurological disorders

Live attenuated /recombinant chimeric JE vaccine[3]

- Hypersensitivity to any component of the vaccine
- Pregnancy
- Immunodeficiency states (refer Chapter 31)
- Leukaemia, lymphoma and other malignancies (refer Chapter 33)
- History of convulsions during the past 1 year
- Progressive neurological disorders

Though it is not contraindicated, JE vaccine (live or inactivated) should be temporarily postponed in the following instances

- Fever more than 38.5°C
- Acute infectious disease
- Acute stage of any chronic illness

The following conditions are NOT contraindications

- Minor illnesses such as common cold, diarrhoea with temperature below 38.5°C
- Stable neurological conditions E.g. cerebral palsy, Down syndrome
- Treatment with topical steroids or systemic use of steroids at low dosages, less than 0.5mg/Kg body weight[6]
- Family history of convulsions

Adverse effects

Local: pain, induration and redness at site of inoculation

Systemic: headache, fever, malaise, myalgia, urticaria, nausea and vomiting

Most of the adverse reactions occur 12-72 hours after the administration of the vaccine. These reactions appear to be more common in those with a previous history of urticaria.

Acute encephalitis, shock and anaphylactic reactions are rare.

Storage

2-8°C. Avoid exposure to direct sunlight. The liquid vaccine should not be frozen.

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CHAPTER 15

MEASLES, MUMPS AND RUBELLA VACCINE (MMR)

Introduction

Measles, mumps and rubella (MMR) is a live attenuated combined vaccine which prevents measles, mumps, rubella and congenital rubella syndrome (CRS). MMR vaccine was included in the National Immunization Programme (NIP) of Sri Lanka in 2011.

Measles

Measles is one of the most highly contagious of all infectious diseases where humans are the only hosts for the virus. The incubation period is approximately 10 days, but varies from 7-18 days from exposure. Measles virus is an RNA virus with one serotype, of the genus Morbillivirus in the Paramyxoviridae family. The virus is commonly transmitted by direct contact with infectious droplets and less commonly, by airborne spread.

Measles is characterized by fever, cough, coryza and conjunctivitis, followed by a maculopapular rash appearing on the face and spreading cephalocaudally and centrifugally. During the prodromal period, a pathognomonic enanthema (Koplik's spots) may be detected. Case fatality rates are higher among children younger than 5 years, the immunocompromised and in the severely malnourished, inclusive of vitamin A deficiency as well[1,2].

A significant favourable impact on childhood mortality was shown with accelerated coverage with measles vaccination. During the period between 2000 and 2018, more than 23 million deaths from measles were prevented[3]. Despite the efficacy and availability of the measles vaccine, the disease remains one of the leading causes of childhood deaths globally. In 2018, more than 140,000 deaths below the age of 5 years had been reported[3]. Moreover, data reveals that after a steady

progress of controlling deaths due to measles, for six consecutive years from 2010, there had been an increase in reported cases of measles, reaching a peak in 2019. Data analysis showed that failure to vaccinate children on time and not completing the vaccination with the 2nd measles containing vaccine were possible reasons. In addition, wide susceptibility due to rapid waning of maternal antibodies at 9 months leave infants at risk of developing serious complications following measles[4].

During the recent past, many outbreaks of measles have been reported among effectively vaccinated communities. The Americas, Europe, South East Asia and the Eastern Mediterranean had large measles outbreaks in 2017 and in 2019[4].

Evidence strongly indicates that accumulation of non-immune persons due to lower participation in vaccination programmes led to measles outbreaks in Europe[4,5,6]. In addition, expanding global tourism and migration due to war and poor socio-economic situations have posed challenges to the WHO measles elimination project[5,6]. It has been emphasized that more than 95% of a population has to be successfully vaccinated in order to prevent outbreaks of measles. WHO has consistently noted that the quality of measles and rubella surveillance remains inadequate in many countries[7,8]. In July 2019, WHO declared that Sri Lanka has eliminated measles which means interruption of the transmission of endogenous virus in the country. Vaccine hesitancy has been identified as one of the top 10 threats to global health and is a serious hurdle to the global elimination and eradication of measles and other vaccine preventable diseases[9].

Complications of measles: Complications of measles include otitis media, bronchopneumonia, laryngotracheobronchitis (croup), keratomalacia and diarrhoea, particularly occurring among young children. Acute encephalitis which occurs in approximately 1:1000 cases, often leads to permanent brain damage. Subacute sclerosing pan encephalitis (SSPE) is a rare degenerative central nervous system disease which occurs 7-11 years after measles, which is characterized by behavioural and intellectual deterioration and seizures[1].

Mumps

Mumps usually occurs during childhood and is caused by a RNA virus in the Paramyxoviridae family and is transmitted by respiratory droplets. The incubation period is 14-18 days. After 3-5 days of viraemia, the virus spreads to multiple tissues leading to parotitis, orchitis, oophoritis, pancreatitis and aseptic meningitis. Parotitis is the most common manifestation (30-40%) which may be unilateral or bilateral and any combination of single or multiple salivary glands may be affected. Parotitis may be absent in as many as 50% of patients[1].

Although the incidence of mumps has been significantly reduced by successful vaccination, outbreaks of mumps continue to occur worldwide[8].

Complications of mumps: A Japanese epidemiological study (2021) showed that the incidence of mumps related complications (per 1000 mumps cases) was highest for orchitis (6.6), followed by meningitis (5.8), deafness (1.3), pancreatitis (0.5) and encephalitis (0.3). Moreover, the incidence of mumps was highest among children aged 0-5 years, while the incidence of mumps-related complications was highest among adults aged 26-35 years[10].

Orchitis is a commonly reported complication among post pubertal males (30%), with half of these patients developing testicular atrophy on the affected side. However, there is a growing concern that the incidence of mumps has shifted from children to young adults and this is associated with a high rate of orchitis and severe reproductive problems[5].

Uncommon complications include oophoritis (5%) among the post pubertal females but there is no association with impaired fertility. Mumps during the first trimester of pregnancy is associated with an increased incidence of spontaneous abortions. Nevertheless, there is no evidence to suggest any link with congenital malformations[7].

Rubella

Rubella is an acute viral infection which generally results in a mild disease in children and adults. It is caused by a toga virus and is spread by

droplets and through direct contact with nasal and throat secretions of infected persons.

The incubation period is generally 2-3 weeks. Many infections (25-50%) are subclinical[7]. Clinical infection is characterised by low grade fever, a transient generalised erythematous maculopapular rash and lymphadenopathy, which is commonly sub occipital or post-auricular.

Rubella is of great significance when it occurs in a pregnant woman in the first trimester as it could cross the placental barrier resulting in teratogenicity. Rubella infection in pregnancy may lead to miscarriage or stillbirth. Some infants may be born with CRS which includes ophthalmic, cardiac, auditory and neurological abnormalities. The risk of congenital defects in the first trimester is approximately 80%, with the risk falling to 10-20% by the 16th week of pregnancy[1,6].

Since the introduction of rubella vaccination in the NIP, the incidence of CRS has declined, but sporadic cases of rubella still continue to occur among young adults.

Types of vaccine

Live attenuated combined vaccine of a lyophilised formulation.

Measles strains

- Schwartz – grown in chick embryo fibroblasts
- Edmonston-Zagreb – grown in human diploid cells

Mumps strains

- Jeryl-Lynn; RIT4385 (derived from Jeryl-Lynn) and Urabe

  All grown in chick embryo tissue culture

Rubella strain

- Wistar RA 27/3 grown in human diploid cells

Immunogenicity and vaccine efficacy

A systematic review (2019) has revealed seroconversion rates after one dose in infants at 9 months of age: 87.4% (measles), 92.3% (mumps), and 91.2% (rubella). Several other studies conducted in Europe have reported that immunogenicity for MMR II at ≥7 years of age with seroconversion rates ranging from 96%-100% (measles), 65%-100% (mumps), and 91%-100% (rubella)[10]. The effectiveness of the mumps component of the MMR vaccine is less than that of the measles or rubella components[6].

In the event of an epidemic of mumps, the Advisory Committee on Immunization Practices (ACIP) recommends the administration of a third dose of vaccine for health care workers who may be at an increased risk[11].

Elimination targets of measles, mumps and rubella could be achieved with sufficiently high coverage using a 2 dose MMR vaccination schedule. Consistently high MMR vaccination coverage is required to prevent outbreaks and also to limit their extent if and when they occur[7].

Indications

- Children at 9 months and 3 years of age as per NIP
- Children and adults with unknown or incomplete MMR vaccination
- Persons who lack immunity to any of the individual components
- Non-immune health care workers

Dosage and administration

0.5 mL SC. Could also be given IM

In Sri Lanka, measles vaccine was first introduced in 1984 for infants at the age of 9 months. MR vaccine was introduced as a second dose for measles at the age of 3 years in 2001. Two doses of MMR vaccine was recommended in 2011. Initially, the first dose was given at 1 year and a second dose at 3 years. The first dose of MMR vaccine was brought forward to 9 months in 2015 as there were several outbreaks of measles in the latter half of infancy.

Catch-up vaccination programme

Children presenting at preschool age who have not received the first dose of MMR should be given a dose of MMR, followed by a second dose after three months. The age of 11-12 years also could serve as a catch-up opportunity to verify vaccination status and MMR vaccine should be administered to children who have not yet received the second dose of MMR. The second dose of MMR may be administered as early as 4 weeks after the first dose[7]. Furthermore, individuals of school leaving age who have never received MMR should be offered the vaccine[12].

Post-exposure prophylaxis

The MMR vaccine may be given to susceptible individuals over one year of age who have been exposed to measles within the previous 72 hours. This should be followed by a second dose at least 28 days later.

However, the MMR vaccine is not recommended for prophylaxis following exposure to mumps or rubella as the antibody response to the mumps or rubella components is too slow for effective prophylaxis. Vaccination after exposure is not harmful and may possibly avert later disease. Studies have shown that although two MMR doses are adequate in the prevention of mumps in most settings, administering a third dose may be worthwhile in specific outbreak situations. This may lead to shorter duration of virus shedding, boosting of antibody titres and milder clinical manifestations[12].

Contraindications

- Pregnancy
- Persons with immunodeficiency, HIV/AIDS (refer chapter 32)
- Individuals with a history of allergy to any of the vaccine components (gelatin, bovine serum albumin, neomycin or kanamycin)
- Individuals with a history of anaphylaxis to a previous dose of MMR vaccine

Precautions

- Pregnancy should be avoided for one month after vaccination. Even if pregnancy occurs within one month after MMR vaccination, no teratogenicity has been reported. Therefore, there is no indication for termination of pregnancy.
- Persons with allergy to red meat (beef, pork or mutton), should be investigated in a specialised unit for vaccine allergy before administration. This is due to the presence of bovine products such as gelatin and bovine serum albumin in the vaccine.
- Vaccination should be deferred in persons with an acute febrile illness.
- MMR either should be administered ≥2 weeks before the receipt of a blood product or should be delayed 3-11 months after receipt of the blood product depending on the dose and type of blood product[13](refer chapter 34).

It is recommended to perform the Tuberculin skin testing (TST) before or on the same day or 4 weeks later as the measles component could depress cell mediated immunity[13].

Adverse effects

Malaise, fever or rash may occur following the first dose of MMR vaccination. Most adverse events reported are attributable to the measles or rubella components.

Parotitis may occasionally occur in the third week after vaccination. Thrombocytopaenic purpura has been rarely reported within six weeks after the first MMR. However, the risk of developing thrombocytopaenia after MMR vaccination is much less than the risk of developing it after an infection with measles, rubella or mumps virus[7]. Adverse reactions are less common after the second dose of vaccination than the first dose.

Concerns about the probable associations of MMR vaccine and infantile autism and inflammatory bowel disease have been evaluated. Many epidemiological studies have firmly disproved the remotest possibility of a cause-and-effect phenomenon with regard to the MMR vaccine and pervasive and regressive developmental disorders in children[14,15].

Storage

2-8°C.

MMRV Vaccine

Since 2005 tetravalent vaccine against measles, mumps, rubella and varicella (MMRV) has been available. MMRV vaccination has shown similar immunogenicity and overall safety profiles compared to MMR vaccine[16].

The MMRV vaccine is currently not available in Sri Lanka.

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CHAPTER 16
MENINGOCOCCAL VACCINE

Introduction

Neisseria meningitidis, the agent that causes bacterial meningitis is a Gram-negative diplococcus with 13 serogroups based on capsular type.

N. meningitidis is a commensal bacterium residing in the upper respiratory tract of humans and is transmitted through aerosols. Crowding is an important risk factor for transmission of the organism. Tobacco smoke, functional or anatomic asplenia, complement factor deficiencies, HIV infection and travel to endemic areas are associated with an increased risk for meningococcal disease. Those who have been exposed to oral secretions of an infected person, such as through kissing or sharing of food and drink, should receive chemoprophylaxis.

Infected people are not considered contagious after 24 hours of appropriate antimicrobial therapy. Prophylactic antimicrobial therapy or vaccination is not recommended without assessment.

Meningococci may be present asymptomatically in up to 30% of the population for periods exceeding 2 years. They adhere to epithelial surfaces in the nasopharynx to form microcolonies which resemble biofilms which help them to persist under adverse conditions. *N. meningitidis* has evolved different mechanisms to evade the host immune system and to compete with other members of the oral microbiome showing a better survival adaptation.

Certain lineages of *N. meningitidis* are highly invasive and are frequently associated with disease. It becomes pathogenic when it crosses the epithelial barriers of the nasopharynx to reach the bloodstream, causing septicaemia. From there, it can cross the blood-brain barrier causing meningitis. Meningococcal disease has an incidence rate that ranges

from <1 to 1,000 cases per 100,000 population per year with significant geographical and temporal differences[1]. The African meningitis belt, stretching from Senegal in the west to Ethiopia in the east has the highest annual incidence of meningococcal disease in the world[2]. It is lethal in 10% of the cases and causes severe sequelae in 30-50% of the survivors, including neurological disabilities, seizures, hearing or visual loss or cognitive impairment[3].

Based on the structure of the capsular polysaccharide, *N. meningitidis* is divided into 13 serogroups, five of which (A, B, C, W and Y) are responsible for the majority of meningococcal disease. Serogroup X causes minority of infections.

In Sri Lanka, according to data from the National Reference Laboratory, Medical Research Institute, eleven cases of invasive meningococcal disease (IMD) had been reported in children and adults from Western, Eastern, Northern and North-Central Provinces with no recent overseas travel. Meningococcemia, skin rash, meningitis and sepsis were the common clinical manifestations observed. The meningococcal isolates belonged to serogroups B and C. Majority of the isolates was intermediate-susceptible to penicillin. Some strains showed resistant to quinolones (ciprofloxacin, levofloxacin).

However, meningococcal meningitis is uncommon in Sri Lanka and the cases encountered are mostly imported.

Mortality of IMD remained between 10-15%, even with antimicrobial therapy in developed countries and higher in developing countries[5].

Types of vaccine

Serogroups A, C, W, and Y (MenACWY) vaccines and serogroup B (MenB) vaccines are conjugate vaccines. Polysaccharide vaccines are no longer used in many countries.

Serogroup A, C, W, and Y vaccines

MenACWY vaccines are protein conjugate vaccines.

- MenACWY-D is licensed for use from 9 months to 55 years of age. This intramuscular vaccine is administered as a 2-dose primary series, 3 months apart, among children 9 through 23 months of age
- MenACWY-CRM is licensed for use from 2 months to 55 years of age.

Serogroup B meningococcal vaccines

There are two types of Men B vaccines which use 2 different technologies.

- MenBFHbp is based on a surface-exposed lipoprotein-factor H binding protein (FHbp) that functions as an important virulence factor. It could be administered as either a 2- or 3-dose series (0 and 6 months or 0, 1-2 and 6 months), depending on risk factors for disease and on outbreak conditions. It has been used in several outbreaks.
- MenB-4C contains 4 antigenic components. It is administered as a 2-dose series (0, 1 month).

Efficacy

Efficacy varies between 85-93%, for conjugated vaccines and lowest antibody titres were observed against the Y serogroup.

Indications

It is not recommended for routine immunization in Sri Lanka.

Currently, vaccines are recommended for use in:

- epidemic or outbreak situations
- travellers to endemic countries

- pilgrims to Mecca and Medina
- laboratory workers handling meningococci
- students travelling abroad for studies in countries where the disease is endemic
- following specified conditions with a higher risk for invasive meningococcal disease
- deficiency of complement components
- functional or anatomical asplenia including sickle cell disease and congenital or acquired asplenia
- HIV, regardless of disease stage or CD4+ cell count
- haematopoietic stem cell transplant

Persons exposed to patients with meningococcal disease – meningococcal vaccination is not recommended for post-exposure prophylaxis following exposure to a single case[4].

Dosage and administration

The schedules of vaccination, number of doses and interval between doses vary with the type of vaccine. It is recommended to adhere to manufacturer's instructions for administration of the different vaccines.

Table 1. Recommended schedule for immune competent children and adults

Age groups/ categories	Vaccine type	Available preparations	Dose and route	Remarks
Pregnancy	conjugate	Men ACWY	0.5 mL IM single dose	During outbreaks or before travel to endemic countries. After 1st trimester (this covers infants up to 2 months of age)
		MenB		During B serotype outbreaks and with high risk only when benefits out-weigh the risks
2 months – 10 years	conjugate	MenACWY -CRM or Men ACWY-D	0.5 mL IM	Not recommended for routine use (refer Table 2 for recommended groups)
Primary 11-21 years Booster Adolescent	conjugate	Men ACWY-D or Men ACWY-CRM	0.5 mL IM single dose	If not vaccinated before Recommended if 1st dose taken before 16 years
During outbreaks 16-22 years	conjugate	MenB-FHbp or MenB-4C	0.5 mL IM	1 or 2 doses one month apart based on outbreak situation
>22 years	conjugate	Men ACWY-D or MenACWY -CRM	0.5 mL IM single dose	refer Table 2 for recommended groups

Table 2. Recommended schedules and intervals for people at increased risk of invasive meningococcal disease

- Children who have persistent complement deficiencies (E.g. C3, C5-C9, properdin or factor D or factor H or receiving eculizumab)
- Anatomic or functional asplenia
- Travellers to or residents of countries in which meningococcal disease is hyperendemic or epidemic
- Children who are part of a community outbreak of a vaccine-preventable serogroup

Age groups/categories	Vaccine type	Available preparations	Dose and route	Remarks
Primary				
2-23 months with high risk conditions • Persistent complement deficiencies • Functional or anatomic asplenia • HIV infection • Travel to or are residents of countries where meningococcal disease is hyperendemic or epidemic	conjugate	MenACWY-CRM	0.5 mL IM at 2, 4, 6 and 12 months	*MenACWY-D should not be used before 2 years of age to avoid interference with the immune response to the pneumococcal conjugate vaccine (PCV) series

• At risk during a community outbreak attributable to a vaccine serogroup Children initiating vaccine at 7-23 months of age			0.5 mL IM as 2 doses where 2nd dose to be given at 2 years of age at least 3 months after 1st dose	
Booster doses				
If the person remains at increased risk and first dose received at age: • 2 months to 6 years of age	conjugate	MenACWY-CRM	Additional dose of MenACWY 3 years after 1ry immunization Boosters should be repeated every 5 years thereafter	
• ≥7 years of age			Additional dose of MenACWY 5 years after 1ry immunization Boosters should be repeated every 5 years thereafter	

2-55 years with high-risk conditions, not immunized previously • Persistent complement deficiencies • Functional or anatomic asplenia • HIV infection	conjugate	MenACWY-CRM or MenACWY-D	0.5 mL IM 2 doses 8-12 weeks apart	MenACWY-D may be used at least 4 weeks after completion of pneumococcal vaccine doses
10 years or older not immunized previously who have following high-risk conditions: • Persistent complement deficiencies • Functional or anatomic asplenia • At increased risk because of a serogroup B meningococcal disease outbreak • Laboratory workers routinely exposed to isolates of *N. meningitidis*	conjugate	MenB-4C MenB-FHbp	0.5 mL IM 2 doses 1 month apart	

Contraindications

- Acute febrile illness
- Hypersensitivity to any component of the vaccines

Adverse effects

- Local – erythema, slight induration, tenderness or pain at the injection site.
- Systemic – febrile reactions, chills, fatigue, headache, irritability, muscle or joint pains could occur infrequently and lasts about 24 hours with MenACWY vaccines and may last up to about 3 days with MenB.
- Similar adverse effects are observed after MenB vaccines but are more common and may be more severe.
- Syncope can occur after any vaccination and is most common among adolescents and young adults. Adolescents should be seated or lying down during vaccination, and having vaccine recipients sit or lie down for at least 15 minutes after immunization could avert many syncopal episodes and secondary injuries.

Storage

2-8°C

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CHAPTER 17
PNEUMOCOCCAL VACCINE

Introduction

Pneumonia is the single largest cause of death in children globally[1]. In 2019, pneumonia accounted for 14% of all deaths of children under 5 years of age, killing 740,180 children, or around 2,000 every day[1,2]. Almost all of these deaths are preventable and, according to the WHO, immunization against pneumococcus, *Haemophilus influenzae type b* (Hib), measles and pertussis is the most effective way to prevent pneumonia[2]. *Streptococcus pneumoniae* was the commonest cause of bacterial meningitis and subdural hygromas in infants and children over two years of age in the United States from 1998 to 2007[2]. Vaccines are available against all four infections. Pneumococcal disease (pneumonia, meningitis and septicaemia) is recognised as the world's leading vaccine preventable child killer[3].

After introduction of the pneumococcal conjugate vaccine (PCV) in 2000, several studies described a decrease in invasive pneumococcal disease in the United States. One year after its introduction, there was a 69% decrease in the rate of invasive disease in those less than two years of age[4]. By 2004, all-cause admission rates had declined by 39% and rates of hospitalisation for pneumococcal meningitis decreased by 66% in children younger than two years of age[5,6]. The reduction in all-cause pneumonia admissions in children younger than two years provides an estimate of the proportion of childhood pneumonia attributable to *S. pneumoniae* in the USA that are vaccine preventable. There is a growing body of evidence supporting the beneficial effects of the PCV in children[7]. Interestingly, rates of invasive pneumococcal disease among adults also decreased since the introduction of the vaccine[6,8]. There are about 90 distinct serotypes. Globally, about 20 serotypes are associated with >80% of invasive pneumococcal disease occurring in all age groups.

The introduction of the 7-valent pneumococcal conjugate vaccine (PCV7), has changed the epidemiology of pneumococcal infections

significantly, including invasive pneumococcal disease (IPD). PCV7 was first introduced to children in 2000 in USA and within a decade, pneumococcal infections were almost eliminated in that age group[6]. Furthermore, herd immunity has significantly reduced the incidence of such infections in the over 65 year age group, as well as in older children. Although there has been some increase in the incidence of pneumococcal infections caused by serotypes not covered by PCV7, especially serotype 19A, the overall incidence of pneumococcal disease has been significantly reduced[2].

In 2009, PCV10 and in 2010, PCV13 were introduced. Data suggest that changing from 7-valent to 10-valent vaccine would increase the proportion of serotypes covered from 80% to 88% in the USA and from 74% to 84% in Europe. With regard to developing countries; in Africa the corresponding increase would be from 67-81% and in parts of Asia it could increase from 43-66%. Changing from 10-valent to 13-valent vaccine would further improve coverage of serotypes by 4-7% globally[8,9,10,11]. In developed countries, the newer vaccines are fast replacing PCV7 which is being phased out and is no longer available. Two new PCVs were introduced later, namely PCV15 and 20, the former being effective against 15 serotypes and the latter against 20 serotypes[12].

In the UK, there has been an overall 37% reduction in the incidence of IPD since the introduction of PCV7 and a further 7% reduction since the introduction of PCV13[13]. PCV13 serotypes were responsible for 19% of IPD cases overall, mostly in adults aged >15 years (96%). PCV13 serotypes are now rare in children, accounting for around 10% of IPD cases of children under 2 years of age, with serotypes 3 and 19A being responsible for nearly all cases. It was estimated that nearly 40,000 cases of IPD had been prevented since the start of the PCV programme and the case fatality rate for IPD has reduced significantly from the pre-PCV era[13]. PCV is included in the EPIs of 132 (68%) countries. Pneumococcal vaccination programmes appeared to be a cost-effective intervention in the Asian region and even cost saving under certain conditions[14].

Sri Lanka's National Reference Laboratory identified the Pneumococcus as an important pathogen responsible for serious infections in children and adults. The inclusion of the PCV in the EPI schedule has been strongly recommended[15]. The South Asian Pneumococcal Network Alliance (SAPNA) surveillance revealed that in Colombo, the common serotypes isolated were 6B, 14, 19F and 23F[16]. There was a very high degree of resistance to commonly used antibiotics, penicillin (91%), co-trimoxazole (70%), erythromycin (67%) and chloramphenicol (28%).

There are recommendations for giving the PCV vaccine for adults >65 years of age[17-20].

Types of vaccine

Two types of vaccine are available, pneumococcal polysaccharide vaccine and pneumococcal conjugate vaccine.

Pneumococcal polysaccharide vaccine (PPSV23)

It contains purified polysaccharide for 23 capsular types of pneumococci.

Efficacy

It is effective in adults and children over 2 years of age. Efficacy depends on an individual's antibody response to each of the 23 antigens and serotype of subsequent infections.

Indications

- Persons over 65 years
- Persons aged over 2 years who are at increased risk of pneumococcal infection
  - Asplenia or severe dysfunction of the spleen
  - Splenectomy – in elective splenectomy, at least two weeks prior to surgery (refer Chapter 32)
  - Patients awaiting cochlear implants, at least two weeks prior to surgery

- Chronic renal disease or nephrotic syndrome
- Immunodeficiency or immunosuppression due to disease or treatment, including HIV infection
- Chronic heart disease
- Chronic lung disease
- Chronic liver disease including cirrhosis
- Diabetes mellitus
- Fracture of base of skull
- Coeliac disease

Administration of PCV under special categories – refer Chapters 27, 31, 32, 34.

Dosage and administration

Single dose of 0.5 mL IM. It can be administered simultaneously with routinely used vaccines. As re-vaccination in individuals with higher concentration of antibodies can produce adverse reactions, re-vaccination is not recommended, except once after 5 years in individuals in whom the antibody concentration is likely to decline rapidly (e.g. asplenia, splenic dysfunction and nephrotic syndrome).

Contraindications

Severe adverse reaction to a previous dose of vaccine.

Precautions

Acute febrile illness. Postpone vaccination until the person is well.

Adverse effects

Local reactions such as pain, erythema, induration, muscle pain, fatigue, headache, decreased appetite, low grade fever, crying and irritability may occur which lasts 1-3 days.

Storage

2-8°C (should not be frozen).

Pneumococcal conjugate vaccine (PCV)

PCVs are more immunogenic than polysaccharide vaccine, especially in children under 2 years of age. Currently, 4 types of vaccines are available PCV10, PCV13, PCV15 and PCV20 as PCV7 has been discontinued. In developed countries PCV7 is being replaced by PCV13, due to its formulation. PCV10 provides protection against some non-typeable *H. influenzae* (NTHi) infections such as acute otitis media. PCV10 contains serotypes 1, 5 and 7F, in addition to the 7 serotypes found in PCV7.

Indications

Recommended routinely for children mainly under 2 years of age but could be given up to 5 years.

Efficacy

PCV10 provides cover against serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F. It provides cover against 70% of serotypes globally and also against NTHi.

PCV13 provides cover against serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F. It provides cover against serotype 19A which became an important pathogen after the introduction of PCV7 in 2000, in some countries.

Dosage and administration

0.5 mL IM per dose

- For infants
    - USA – a 3 dose primary series at 2, 4, 6 months and a booster dose at 12-15 months

- UK – a single dose at 3 months and a single booster dose at 1 year of age
- Europe – a 3 dose schedule at 2, 4 and 12 months (3rd dose could be advanced to 10 months of age)
- Children between 1-2 years will need 2 doses, with an interval of 2 months
- Children between 2-5 years will need 1 dose only
- For adults >65 years one dose of PCV10 or 13 followed by PPSV23 at least one year later

Contraindications

Severe adverse reaction to a previous dose of vaccine or an adverse reaction to the diphtheria toxoid component.

Precautions

Acute febrile illness. Postpone all vaccinations until the child is well.

Adverse effects

Local reactions such as pain, erythema and induration may occur which lasts 1-3 days.

Storage

2-8°C (should not be frozen).

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CHAPTER 18
POLIOMYELITIS VACCINE

Introduction

Poliomyelitis is a highly infectious viral disease caused by polio virus, resulting in acute flaccid paralysis. Polio virus is an enterovirus that is mainly transmitted person-to-person through the faeco-oral route. It multiplies in the intestine, spreads to the central nervous system through the blood stream and affects motor neurones. It initially causes generalized symptoms such as fever, headache, vomiting and muscle pain and results in irreversible paralysis among 1 in 200 infected persons. Among them, 5-10% will die due to respiratory failure. The paralysis can occur at any age but mainly affects children below 5 years of age[1].

There are three antigenic types (type 1, 2, and 3) of wild polio virus (WPV) and paralysis can be caused by all three types[2]. At present, WPV type 1 is continuing to circulate. The WPV type 3 has not been detected since 2012 and the WPV type 2 has not been detected since 1999. The WPV type 2 was declared globally eradicated in September 2015[1].

Poliomyelitis occurred worldwide in epidemic form in the first half of the 19th century. The Global Polio Eradication Programme has dramatically reduced polio virus transmission throughout the world. At present only 2 countries remain endemic for polio namely Afghanistan and Pakistan[1]. The WHO South East Asia Region was declared polio free in 2014, three years after the last polio case in India[3].

In Sri Lanka, poliomyelitis was made a notifiable disease in 1944 and the surveillance of acute flaccid paralysis (AFP) commenced in 1990. The last virologically confirmed case of polio was detected in 1993.

The Polio Eradication and Endgame Strategic Plan 2013-18 addressed the requirement of gradual withdrawal of oral polio vaccine (OPV) and steps taken for global withdrawal of poliovirus type 2[4]. In line with

global strategies, Sri Lanka has taken measures and introduced 2-fractional doses of IPV (which contains killed polio virus for all 3 antigenic types) together with bivalent OPV (which contains live attenuated polio virus for types 1 and 3) through the National Immunization Programme.

Types of vaccine

- Live attenuated OPV (Sabin vaccine) bivalent oral polio vaccine (bOPV) which contains types 1 and 3
- Injectable inactivated polio vaccine (IPV-Salk vaccine) which contains types 1,2 and 3

  IPV is available as standalone or combined with other antigens (hexavalent vaccine)
- Novel oral poliomyelitis (Sabine derived) monovalent type 2 vaccine (nOPV2): available for emergency use in countries experiencing outbreaks of vaccine derived polio type 2[1].

Efficacy

Oral polio vaccine (bivalent OPV/ bOPV)

bOPV is highly effective in producing immunity in the mucosa of the intestine and humoral antibody response to types 1 and 3 of the polio virus. Three primary doses of bOPV produces immunity to types 1 and 3 in more than 95% of recipients and booster doses are expected to maximize the immunity. As with other live virus vaccines, immunity from bOPV is probably lifelong against paralytic disease[5].

Inactivated poliovirus vaccine (IPV)

IPV is highly effective in producing immunity against polio virus and protection from paralytic poliomyelitis by the development of a humoral antibody response[1].

Indications

For prevention of poliomyelitis.

Infants at 2, 4 and 6 months as primary immunization

Boosters at 18 months and at 5 years

Both OPV and IPV could be used as a combination. bOPV is used at present in the NIP in Sri Lanka at 2, 4, 6, 18 months and at 5 years together with a fractional dose of IPV (fIPV) intradermally at 2 and 4 months. fIPV is administered for protection against type 2 in conformity with the OPV type 2 withdrawal recommendations of WHO.

Dosage and administration

- bOPV is administered as 2 drops orally at 2, 4, 6,18 months and 5 years

  One multi dose vial contains 2 mL (20 drops) and contains 10 doses

  Open vial policy is applicable to bOPV (see Chapter 38)

  Additional doses could be given during mass campaigns if recommended

  Both bOPV and IPV could be administered with other vaccines including DTP, hepatitis B, MMR and Hib.

- fIPV dosage is 0.1mL administered intradermally at 2 and 4 months together with bOPV.

- When IPV is given in combination with other vaccines such as diphtheria, tetanus, pertussis and hepatitis B the vaccine should be administrated intramuscularly and contains 0.5 mL

Contraindications

- History of allergic reaction to a previous dose of any vaccine type or to any component of the vaccine.

- bOPV should not be given to immunodeficient individuals or household contacts of individuals who have immune deficiency diseases or immune suppression due to therapy. IPV (0.5 mL intramuscularly) must be substituted for bOPV in these circumstances.

Diarrhoea and/or vomiting may hinder the achievement of the required immune response to OPV. Therefore, the administration of the dose should be postponed until recovery.

Adverse effects

- Local reactions are uncommon
- Allergic reactions are very rare

Vaccine associated paralytic poliomyelitis (VAPP)

The vaccine virus carries a small risk (2-4 cases/million birth cohort per year) of causing paralytic poliomyelitis in the vaccine recipient and unimmunized close contacts[5]. VAPP risk is increased in persons with immunodeficiency and in under-immunized populations[2].

Vaccine derived polio virus (VDPV)

In very rare instances, the vaccine virus could change genetically. These mutated viruses may be excreted and could lead to paralysis or outbreaks, if a population is under-immunized. These mutated viruses are called circulating vaccine derived polio virus (cVDPV). The commonest type identified is cVDPV type 2[5]. Patients with immune deficiency may also harbour mutated viruses derived from the oral polio vaccine (iVDPV). These strains may be pathogenic, and may cause paralytic poliomyelitis in the patient. Excretion of iVDPV is very rare, and two cases have been reported among patients with immunodeficiency in Sri Lanka[6].

Storage

OPV

At 2-8°C in the refrigerator compartment up to 3 months. If long term storage is required vaccine could be stored at -20°C for up to two years.

IPV

2-8°C. Do not freeze.

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CHAPTER 19
RABIES VACCINE

Introduction

Rabies is a viral zoonotic disease caused by the rabies virus (RABV) and is responsible for an estimated 59,000 human deaths annually. It causes an acute progressive encephalomyelitis and is almost invariably fatal once clinical signs appear. Human rabies occurs mainly in underserved populations, both rural and urban and has been documented for more than 4000 years[1].

RABV belongs to the genus *Lyssavirus* in the family rhabdoviridae. It causes primarily an infection of mammals, spread by bites of infected animals. In many parts of the world especially in South East Asia, dogs are the principal reservoir of rabies[1]. Humans are occasionally infected by wild animals, but domestic/stray dogs and cats are responsible for the majority of cases[2]. In Sri Lanka in addition to dogs and cats, rabies has been detected in animals such as mongoose, cattle, goats, pigs, bandicoots, jackals, pole cats, civet cats, squirrels, monkeys, horses and elephants. House rats have not been implicated in the transmission of rabies in Sri Lanka.

Human to human transmission of rabies has not been documented except rarely, as a result of infected tissue or organ transplantation[2]. RABV infection in rodents is very uncommon and no human rabies cases have been reported following bites by rodents[3].

Rabies virus can penetrate broken skin or intact mucous membranes. Humans are usually infected when virus laden saliva is inoculated through the skin, mostly by a bite of a rabid animal or rarely through scratches contaminated with saliva. Infection can also occur through abraded skin, such as a lick on an open wound.

The virus has been isolated in an animal's saliva up to 14 days before it exhibits the first signs of rabies. Intermittent excretion of the virus in

saliva continues throughout the illness. The incubation period in humans averages 1-3 months, but can range from 5 days to more than one year[3].

Infection with rabies virus characteristically produces an acute illness with rapidly progressive central nervous system manifestations including anxiety, dysphagia, hydrophobia, aerophobia, photophobia, paraesthesia or localized pain and seizures. These features dominated by forms of hyperactivity are typically seen in furious rabies. Less frequently, patients may present with paralytic signs which could mimic Guillain-Barre syndrome (paralytic/dumb rabies). Both forms of the illness almost invariably progress to death.

The comparatively long incubation period provides an opportunity for highly effective post exposure prophylaxis (PEP) to prevent rabies.

PEP consists of

- thorough washing and flushing of the wound/s with soap and water immediately
- prompt administration of a series of anti-rabies vaccine
- if indicated, infiltration of rabies immunoglobulin (RIG) in and around the wound/s[3]

Types of vaccine

Inactivated anti rabies cell culture vaccines

- Human diploid cell vaccine (HDCV)
- Purified vero cell rabies vaccine (PVRV)*
- Purified chick embryo cell vaccine (PCEC)*

*Vaccines registered in Sri Lanka

These freeze-dried vaccines have a potency of ≥2.5 IU/IM dose

Efficacy

100% seroconversion is achieved with a full course of vaccine.

The WHO specified minimum serum antibody concentration of 0.5 IU/mL is widely used as a measure of adequate seroconversion after vaccination[1].

Indications

Pre-exposure prophylaxis (PrEP)

Pre-exposure immunization is recommended for persons with a higher risk of exposure to rabies virus, such as

- Veterinary surgeons/students and support staff
- Laboratory staff handling material contaminated with rabies virus
- Abattoir workers, animal handlers and vaccinators
- Wild life officers
- Employees in animal quarantine premises and zoological establishments

Dosage and administration

Freeze-dried vaccine should be reconstituted with the diluent provided.

Administration is by ID or IM route[1,3,4].

Primary immunization

A single dose of 0.1 mL ID or one full vial administered IM in the deltoid on days 0,7 and 28.

One booster dose to be taken 1 year later.

Further boosters to be taken every 5 years, for the maintenance of rabies protective antibody levels.

Recent data indicate that PEP and PrEP regimens could be shortened in duration and the number of doses required. Comparative non-inferiority studies have shown ID and IM PrEP regimens could be shortened to 1 week, with single dose of ARV 0.1 mL ID or one full vial administered IM in the deltoid on day 0 and day 7[1].

Management of a person who is on pre-exposure anti rabies vaccine

Following an exposure

- Administration of rabies immunoglobulin is not indicated.
- If the animal is healthy and observable – no immediate booster doses are needed. Only wound management and observation of the animal for 14 days to confirm that the animal remains healthy is recommended.
- If the animal is unobservable, ill, dead or proven rabid – irrespective of the severity of the exposure, two booster doses of anti-rabies vaccine (ARV) are recommended on day 0 and day 3 (2 site ID 0.1 mL doses or a single IM dose), using the same route used for the pre-exposure prophylaxis[4].

Post-exposure prophylaxis (PEP)

It is essential to screen the patient and the animal before a decision is made regarding post-exposure treatment (PET).

If the animal concerned is a dog or a cat, is healthy and alive for 14 days following the bite, the person is not at risk of developing rabies[3].

Screening the patient – Categorization of the exposure

Major exposures:

- Single or multiple bites with bleeding on head, neck, face, chest, upper arms, palms, tips of fingers, toes and genitalia
- Single or multiple deep bites with free flowing of blood on any part of the body
- Multiple deep scratches with free flowing of blood on the head, neck and face
- Contamination of mucous membranes with saliva
- Bites of wild animals with bleeding

Minor exposures:

- Single, superficial bite with oozing of blood or scratches with bleeding on any part of the body
- Multiple scratches with oozing of blood on any part of the body
- Nibbling of uncovered skin
- Contamination of open wounds with saliva
- Superficial bites and scratches of wild animals without bleeding

The following are not considered as exposures:

- Contamination of intact skin with saliva of a suspected or proven rabid/stray animal
- Petting, bathing or coming in contact with utensils of a suspected or proven rabid /stray animal
- Eating left overs which were previously eaten by suspected or proven rabid/stray animal
- Drinking of raw milk of rabid cow or goat

Screening the animal

- In case of **major** exposure to dogs and cats:
    - With a reliable history, if the animal is healthy, observable and has documented proof of – a minimum of 2 rabies vaccinations
- given not more than 2 years apart
- the last vaccination given within 1 year of the incident
    - PET could be delayed while observing the animal for 14 days. If the animal goes missing, becomes sick, develops suspicious behavior or dies, the patient should be advised to report to the hospital immediately to commence PET.
    - When the animal is suspected to have rabies or is sick, but observable (irrespective of vaccination status of the animal), initiate

PET while observing the animal. Discontinue treatment if the animal is healthy after 14 days.

- If the animal is having rabies, confirmed by laboratory diagnosis or is unobservable (missing, stray or dead) initiate PET and continue the full course of vaccine.

- In case of **minor** exposure to dogs and cats:
  - **When the animal is healthy and observable**

Superficial/minor bites:

If the animal has had a minimum of 1 rabies vaccination with documented evidence;

- within 1 year of the incident
- at an age above 3 months
- incident occurring at least 1 month after the vaccination

PET is not indicated immediately. The animal should be kept under observation for 14 days from the day of the exposure. If the animal remains healthy and has not developed any behavioural changes during this period, no PET is needed.

Scratches:

Compared to bites, scratch injuries have a very low risk of rabies transmission[1].

If caused by healthy observable domestic animal (irrespective of vaccination status), PET could be delayed while observing the animal for 14 days[4].

- **When the animal is suspected of having rabies or sick, but observable**

Initiate PET while observing the animal. Discontinue PET if the animal is healthy after 14 days.

- **When the animal is suspected of having rabies, confirmed by laboratory diagnosis or unobservable**

Initiate PET and continue the full course of vaccine. RIG is not indicated.

The patient must be clearly advised that the animal should be caged or leashed during the observation period. If the animal becomes sick, develops any abnormal behaviour or dies; the patient should be advised to report to the hospital immediately. In case of death of the animal, patient should be encouraged to send the head of the animal, to a rabies diagnostic laboratory* for confirmation/exclusion of rabies[5].

- National Rabies Reference Laboratory at Medical Research Institute, Colombo 8
- Rabies Laboratory at Faculty of Veterinary Medicine and Animal Science, University of Peradeniya
- Rabies Laboratory at Teaching Hospital, Karapitiya

Anti rabies PET when indicated:

- Patients in the **major** category should be given rabies immunoglobulin (equine or human) followed by a course of anti rabies vaccine (ARV).
- Patients in the **minor** category should be given only a course of ARV.

Rabies immunoglobulin (RIG)

RIG available in Sri Lanka at present:

- Equine rabies immunoglobulin (ERIG)
- Human rabies immunoglobulin (HRIG)

When PET is indicated, RIG is recommended for patients presenting following a major exposure, if they have not taken a previous course of ARV.

RIG should be given immediately or as soon as possible after the incident. However if the patient reports late, RIG could be given up to 3 months after exposure, if the patient has not taken more than 2 doses of anti-rabies vaccine[3,4,6].

Administration of ERIG

The present WHO guideline does not recommend skin testing (ST) before administration of ERIG, as such tests poorly predict severe adverse events and their results should not be the basis for non-administration of ERIG when indicated[1,4].

However, the treating medical officers should be prepared to manage anaphylaxis, which although rare, could occur during the administration of ERIG.

Administration of ERIG should be done in a unit where emergency care and resuscitation facilities are available (ETU, PCU, A and E, ICU etc.)[4].

The drug of choice in managing anaphylaxis is 1:1000 adrenaline 0.5 mL for an adult given IM immediately (please refer Chapter 36).

Oral or parenteral steroids are best avoided as it could depress the immune response.

Administration of HRIG

HRIG is a very costly biological with limited availability. Hence, this product should be used strictly for the following indications in government hospitals, if/when available[4].

- History of severe allergic reaction/anaphylaxis to red meat or cow's milk
- Patients who develop severe allergic reaction/anaphylaxis while infiltrating wounds with ERIG, before completing the wound infiltration
- Patients who report back later with a missed wound/s, after infiltration of wound/s with ERIG

Dosage and administration of RIG

Maximum dose recommended for – ERIG is 40 IU/kg body weight

– HRIG is 20 IU/kg body weight

There is no minimum dose.

Only the wound/s should be infiltrated with RIG. The entire immunoglobulin dose or as much as anatomically feasible, should be infiltrated carefully into or as close as possible to all wounds. It is no longer recommended to inject the remainder of the calculated RIG dose IM at a distance from the wound, as evidence suggests that there is no or little additional protection against rabies as compared with infiltration of wound/s alone[1,4].

The remaining RIG may be given to other patients; this practice is particularly useful if RIG is in short supply[1].

In situations with multiple bites, where the volume of RIG is insufficient for infiltration of all wounds (especially in children), RIG could be diluted with sterile saline up to a maximum of 3 times.

Anti rabies vaccine (ARV) schedules:

Intramuscular (IM) schedules

- Patients with major exposures should be given 5 doses of rabies cell culture vaccine with RIG, according to the following schedule.

  One dose (1 vial) to be given in the deltoid on days 0, 3, 7, 14 and 30 following the administration of RIG

- Patients with minor exposures could be given a total of 4 doses of rabies cell culture vaccine administered IM (2:1:1 schedule) on the following days:

  Day 0 – 2 doses to be given IM, one in each deltoid.

  Day 7 – 1 dose IM

  Day 21 – 1 dose IM

Intradermal (ID) schedules

The cost-effective ID vaccination schedules have been recommended by the WHO. Studies have shown that the ID route of immunization is as effective as the standard IM route in immunocompetent persons[1,3].

Recommended ID dose is 0.1 mL per site for both PCEC and PVRV

2 Site ID Schedule (2-2-2-0-2)

Standard schedule used in government hospitals.

One dose (0.1 mL) is given ID at each of 2 sites in the deltoids on days 0, 3, 7 and 30.

2 site schedule is routinely used in patients irrespective of the use of RIG.

E.g. Major exposure – RIG + 2 site ID schedule of anti-rabies vaccine

Minor exposure – 2 site ID schedule of anti-rabies vaccine only

Modified 4 Site ID Schedule (4-2-2-0-2)

One dose (0.1 mL) given ID at each of 4 sites on day 0 (both deltoids and antero-lateral thighs) and 0.1 mL given at 2 sites in the deltoids on days 3, 7 and 30.

This schedule gives an early antibody response when compared to the 2 site ID schedule.

The modified 4 site schedule could be offered for

- patients with minor exposures, presenting late for treatment
- patients presenting with borderline exposures
- patients with major exposures from healthy observable animals with unsatisfactory immunization status, presenting with a reliable history,
  - where the patient / parent of a child is responsible and reliable
  - wounds are not in the head and neck
  - the animal is healthy and observable
  - the bite was due to provocation
  - when wound/s do not require major surgical manipulation

In this situation, the patient must be clearly advised that the dog/cat should be closely monitored to make sure that it remains healthy during the observation period of 14 days.

If the animal becomes sick, develops any suspicious behaviour, goes missing or dies, patient should be advised to report to hospital immediately for RIG to be administered when indicated.

- If the patient reports back before the day 7 dose of ARV, wound/s should be infiltrated with RIG and a fresh course of ARV is recommended[4].
- If the patient reports after the day 7 dose (3rd dose) of ARV, continue and complete the modified 4 site ID ARV schedule, RIG is not recommended[1].

  In such situations, additional doses of ARV could be considered.

Please note: In a patient with a major exposure, modified 4 site ID ARV schedule should not be considered as equivalent to RIG and a course of ARV.

Precautions that should be taken when using ID ARV schedules

- All ID injections should be administered only by trained staff under supervision of a medical officer. Once the vaccine is reconstituted, the contents should be used as soon as possible (preferably within 6 hours stored at 2-8°C).
- Sterile 1 mL fixed needle-syringes should be used for administration of ID ARV to minimize vaccine wastage.

Post exposure therapy for immunocompromised patients

ID schedules of ARV are not recommended for these patients. They may require RIG even for minor exposures with IM schedule of ARV.

In certain situations, the rabies antibody titre may need to be assessed (contact the Department of Rabies, MRI).

Management of patients with a previous course of ARV with a subsequent exposure to rabies infection

With a reliable history, irrespective of the vaccination status of the animal, for both major and minor exposures: If the animal is **healthy and observable**, PET could be delayed while observing the animal for 14 days.

- With documented evidence of a full course of ARV

If the animal is **proven rabid, suspected of rabies or unobservable** for individuals who are not immunocompromised, have been previously vaccinated with a full course of a potent and effective rabies vaccine and have adequate documentation

- If the previous course of ARV is within 3 months, no anti rabies PET indicated. Only proper wound management is recommended[1].
- If the previous course of ARV is more than 3 months back, two booster doses of ARV recommended on days 0 and 3 (one IM dose / 2 site ID 0.1 mL)[1,4, 7]
- As an alternative, the patient may be offered a single visit "4 site" ID doses consisting of 4 injections of 0.1 mL, over both deltoids and supra-scapular/antero-lateral thigh areas.

These patients do not require administration of RIG[1,3].

In any doubtful or complicated situations, expert opinion should be sought.

- With documented evidence of a partial course of ARV (3 doses on days 0, 3 and 7)

If the animal is **proven rabid, suspected of rabies or unobservable:**

The management will depend on the time duration from previous course of ARV[4].

- If the previous course of ARV is within 10 years – two booster doses of ARV are recommended on days 0 and 3.
- If the previous course of ARV is more than 10 years back – a full course of ARV is recommended.

These patients do not require administration of RIG[1,3].

If a person develops an allergic reaction to one type of cell culture anti rabies vaccine, switching over to another type of cell culture ARV could be recommended, if available.

Contraindications

In view of the gravity of the disease, all contraindications are secondary in cases of exposure to suspected rabies infection. This also pertains to post-exposure rabies prophylaxis in infancy and pregnancy.

Adverse effects

Local – pain, tenderness, erythema.

Systemic – malaise, headache, nausea, mild fever, urticaria.

Storage

2-8°C.

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CHAPTER 20
ROTAVIRUS VACCINE

Introduction

Globally, rotavirus is the leading cause of acute gastroenteritis and severe dehydrating diarrhoea in children less than 5 years of age. Prior to the introduction of the vaccine, rotavirus caused about 37% of deaths due to diarrhoea in children less than 5 years of age. While nearly every child experiences at least one rotavirus infection in early childhood regardless of setting, most rotavirus-associated deaths occur in children in low- and middle-income countries, particularly in sub-Saharan Africa and in the Indian subcontinent[1,2]. In high-income countries, where deaths due to rotavirus are rare, it accounted for 40-50% of hospital admissions due to diarrhoeal disease in the pre-rotavirus vaccine period.

The World Health Organization (WHO) has recommended that rotavirus vaccine for infants should be included in all national immunization programmes, particularly in countries in which high fatality rates are observed; South and South-East Asia and Sub-Saharan Africa[2]. Implementation of the rotavirus vaccination programme has markedly reduced the prevalence of rotavirus disease in the United States[3]. Ninety-two countries had introduced rotavirus vaccination into their national immunization programmes by the end of 2018, with six other countries introducing on a phased basis[4].

Rotavirus infection in Sri Lanka is a significant cause of morbidity. Several rotavirus surveillance studies show that rotavirus causes about 24% of the watery diarrhoeal infections[4]. Of this, 80% occur in the age group <2 years. However, mortality due to rotavirus infection is low.

Virology and transmission

Infection is caused by rotavirus which is a member of the genus reoviridae. It is divided into 7 groups, A-G, of which only group A infects

humans. The virus has 2 surface glycoproteins, G and P. The genotypes of rotavirus are based on these glycoproteins. Twenty-seven G types and 35 P types have been identified in group A. Among these, 5 G types are commonly detected, G1-4 and G9. The common P types are 8, 6 and 4. The most common genotype seen in the developed world is G1, while the developing countries show a more diverse scenario. The Sri Lankan genotypes found commonly are G1-3 and G9[5,6].

Rotavirus is shed in very high numbers during the acute phase of the infection (10^{12} viral particles per gram of stools). It is transmitted from person to person by the faeco-oral route via contaminated fomites. Transmission by contaminated food and water is not common. Transmission via the respiratory route has been suggested. It is infectious in low doses (about 100 viral particles). The virus could survive in the environment for days and in stools for months.

The incubation period is 1-3 days and an infected child will excrete the virus a few days before and after the clinical illness. The clinical spectrum of the disease is wide, with transient loose stools to severe diarrhoea with dehydration leading to death. Typically, the clinical illness is of sudden onset, with fever, vomiting and explosive watery diarrhoea, up to 10 times a day. There is no blood in the stools but it may be mucoid. The illness usually lasts about 3-7 days but may be prolonged up to 2-3 weeks. About 50% of the infections could be subclinical.

The first infection, which occurs around 3 months of age, is the most likely to cause severe gastroenteritis with dehydration. The primary infection confers protection against rotavirus gastroenteritis in 77% and against severe gastroenteritis in 87%, of patients. The primary infection confers homotypic immunity and subsequent infections, a broader heterotypic immunity.

Types of vaccine

Four types of live, attenuated, oral vaccines have been pre-qualified by the WHO. There is one human monovalent vaccine (RV1) against G1P[8], bovine-human reassortant pentavalent vaccine (RV5) against G1-4 and P[8], bovine-human reassortant monovalent vaccine containing

G9P[11] strain and a bovine human reassortant pentavalent vaccine containing G1-4 and G9. All vaccines give cross immunity to other genotypes of rotavirus[2].

Efficacy

The vaccine will prevent about 74-87% of all rotavirus gastroenteritis, >80% of severe cases, and about 95-100% of hospitalizations due to rotavirus[2].

Indications

Prevention of childhood gastroenteritis due to rotavirus.

Dosage and administration

Human monovalent vaccine (2 doses)

Lyophilised vaccine to be reconstituted with the diluent (supplied with the vaccine), 1 mL/dose at 2 and 4 months of age. The minimum age for the first dose is 6 weeks and the minimum interval between the doses is 4 weeks. The vaccine schedule should be completed before 24 weeks of age.

Bovine-human reassortant pentavalent vaccine (3 doses)

Liquid vaccine, 2 mL/dose at 2, 4 and 6 months. The minimum age for first dose is 6 weeks and should be given between 6-12 weeks of age. The minimum interval between the doses is 4 weeks. The 3rd dose should not be administered after 32 weeks of age.

Bovine-human reassortant monovalent vaccine (3 doses)

Frozen liquid vaccine, 0.5 mL/dose, 3 doses 4 weeks apart, starting at 6 weeks of age. The series should be completed by the age of 8 months. This is not available in Sri Lanka at present.

Bovine human reassortant pentavalent vaccine (G1-4, G9)

Lyophilized and liquid forms, 2.5 mL (lyophilized) or 2 mL/dose (liquid), 3 doses 4 weeks apart, starting at 6 weeks of age. The series should be completed by the age of 12 months. This is not available in Sri Lanka at present.

WHO recommends the first vaccine dose to be given as soon as possible, after 6 weeks of age, and the recommended number of doses of vaccine to be given at a minimum interval of 4 weeks. A child <24 months of age who has missed a dose or series of vaccines should be administered the dose or series. Interrupted schedules should be resumed without repeating the dose. Rotavirus vaccination of children >24 months of age is not recommended[2]. However, manufactures of all 4 vaccines recommend a shorter maximum age for completion of vaccination.

Rotavirus vaccine can be given simultaneously with other childhood vaccines including DTaP /DTP, Hib, IPV, hepatitis B, pneumococcal conjugate vaccine and OPV. There is no restriction on breast feeding or other liquid milk, before or after vaccination[2].

Contraindications

- Life-threatening allergy to any component of the rotavirus vaccine
- Children with severe immunodeficiency including severe combined immunodeficiency (SCID)
- Children who are moderately or severely ill. This includes children who have acute moderate to severe gastroenteritis

Precautions

Review of recent data indicate that the 4 vaccines prequalified by WHO, show little to no difference in intussusception risk compared to a placebo or to no vaccine and, importantly, a lower risk of intussusception compared to the magnitude observed with the first licensed vaccine (RRV-TV). However, since the data cannot exclude a smaller risk of intussusception or other rare serious adverse events, routine vaccine introduction should be accompanied by safety surveillance[1].

It is accepted that the benefits of the vaccine outweigh the risk of intussuception[2,7]. The manufacturers recommend that the vaccine is contraindicated in children with a history of intussusception or an abnormality of the gastro-intestinal tract which can predispose to intussusception (E.g. Meckel diverticulum)[8].

Adverse effects

Diarrhoea, vomiting, otitis media and nasopharyngitis.

Storage

2-8°C. Protect from light.

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CHAPTER 21
TETANUS VACCINE

Introduction

Tetanus is a life-threatening, but vaccine preventable disease caused by tetanospasmin, an extremely potent neurotoxin produced by *Clostridium tetani*, a Gram-positive anaerobic spore bearing bacterium. The organism is ubiquitous and high concentrations are found in soil and animal excrement. *C. tetani* spores enter the body through contamination of breaches of skin or mucous membranes. Spores germinate under anaerobic conditions and vegetative bacilli produce tetanospasmin. Neonatal tetanus is caused by contamination of the umbilical stump[1]. Tetanus does not spread from person to person. The incubation period is between 3-21 days but extremes of 1 day to several months have been reported[3].

The disease is characterised by painful contraction and spasm of skeletal muscles. Muscle spasms initially involving the face (trismus), jaw (lockjaw) and the neck, then become generalised[2]. Sustained spasm of muscles of the back causes backward arching of spine (opisthotonos). Abdominal rigidity is commonly noted[2]. Seizures may occur and the autonomic nervous system may be affected. History of an injury or portal of entry may not be clear. Course of the disease is usually intense for 4 or more weeks and long-term sequelae can debilitate patients for a longer period. Case fatality rates of 10-20% are reported with modern health care facilities but could reach 100% in infants and the elderly without high quality medical care[3].

Tetanus cannot be eradicated because the spores are commonly present in the environment. Protective immunity is not acquired following an infection[3]. Protection against tetanus is antibody-dependent and could be achieved only through active (tetanus vaccine) or passive (tetanus-specific immunoglobulin) immunization[4].

- Active immunization with tetanus vaccine is indicated for all persons who have not been adequately immunized. Adequate immunization coverage is the key strategy for prevention of tetanus, as there is no place for herd immunity or natural immunity.
- Passive immunization using tetanus antitoxin, preferably of human origin, is essential for treatment and occasionally for prophylaxis (E.g. in cases of contaminated wounds in incompletely immunized people). While tetanus antitoxin is useful in the management of tetanus, its use cannot substitute the need to achieve and sustain a high vaccination coverage[4].

Types of vaccine

Tetanus toxoid (TT)

The single antigen vaccine is made from a cell-free, purified toxin extracted from a strain of *C. tetani*. This is inactivated with formaldehyde to convert it into tetanus toxoid which is adsorbed onto an adjuvant, either aluminium phosphate or aluminium hydroxide, to improve its immunogenicity[1].

It is a cloudy white suspension, supplied either in single or multi-dose form. The vaccine may sediment during storage and should be shaken to get a uniform suspension before administration[1]. If the vial contains clumps of material that cannot be re-suspended with vigorous shaking, it should not be used.

Tetanus toxoid containing vaccines[4,5,6] (TTCV)

Several preparations of vaccines contain tetanus toxoid as a component of a combination of vaccines and an age-appropriate vaccine should be selected for immunization[2,3] (Table 1). In order to offer protection against diphtheria, WHO recommends the use of vaccines combining tetanus toxoid with diphtheria toxoid (Td) replacing the use of TT as a single antigen[6,7]. However, Sri Lanka has not implemented this strategy in the routine pregnancy and post exposure immunization schedules since confirmed cases of diphtheria have not been notified in the country after 2001[8,9].

Table 1. Tetanus toxoid containing vaccines[5] (TTCV)

	Diphtheria	Tetanus	Pertussis
DTwP - Diphtheria, tetanus and whole cell pertussis vaccine	≥30 IU/dose	≥40 IU/dose	≥4 IU/dose
DTaP - Diphtheria, tetanus and acellular pertussis vaccine	≥30 IU/dose	≥40 IU/dose	≥25 µg pertussis toxoid ≥25 µg filamentous haemagglutinin ≥8 µg pertactin/dose
DT - Diphtheria and tetanus vaccine	≥30 IU/dose	≥40 IU/dose	-
Tdap - Low antigenic diphtheria, tetanus and acellular pertussis vaccine - for 7 years and above	≥2 IU/dose	≥20 IU/dose	≥8 µg pertussis toxoid ≥8 µg filamentous haemagglutinin ≥2.5 µg pertactin/dose
aTd (Td) - Diphtheria and tetanus vaccine for adolescents and adults	≥2 IU/dose	≥40 IU/dose	-
TT - Tetanus toxoid vaccine for adults	- -	≥40 IU/dose	
DTP-HepB-Hib - Diphtheria, tetanus, pertussis, Hib, hepatits B vaccine (pentavalent)	≥30 IU/dose	≥40 IU/dose	≥4 IU/dose
DTaP-HepB-Hib-IPV - Diphtheria, tetanus, acellular pertussis, Hib, hepatitis B, and inactivated polio vaccine (hexavalent)	≥30 IU/dose	≥40 IU/dose	≥25 µg pertussis toxoid ≥25 µg filamentous haemagglutinin ≥8 µg pertactin/dose

Vaccine efficacy

Efficacy ranges from 80-100% following a full course of vaccination. Antitoxin levels decline with time. Disease is extremely rare after completion of a full course of tetanus vaccine with the last dose given within 10 years[2]. Two doses of TT administered during pregnancy has 94% efficacy in preventing neonatal tetanus[10].

Indications for active immunization against tetanus

- Routine immunization
- Immunization following an injury with risk of wound contamination
- Immunization during active tetanus disease

Routine Immunization

WHO recommends that all populations worldwide should be immunized against tetanus[7]. In order to achieve this target, pre-scheduled courses of TT or TTCV are recommended for several populations including children, adolescents and pregnant women.

Routine childhood immunization

National Immunization Programmes (NIP) are recommended to initiate a tetanus vaccine course of 6 doses with 3 doses of TTCV as primary immunization. E.g. DTP, DTaP, DTP-HepB-Hib (pentavalent vaccine) or DTaP-HepB-Hib-IPV (hexavalent vaccine). The primary series of 3 doses of a TTCV should be given in infancy on completion of 2nd, 4th and 6th months (pentavalent/hexavalent) with a booster on completion of 18th month (DTwP/DTaP/pentavalent/hexavalent). A second booster dose should be given before school entry on completion of 5 years of age (DT/DTaP/Tdap)[2,4,8].
(refer Chapter 8 and Annex I and II).

Routine immunization of adolescents and adults

WHO recommends a sixth dose of TTCV to be administered during adolescence to extend protection into adolescence and adulthood[7]. This

is expected to provide additional assurance of long lasting, possibly lifelong, protection against tetanus[10]. The sixth dose is recommended after completion of 11 years of age as a Td or Tdap.

For young adults who missed the 6th dose during adolescence, it can be routinely given as TT/TTCV administered at the time of first pregnancy, induction to military service, the medical examination before first employment or admission to higher education institutes.

Adolescents and adults with no past immunization against tetanus should receive 5 doses of TT/TTCV to ensure sustained protection. The course should be started as soon as possible, with the 2nd dose at least 4 weeks later, 3rd dose at least 6 months after the 2nd, 4th dose 1-5 years after the 3rd and the 5th dose 1-10 years after the 4th dose[1,6,7,8]. Longer intervals between the 3rd and 4th doses (5 years) and the 4th and 5th doses (10 years) are preferred[1].

Routine immunization of pregnant women to prevent maternal and neonatal tetanus

Evidence of previous tetanus immunization should be verified before tetanus vaccine is given in pregnancy. If there is no documented evidence of previous vaccination against tetanus, 2 doses of TT/Tdap should be given during the first pregnancy. One dose of TT is recommended during each subsequent pregnancy, up to a total of 5 doses (Table 2).

Table 2. Immunization schedule for pregnant women[4,7,8]

Tetanus toxoid for previously unvaccinated pregnant women		
1st Dose	Tetanus toxoid	During 1st pregnancy, after 12 weeks of gestation
2nd Dose	Tetanus toxoid	During 1st pregnancy, 6-8 weeks after the 1st dose (at least 2 weeks before delivery)
3rd Dose	Tetanus toxoid	During 2nd pregnancy, after 12 weeks of gestation
4th Dose	Tetanus toxoid	During 3rd pregnancy, after 12 weeks of gestation
5th Dose	Tetanus toxoid	During 4th pregnancy, after 12 weeks of gestation

For pregnant women with documented evidence of previous immunization		
Booster doses indicated	Tetanus toxoid	• 6 doses of TTCV as per NIP during childhood and adolescence and a gap of 10 years or more after the last TTCV – need one booster dose during 1st pregnancy. • 4 doses of TTCV during childhood – need one booster dose in first pregnancy and a 6th dose at least one year later or during next pregnancy. • 3 doses of TTCV during childhood – need two booster doses in first pregnancy and a 6th dose at least one year later or during next pregnancy.
Tetanus toxoid immunization not indicated	Tetanus toxoid is not indicated for those having documented evidence of previous immunization with • 5 doses of tetanus toxoid during previous pregnancies or • 6 doses of TTCV according to the NIP during childhood and adolescence and the gap between the last TTCV and the current pregnancy is less than 10 years or • 6 doses of TTCV according to the NIP during childhood and adolescence and at least 1 dose of TT/TTCV during pregnancy or following trauma within the last 10 years	

Immunization following an injury with risk of wound contamination[1,2,3,8]

- A history regarding tetanus immunization should be taken before TT is given for wound prophylaxis.
- For persons who have not been immunized against tetanus previously or whose vaccination status is unknown or uncertain, a primary course of 3 doses of TT is recommended as follows – 1st dose immediately, 2nd dose 4-6 weeks later and 3rd dose 6 months later. A minimum of 3 doses of TT/TTCV is required to produce effective immunity. A booster dose could be given once in 10 years[2].
- For adults with a history of completing a primary course of 3 doses of TT/TTCV,

- if the last dose was given within 5 years no further doses are required as part of management of the current injury.
- if the last dose was given 5 or more years earlier a booster dose of TT is recommended.

- TT need not be given to children below 11 years of age with a history of complete immunization with 5 doses of TTCV.
- Adults with a history of immunization with only 5 doses of TTCV in childhood need 1 booster dose of TT/TTCV.
- Adults with documented evidence of immunization with 6 doses of TT/TTCV including the 5 doses received in childhood do not need further doses of TT for wound prophylaxis up to 10 years from the last dose of TT/TTCV.
- Although adequate previous vaccination should provide sufficient protection against tetanus, a dose of TT/TTCV could be given, as a part of comprehensive wound management in the following occasions[1,2,3,8].
  - in the case of a severely contaminated or high-risk tetanus prone injury within 10 years from the last dose of TT/TTCV or between doses of routine childhood immunization
  - when the patient's previous tetanus immunization history is unreliable

Immunization of a patient with tetanus

Since tetanus does not result in immunity against future episodes of infection, a 3-dose schedule of vaccine should be initiated as soon as the patient's condition has stabilized[2,10].

Dosage and administration

0.5 mL[1] deep intramuscularly into deltoid or antero-lateral aspect of thigh

(refer Chapter 8 for further details on dosage and administration of TTCV)

Contraindications

Hypersensitivity to any component of the vaccine.

Adverse effects

Pain, swelling and redness of the injection site may occur, more frequently after subsequent doses.

Subcutaneous injection could cause local irritation, inflammation, granuloma formation and necrosis.

Anaphylactic reactions, Guillain-Barre syndrome and brachial neuritis have been reported rarely[2].

Storage

2-8°C, protected from light. Do not freeze[1].

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CHAPTER 22
TYPHOID VACCINE

Introduction

Enteric fever (the collective term for typhoid and paratyphoid fever) is a prolonged bacteraemic illness important in children (particularly the 0-4 year age group) in low and middle income countries[1,2]. The prototype of this syndrome is typhoid fever caused by *Salmonella enterica* serovar Typhi while paratyphoid fever is caused by *Salmonella enterica* serovar Paratyphi A, Paratyphi B and Paratyphi C. Although paratyphoid fever due to *S. enterica* serovar Paratyphi A is seen in many South Asian countries including Sri Lanka[3,4], the burden of disease due to typhoid fever is more important, globally[5]. *S. enterica* serovar Typhi and *S. enterica* serovar Paratyphi are exclusively pathogens of humans. Bacteria are shed in the faeces of patients with acute infection and chronic carriers. Transmission is via the faeco-oral route, through consumption of food and water contaminated by human faeces due to inadequate sanitation or pollution of water supplies by untreated sewage. The incubation periods are 7-14 days for typhoid and 1-10 days for paratyphoid. Typhoid and paratyphoid fever cannot be differentiated clinically[1]. Clinical features include continued fever, headache, abdominal pain, constipation or diarrhoea and splenomegaly. Bacteraemia is present and blood cultures are positive in 50-70% of cases. Complications, particularly gastrointestinal bleeding, occur in 10-15% of hospitalized patients. Case fatality rates range from 1-4%. Two to five percent become chronic carriers[2].

Multidrug resistant (MDR) and extensively drug resistant (XDR) strains of *S. Typhi* have emerged recently and caused major outbreaks[6]. Antimicrobial resistance limits the available treatment options while increasing treatment costs and infection with such strains increases the severity of illness, mortality and rate of subsequent chronic carriage. This has heightened the need to control the disease through population-

level access to safe drinking water and adequate sanitation, health education, hygiene among food handlers and intensified the requirement for effective vaccination.

The effectiveness of vaccines against *S. Typhi* was previously limited by the presence of a poorly immunogenic carbohydrate capsule (Vi antigen). However, this has been overcome with the availability of low cost, highly effective and safe conjugate vaccines that are able to elicit a T-cell response, resulting in more effective and prolonged protection.

Types of vaccine

Three types of safe and moderately efficacious vaccines against typhoid fever are recommended by the WHO[2]. The currently available typhoid vaccines do not protect against paratyphoid fever. Ideally, a bivalent vaccine protecting against both typhoid and paratyphoid is required.

Typhoid Vi conjugate vaccine (TCV)

TCV consists of the Vi polysaccharide of *S. Typhi* conjugated to tetanus toxoid protein (Vi-TT) to convert a T-independent immune response to a T-dependent response. This results in higher efficacy, longer duration of protection, efficacy in young children and infants and improved safety. It has been prequalified by the WHO and is preferred at all ages[2,7].

Unconjugated Typhoid Vi polysaccharide (ViPS) vaccine

The typhoid Vi polysaccharide vaccine, consisting of purified Vi capsular polysaccharide, is licensed for persons over 2 years of age. Combined typhoid Vi polysaccharide/hepatitis A vaccines are available, mainly for use by travellers.

Ty21a vaccine

An oral, live-attenuated vaccine, manufactured from the *S. Typhi* Ty21a strain as an enteric-coated capsule, is licensed for persons ≥6 years.

Efficacy

Typhoid Vi conjugate vaccine (TCV)

TCV produced an estimate of efficacy of 87.1% (95% CI, 47.2, 96.9) in an observer-participant-blinded study that used an established controlled human typhoid infection model in naive adult volunteers (Vi-TT attack rate 5% vs control attack rate 42%)[8].

Unconjugated Typhoid Vi polysaccharide (ViPS) vaccine

Field effectiveness trials of ViPS in India and Pakistan showed moderate protection (56-57%) of older children (5-16 years old) while there was variable protection of preschool children 2-4 years of age in the two settings[2]. In the established controlled human typhoid infection model ViPs had an efficacy of 52.3% (95% CI-4.2, 78.2) with an attack rate of 20%[8].

Ty21a vaccine

Efficacy for 2.5-3 years is around 50-67% after 3 or 4 doses[2,9].

Typhoid vaccines do not provide reliable protection against *S. Paratyphi* A. Results of two field trials suggest that Ty21a may provide partial cross-protection against *S. Paratyphi* B[7].

Indications[2]

- WHO recommends programmatic use of typhoid vaccines, preferably TCV. Decisions on the age of TCV administration, target population and delivery strategy for routine and catch-up vaccination should be based on the local epidemiology of typhoid fever, including antimicrobial resistance patterns and programmatic considerations of the routine childhood immunization programme. Vaccination is also recommended during outbreaks and may be considered during humanitarian emergencies (when appropriate).
- Travellers visiting typhoid endemic areas could be vaccinated using any of the available vaccines including the combined typhoid-hepatitis

A vaccine. They should adhere to standard hygienic precautions to reduce risk of infection.

- Professional food handlers in endemic areas may be vaccinated but the benefits are not clear.
- Clinical microbiology laboratory personnel who may handle *S. Typhi* in the course of their work may be vaccinated based on the risk of occupational exposure.

Dosage and administration

Typhoid Vi conjugate vaccine (TCV)

TCV is recommended for use in infants as young as 6 months of age, as well as in older children and adults up to 45 years[2,7]. The vaccine is administered as a single, IM dose 0.5 mL (25 µg) and provides greater protection against typhoid fever than the other available vaccines. The need for boosting with TCV is still not clear[2].

Single 0.5 mL (25 µg) dose IM or SC in individuals ≥ 2 years. In travellers to endemic areas it should be administered at least 2 weeks before the anticipated exposure. ViPS vaccine elicits a T-independent antigen response that does not create immunologic memory to allow boosting of serum Vi antibody titers following an initial immunization[7]. Reimmunization is recommended every 3 years if continued or renewed exposure is expected[2].

Ty21a vaccine

The Ty21a vaccine is administered orally as one enteric-coated capsule, every other day, for a total of 3-4 doses, in individuals ≥6 years[2,7]. Each capsule should be swallowed whole (not chewed) with liquid no warmer than 37°C (98°F), approximately 1 hour before a meal. The capsules should be kept refrigerated and all 3-4 doses must be taken to achieve maximal efficacy. It may be administered simultaneously with or at any interval before or after inactivated or live injectable vaccine. Immunization should be completed at least 1 week before possible exposure[7]. It is unlikely to be effective if the patient has ongoing diarrhoea. The Ty21a

vaccine should not be used in persons taking antibiotics. Antibiotics and mefloquine in therapeutic doses should be avoided from 3 days before the first dose to 3 days after the last dose of Ty21a vaccine[2,7]. Anti-malarial drugs mefloquine and chloroquine and the combination antimalarials atovaquone/proguanil and pyrimethamine/sulfadoxine, at doses used for prophylaxis, can be administered with the Ty21a vaccine. The manufacturer advises that other antimalarial agents be administered at least 3 days after the last dose of Ty21a vaccine[7]. Those living in endemic areas should be revaccinated (entire 3-4 dose series) every 3-7 years and travellers from non-endemic areas need revaccination every 1-7 years[2].

There are currently no data on the interchangeability or sequential use of the different typhoid vaccines.

Contraindications

- Known hypersensitivity reaction to any component of the TCV or ViPS vaccines
- No information is available on the safety of either typhoid vaccine in pregnancy. Use of the live attenuated Ty21a vaccine during pregnancy should be avoided[7]
- Use of the live attenuated Ty21a vaccine should be avoided in immunocompromised persons, including those with HIV infection

Precautions

- The oral Ty21a vaccine should not be administered during acute febrile illness or gastrointestinal tract illness[7]

Adverse effects

No serious vaccine-attributable adverse events were observed with TCV[8]. Fever, pain and swelling were reported in approximately 1-10% of vaccinees in any age group[2].

Reported adverse reactions to ViPS vaccine are minimal and include fever, headache, malaise, myalgia, and local reaction of tenderness and pain, erythema, or induration of 1 cm or greater.

The oral Ty21a vaccine is well tolerated, but mild adverse reactions may occur; these include abdominal pain, nausea, diarrhoea, vomiting, fever, headache and rash or urticaria[7].

Storage

2°-8°C. Do not freeze.

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CHAPTER 23
VARICELLA VACCINE

Introduction

Chickenpox in childhood is characterized by fever and a pruritic vesicular rash of generalized distribution. Although the majority of the population in temperate climes is immune to the varicella zoster virus by 5 years of age, the epidemiology is remarkably different in Sri Lanka. In Sri Lanka, only 76.3% has had chickenpox by the age of 60 years[1]. In addition, 38% of women of child bearing age were not immune to chickenpox[1].

Complications are 25 times more common in adults than in children and mortality rates are far higher[2]. The most common complications are bacterial super-infection of the pustules, laryngitis, pneumonia, thrombocytopaenia and neurological problems[3]. Chickenpox during pregnancy is associated with high morbidity and mortality due to a higher incidence of serious complications such as pneumonia[4]. Maternal chickenpox during the first trimester may cause foetal varicella syndrome. Infections around the time of delivery results in neonatal varicella, which may have a mortality of 30%[5]. Clinical disease is prolonged (more than 10 days) in the immunosuppressed. Complications are more frequent and include encephalomyelitis, cerebellar ataxia, arthritis, hepatitis, haemorrhagic nephritis, myocarditis and otitis media[3].

Herpes zoster

Reactivation of varicella virus causes herpes zoster. Highest incidence of reactivation is seen in the elderly and among immunocompromised individuals – persons with impaired cell mediated immune responses such as those with malignancy, organ transplant recipients and those on immunosuppressive treatment[6]. The incidence increases with age, from five cases per 1,000 population in adults aged 50-59 years to 11 cases per 1,000 population in persons aged ≥80 years[7]. The most common complication of zoster, particularly in older persons, is post-herpetic

neuralgia (PHN), which occurs in 10-13% of patients[7]. PHN is the persisting debilitating pain weeks to months after resolution of zoster.

As the VZV vaccine is a live attenuated vaccine, the vaccine virus also establishes latency similar to the wild type virus. The prevalence of zoster among young adults who received the vaccine 20 years previously was shown to be 0.9/1,000 person-years, which is significantly less than the prevalence of zoster following natural infection[2].

Types of vaccine

All varicella vaccines contain the Oka strain of live attenuated VZV, lyophilized vaccine supplied with sterile diluent.

Efficacy

The effectiveness of 1 dose of varicella vaccine is reported to be 82% against any clinical varicella and 98% against severe disease. Two doses of vaccine demonstrated 92% effectiveness against any clinical varicella[8]. Twenty-five years after the introduction of the varicella vaccine in the United States, disease has declined overall by >97%; declines have occurred in all age groups and have been greatest (99%) among persons <20 years of age[9].

The number of doses given, immune status and the age of receiving the vaccine, influence the immune response.

- Age of receiving the vaccine: seroconversion rates are between 77-96% in adult vaccinees, which is lower than the seroconversion rates in children.
- Immune status: seroconversion rates are lower in children with malignancies.
- Number of doses: One dose is thought to offer protection against approximately 80% for all types of varicella. However, breakthrough varicella is observed in 20-30% of children who only received one dose of the vaccine[10].

Indications[8,10]

- Susceptible children over 1 year of age, adolescents and adults
- Strongly recommended in the following groups:
  - healthcare workers
  - family contacts of immunocompromised persons
  - residents and staff in institutional settings
- Non-pregnant women of childbearing age. They should be advised to avoid pregnancy for 1 month following each dose of vaccine. No adverse effects have been reported in instances where the vaccine has been mistakenly administered in pregnant women
- Patients with HIV infection, if CD4 >200 cells/μL (in people>5 years of age), or if CD4 counts >15% of the total lymphocyte count (in children <5 years of age)

Dosage and administration

0.5 mL SC.

Age – 12 months to 12 years

First dose of varicella vaccine could be given at over 12 months of age. A second dose of varicella vaccine is recommended routinely for all children with a gap of 4 to 6 years.

The second dose may be administered at an earlier age provided that the interval between the first and second dose is more than 3 months.

Those who have received only one dose of the vaccine during childhood based on earlier guidelines are recommended another dose of the vaccine.

Age – >13 Years

They should receive two 0.5 mL doses of varicella vaccine, 4-8 weeks apart.

Post-exposure prophylaxis

The varicella vaccine is effective in preventing illness or modifying the illness, if given to individuals within 3-5 days following exposure to a rash[11]. Vaccination within 3 days of exposure to rash was >90% effective in preventing varicella, whereas vaccination within 5 days of exposure was approximately 75% effective in preventing varicella and 100% effective in modifying severe disease[12]. The VZV vaccine should be given >5 months after administration on varicella zoster immunoglobulin (VZIG) in eligible patients[11].

Contraindications

- Those suffering from immune deficiencies including individuals who have any malignant condition which is not in remission
- Persons receiving high-dose systemic immunosuppressive therapy, including persons on oral steroids >2 mg/kg of body weight or 20 mg/day for more than 2 weeks
- Although pregnancy is an absolute contraindication, no adverse effects have been reported in instances where the vaccine has been administered inadvertently
- Those who are allergic to any components of the vaccine such as fetal bovine serum and gelatin[13]

Precautions

- Patients on steroids <2 mg/kg of body weight per day for over 2 weeks (refer Chapter 32)
- Those with leukaemia, lymphoma or other malignancies. The vaccine could be administered when the disease is in remission and at least 3 months after termination of chemotherapy
- Patients with HIV infection could receive the vaccine if

  CD4 >200 cells/μL – adults

  CD4 counts >25% of the total lymphocyte count – children

Adverse effects

- Mild pain, redness at site of administration
- Varicella type rash in 3% of recipients[7]. These rashes are mostly maculopapular and occur within 2 weeks of immunization
- Latent infection and zoster due to the vaccine virus in the vaccinated host has been reported. However, reactivation of the vaccine virus occurs less frequently than in those following natural infection[2].

Storage

2-8°C

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CHAPTER 24
YELLOW FEVER VACCINE

Introduction

Yellow fever (YF) is a mosquito-borne viral disease of humans and other primates. The disease occurs in parts of the tropical and sub-tropical regions of Africa and South and Central America. It has never been reported in Asia despite the presence of the vector[1]. Three epidemiological patterns of YF are recognized in endemic regions, although the disease is clinically and aetiologically identical[1]. Sylvatic (jungle) YF is usually a disease of non-human primates and transmission to humans is incidental through bites from infected mosquitoes in or near the rain forests. Sylvatic YF is the type most commonly seen in Central and South America. Intermediate (savannah) YF transmission is seen in humid regions in Africa where *Aedes* species are able to breed both in the wild and around households. It usually results in sporadic cases in humans. Urban YF transmission occurs when infected people move to densely populated areas where the local population has little or no immunity to YF and *Aedes aegypti* is active. This results in large epidemics through vector transmission[2].

YF has never been reported in Sri Lanka[3]. However, there is a risk of transmission from imported cases since the mosquito vector, *Aedes aegypti* is abundant.

YF poses a significant health hazard to people living in the endemic regions or to unvaccinated travellers to these areas. It ranges in severity from nonspecific, self-limited symptoms of fever, malaise, photophobia and headache to more severe haemorrhagic disease. The case fatality rate may reach 20-30% in patients with severe disease[1,4].

There is no specific treatment for YF[1]. Vaccination is the single most important measure for prevention. Prophylactic immunization can be offered through routine infant immunization, mass immunization and traveller's immunization[1].

Types of vaccine

Live attenuated vaccines are produced using the 17D strain of yellow fever virus in embryonated chicken eggs. Two 17D sub strain vaccines are manufactured today: 17DD and 17D-204YF vaccines. The yellow fever strains in these two vaccines share 99.9% sequence homology[2,4]. Only the 17D- 204YF vaccine is available in Sri Lanka.

The immunizing dose of live attenuated YF vaccine should not be less than 3.0 log10 (1000 mouse LD50) IU according to WHO recommendations[2,4].

Efficacy

A single dose confers immunity in 95-100% of recipients. Data suggests that with some exceptions, most vaccine recipients will maintain protective antibody titres for several decades or potentially life long[1,2,4,5].

Indications[1]

- Persons nine months or older who are travelling to or living in countries that require an International Certificate of Vaccination or Prophylaxis (ICVP) for entry
- Persons nine months or older who are travelling to or living in areas or countries with a risk of yellow fever transmission, even if these countries do not require evidence of immunization on entry (updated list of countries with YF risk can be found in **YF vaccination maps** on **http://travelhealthpro.org.uk/**).
- Laboratory workers handling infected material

Immunization should be performed at least ten days prior to travel to an endemic area to allow protective immunity to develop and for the ICVP to become valid. However, vaccine should still be considered for last minute travellers who should be counselled about the importance of insect bite precautions and possible implications of an invalid ICVP[1].

Reinforcing immunization[1,6]

A single dose of yellow fever vaccine appears to confer life-long protective immunity against yellow fever disease[1,2,4,5,6,7]. Therefore, with some exceptions, a booster dose of yellow fever vaccine is not needed to maintain immunity.

People who have received their first dose in the following categories and who are at continued risk should receive a second dose because they may not have developed long term protection[1].

- Children less than two years
- Pregnant women
- Persons living with HIV (PLWHIV)
- Immune suppressed persons
- Patients awaiting stem cell transplant (refer chapter 31)

In addition, following categories should be considered for a reinforcing dose.

- Laboratory workers who routinely handle wild-type yellow fever virus
- Travellers who received yellow fever vaccine at least 10 years previously and who will be in a higher-risk setting based on season, location, activities, and duration of their travel

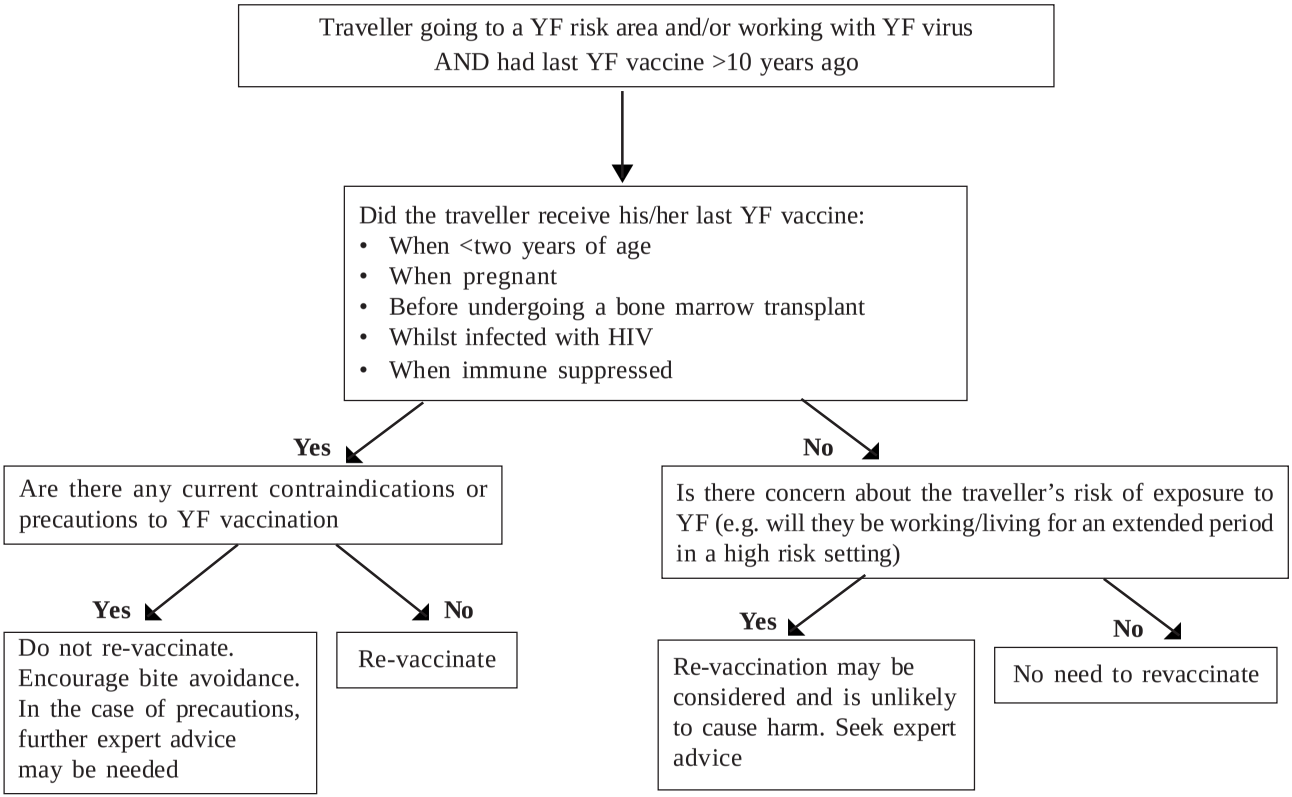

Figure 23.1 Reinforcing immunization for travellers.

International Certificate of Vaccination or Prophylaxis (ICVP)

YF is the only disease specified in the International Health Regulations (IHR) for which countries may require proof of vaccination from travellers as a condition of entry. As per IHR, an ICVP is issued only at a designated yellow fever vaccination center (YFVC).

The YFVC for Sri Lanka is situated at the office of the Assistant Port Health Officer in the premises of the Medical Research Institute, Colombo 8. In accordance with IHR, as of 11th July 2016, Sri Lanka considers ICVP to be valid for life, beginning from the tenth day after primary immunization and immediately after re-immunization.

For the ICVP to be valid, it must include the following:

- Vaccine should be WHO approved
- The signature of the clinician supervising the administration of the yellow fever vaccine
- The official stamp of the designated YFVC where the vaccine was administered

Dosage and schedule

The yellow fever vaccine is available as a lyophilized powder for reconstitution with a diluent. Freeze dried vaccine, once reconstituted, should be used immediately or could be stored for a maximum of 6 hours at 2-8°C.

Single dose of 0.5 mL

Booster doses are not routinely recommended except under special circumstances (see reinforcing immunization)

Administration

0.5 mL deep subcutaneous or intramuscular injection

Fractional YF vaccine (fYF) can be administered intradermally as an off-label use as a part of an emergency response to an outbreak[5].

However, fractional dose administration of YF is not considered equivalent to full dose vaccination in IHR for issuing an ICVP[8].

Contraindications

- Infants below the age of 6 months
- Pregnant women – except during a yellow fever outbreak when the risk of infection is high[4]
- A history of severe allergic reaction or anaphylaxis to a previous dose of yellow fever vaccine or to any of the components of the vaccine
- A history of thymus disorder or thymectomy for any reason
- Primary or acquired immune deficiency due to a congenital condition or disease process including symptomatic HIV infection, and asymptomatic HIV accompanied by evidence of impaired immune function
- A history of immunosuppression as a result of treatment (high dose of steroids, immunosuppressive biological therapy, radiotherapy or cytotoxic drugs)

Egg allergy[9]

Previously, YF vaccine was contraindicated in patients with egg allergy. However, recent guidelines suggest that such patients may be given the vaccine. It should be given in a unit with emergency care facilities, and the patient should be observed for 2 hours following immunization.

Medical waivers (exemptions)

Patients with any of the conditions described above who travel should be informed of the risk of yellow fever and instructed in mosquito avoidance measures. For those who intend to visit countries where an ICVP against yellow fever is required for entry, a letter of exemption should be issued by the YFVC. It should be signed and dated on official stationery, clearly stating the contraindication to vaccination and should

bear the stamp used by the YFVC to validate the ICVP. This letter is only valid for that particular travel. Reasons other than medical contraindications are not acceptable for exemption from vaccination. The traveller should be advised that issuance of a waiver does not guarantee its acceptance by the country of destination.

Precautions

- Minor illness without fever or systemic upset is not a valid reason to postpone immunization. If an individual is acutely unwell, immunization should be postponed until recovery.
- Persons over 60 years of age: The risk of neurological and viscerotropic adverse events increases with age
- Pregnancy: Yellow fever vaccine should not generally be given to pregnant women because of the theoretical risk of foetal infection from the live virus. Pregnant women should be advised not to travel to a high risk area. When travel is unavoidable, the risk from the disease and the theoretical risk from the vaccine have to be assessed on an individual basis and vaccination considered[10].
- Breast feeding: There is some evidence of transmission of live vaccine virus through breast milk to infants less than two months of age[2,6]. Administration of yellow fever vaccine for women who are breast feeding children under the age of nine months should be done with caution[3].
- Infants: Risk of vaccine associated encephalitis is inversely proportional to age. Infants aged six to nine months should only be immunized if the risk of yellow fever during travel is unavoidable.
- Immunosuppression and HIV infection: Unless the yellow fever risk is unavoidable, asymptomatic HIV infected persons should not be immunized. However, yellow fever vaccine may be given safely to HIV infected persons of age less than 60 years with a CD4 count ≥200 /µl[8].

Adverse effects

Common adverse effects

Reactions to yellow fever vaccine are generally mild; reported events typically include low-grade fever, headache, myalgia and/or soreness at the injection site that begin within 1-5 days following vaccination and lasts for 5-10 days.

Severe adverse effects

- **Hypersensitivity**

  Immediate hypersensitivity reactions are uncommon. Anaphylaxis after yellow fever vaccine is reported to occur at a rate of 1.3 cases per 100,000 doses administered[1]. Urticarial rash or bronchospasm rarely occurs, most likely related to egg protein or gelatin in the vaccine.

- **Yellow fever vaccine associated neurologic disease (YEL-AND)**[4]

  YEL-AND is a serious but rarely fatal adverse event[5] which include meningoencephalitis, Guillain-Barre syndrome, acute disseminated encephalomyelitis, bulbar palsy and Bell's palsy[2]. Eight cases occur per 1 million doses[1]. The illness occurs 3-28 days after vaccination, and almost all cases are in first time vaccine recipients. YEL-AND is commoner in people aged >60 years.

- **Yellow fever vaccine-associated viscerotropic disease (YEL-AVD)**[4]

  YEL-AVD is a severe illness similar to wild-type disease, with vaccine virus proliferating in multiple organs and often leading to multisystem organ failure and death. YEL-AVD appears to occur after the first dose of yellow fever vaccine, rather than with booster doses. The onset of illness for YEL-AVD cases averaged 3 days (range 1-8 days) after vaccination. The frequency is 3 cases per 1 million doses[1]. The case fatality ratio for reported YEL-AVD cases is 65%. The rate is higher for persons aged >60 years.

Storage

2-8°C. Do not freeze.

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CHAPTER 25
OTHER VACCINES OF INTEREST
(Ebola, malaria, mpox, zoster)

Ebola vaccine

Introduction

Ebola virus diseases are rare but life-threatening infections caused by viruses of the genus *Ebolavirus*. Ebola viruses (EBOV) belong to the Filoviridae family and are filamentous, enveloped, negative-stranded RNA viruses. Bats are believed to be the natural reservoir of all filoviruses. Four species of EBOV cause haemorrhagic fever in man and other primates, Zaire Ebolavirus (ZEBOV), Sudan Ebolavirus (SUDV), Tai Forest Ebolavirus (TAFV) and Bundibugyo Ebolavirus (BDBV)[1]. Ebolaviruses are transmitted to humans from wild animals such as fruit bats and non-human primates. Ebola virus disease is transmitted between individuals through direct contact with blood, body fluids and secretions of infected persons or with surfaces and objects (clothing, bedding etc.) contaminated with these fluids[2]. While many cases are sporadic, large outbreaks are well described in African countries, most recently in 2022 in Uganda[3].

Ebola presents with fever of acute onset, fatigue, muscle pain, headache and sore throat. This is followed by vomiting, diarrhoea, rash, symptoms of impaired kidney and liver function, and in some cases internal and external bleeding (E.g. oozing from the gums, blood in the stool). Laboratory findings include low white blood cell and platelet counts and elevated liver enzymes. Case fatality rates have varied from 25% to 90%, which have been significantly reduced by early treatment and supportive care[2]. Two monoclonal antibodies (Inmazeb and Ebanga) were approved for the treatment of Zaire Ebolavirus infection in adults and children by the US Food and Drug Administration in late 2020[2].

Types of vaccine

There are 2 approved Ebola vaccines.

Ebola Zaire Vaccine, live – rVSV-ZEBOV

rVSV-ZEBOV vaccine contains live attenuated, recombinant, replication competent vesicular stomatitis virus (VSV) in which the gene encoding the glycoprotein of VSV was replaced with the gene encoding the glycoprotein of Ebola virus species Zaire Ebolavirus[4]. It is protective against the species Zaire Ebolavirus but does not protect against other species of Ebolavirus or Marburg virus. The vaccine has been prequalified by the WHO and is recommended by WHO's Strategic Advisory Group of Experts (SAGE) on Immunization as part of a set of Ebola outbreak response tools[5,6]. The European Medicines Agency and the United States Food and Drug Administration licensed the vaccine in 2019. Since then Burundi, Central African Republic, the Democratic Republic of the Congo, Ghana, Guinea, Rwanda, Uganda and Zambia have also approved the vaccine[6].

Ad26.ZEBOV/MVA-BN-Filo vaccine

This vaccine, delivered in 2 doses called Ad26.ZEBOV and MVA-BN-Filo, uses a prime-boost strategy to enhance immunogenicity and involves the use of two distinct viral vectors that are administered as different doses. The Ad26.ZEBOV component of the regimen is a monovalent vaccine based on adenovirus serotype 26 vector (Ad26) expressing the EBOV glycoprotein, and is designed to provide active specific acquired immunity to the Zaire Ebolavirus. The MVA-BN-Filo component of the regimen is a multivalent vaccine based on modified vaccinia Ankara (MVA) vector expressing EBOV, Sudan virus, and Marburg virus glycoproteins and Tai Forest virus nucleoprotein, and is designed to provide immunity to the Sudan Ebolavirus, Zaire Ebolavirus, Tai Forest Ebolavirus and the Marburg virus[5]. It was given marketing authorization by the European Medicines Agency in 2020[6].

Efficacy

An open-label, cluster-randomized, ring vaccination trial in which contacts of a suspected Ebola case were vaccinated with a single dose of rVSV-ZEBOV was conducted in Guinea. Patients in the treatment arm received the vaccine immediately (n=2108), while vaccination was delayed by 21 days in the control arm (n=1429). No patients who received the vaccine developed Ebola virus infection 10 days or more after randomization in the immediate-treatment arm; however, 10 cases occurred in unvaccinated patients in the comparison group. Vaccine efficacy was 100% (95% CI 63.5%-100.0%)[4]. The duration of protection is unknown[4]. Phase 3 trials of the Ad26.ZEBOV/MVA-BN-Filo vaccine are ongoing[5].

Indications

The WHO recommends that the rVSV-ZEBOV vaccine is used during an outbreak of Zaire Ebolavirus to protect persons at the highest risk under a "ring vaccination" strategy[6]. Vaccinated individuals should continue to adhere to infection control practices to prevent infection and transmission.

The Ad26.ZEBOV/MVA-BN-Filo vaccine has been authorized by the European Medicines Agency for use under exceptional circumstances[5].

Dosage and administration

The rVSV-ZEBOV vaccine is approved for use in at-risk adults ≥18 years of age and is administered as a single intramuscular dose[5]. The WHO SAGE on Immunization is reviewing the data on its use in children over 6 months old and in pregnant and lactating women and further recommendations are expected[6].

Ad26.ZEBOV/MVA-BN-Filo vaccine is authorised for individuals 1 year and older. The vaccine is delivered in 2 doses: Ad26.ZEBOV is administered first and MVA-BN-Filo is given approximately 8 weeks

later as a second dose. This prophylactic 2-dose regimen is therefore not suitable for an outbreak response where immediate protection is necessary. A booster vaccination with Ad26.ZEBOV should be considered in individuals at imminent risk of exposure to Ebola if more than 4 months have passed since the second dose was administered[6].

Contraindications

Severe allergic reaction (E.g. anaphylaxis) to any component of rVSV-ZEBOV including rice protein[4].

Precautions

The effectiveness of rVSV-ZEBOV in immunocompromised individuals may be diminished. The risk of vaccination with rVSV-ZEBOV, a live virus vaccine, in immunocompromised individuals should be weighed against the risk of disease due to Zaire Ebolavirus[7]. Pregnant and breast-feeding women should be offered vaccination with the rVSV-ZEBOV during an active outbreak caused by Zaire Ebolavirus in affected areas, in the context of rigorous research or in accordance with a compassionate use protocol, with informed consent[5].

There are no data on the use of Ad26.ZEBOV/MVA-BN-Filo vaccine in pregnancy; however, vaccination should not be withheld when there is a clear risk of exposure[5].

Adverse effects

Common adverse reactions to both vaccines include injection-site reactions, arthralgia, myalgia, rash, headache, fever and fatigue[5].

Storage

rVSV-ZEBOV should be stored frozen at -80°C to -60°C in the original carton to protect from light. Do not re-freeze thawed vaccine[4]. Refer manufacturer's instructions.

Malaria vaccine

Introduction

Malaria is a parasitic infection caused by *Plasmodium* spp. parasites, transmitted by bites from infected female *Anopheles* mosquitoes. Malaria is of great public health concern and is responsible for high morbidity and mortality rates worldwide. According to the WHO, globally, there were an estimated 247 million malaria cases in 2021 in 84 malaria endemic countries[8]. *Plasmodium falciparum* causes the majority of the global malaria burden and has been the primary focus of vaccine development, and *Plasmodium vivax* is the second major cause of malaria[9]. Although strategies for disease control such as vector control, insecticide impregnated bednets, seasonal malaria prophylaxis and rapid diagnosis and effective treatment with antimalarial medicines have enabled some countries to eliminate malaria, the emergence of resistance to antimalarial drugs threatens to reverse such efforts[8]. The development of an effective preventive vaccine would be a game changer. However, there are many challenges to the development of an effective vaccine such as the parasite's complex life cycle. Prototype vaccines are targeted to specific developmental stages of the parasite's life cycle (pre-erythrocytic stage, the blood stage, and the sexual stage) and/or directed to proteins expressed in those stages or in multiple stages[8]. In the pre-erythrocytic stage, sporozoites travel through the blood and infect hepatocytes. They then undergo schizogony, the multiplication stage that precedes the invasion of red blood cells. The main objective of developing a vaccine against the pre-erythrocytic stage is to inhibit hepatocyte infections and the development of the hepatic parasite, thus limiting the invasion of red blood cells.

RTS,S/AS01 vaccine

After more than four decades of basic research and clinical trials, the WHO recommended the pre-erythrocytic *Plasmodium falciparum* malaria vaccine RTS,S/AS01 in October 2021 for mass vaccine programmes for young children in regions with moderate to high malaria transmission, the first-ever approved vaccine for a human parasitic

infection[9]. RTS,S/AS01 comprises the recombinant fusion protein RTS, containing regions of the *P. falciparum* circumsporozoite protein (CSP), covalently bound to the hepatitis B virus surface antigen (S) to form RTS,S. The formulation comprises 25µg of RTS,S with the AS01 adjuvant system[8,9,10].

Efficacy

The pivotal Phase 3 efficacy and safety trial involved 15,459 infants (6-12 weeks) and young children (5-17 months) in seven sub-Saharan African countries[11]. Vaccine efficacy (after 3 doses) against clinical malaria in the absence of a booster dose was 28.3%, (95% CI 23.3-32.9) in children and 18.3% (95% CI 11.7-24.4) in young infants. Among those who received four doses, vaccine efficacy was 36.3%, (95% CI 31.8-40.5) in children and 25.9% (95% CI 19.9-31.5) in infants. The vaccine reduced malaria episodes by about 40% and severe malaria cases by about 30% over a four-year period. The study also showed that at the trial site with the highest disease burden, more than 6,500 clinical malaria episodes were averted for every 1,000 children fully vaccinated with 4 vaccine doses. A study of the longer-term impact of the vaccine, with a focus on severe malaria, was completed in December of 2016[12]. The study followed some children for an additional three years, for a total of seven years of follow-up. Follow up showed that the incidence of severe malaria decreased as children got older, regardless of whether children received the vaccine. Over the entire 7-year period, vaccine efficacy against clinical malaria was 24% (95% CI 16-31, P<0.0001) for the 3-dose group and 19% (95% CI 11-27; P<0.0001) for the 4-dose group. Thus, children in areas with moderate to high malaria transmission who received 3 or 4 doses of RTS,S/AS01 benefited for at least 7 years after vaccination and did not have an excess risk of clinical or severe malaria.

Further studies showed that seasonal vaccination with the RTS,S/AS01 malaria vaccine was noninferior to four annual courses of chemo-prevention with sulfadoxine-pyrimethamine and amodiaquine in protecting against uncomplicated clinical malaria over a period of 3 years.

Additionally, the combination of the vaccine and chemoprophylaxis was significantly better than either chemoprophylaxis alone or RTS,S/AS01 alone[13].

Indications

WHO recommends the RTS,S/AS01 malaria vaccine be used for the prevention of *P. falciparum* malaria in children living in regions with moderate to high transmission as defined by WHO[9]. The RTS,S/AS01 malaria vaccine should be provided as part of a comprehensive malaria control strategy. All malaria control interventions provide partial protection and the highest impact is achieved when multiple interventions are used concomitantly[9].

The vaccine is not recommended for adults or indicated in travellers to endemic areas[9].

Dosage and administration

The RTS,S antigen is lyophilized and needs to be reconstituted with the liquid AS01 adjuvant system prior to administration. The vaccine is currently produced as a 2-dose RTS,S powder to be reconstituted with a 2-dose AS01 adjuvant system suspension. After reconstitution, the total volume is 1 mL (2 doses of 0.5 mL). No preservative is included in either the RTS,S formulation or the AS01 adjuvant system. The vials should therefore be discarded at the end of the vaccination session, or within 6 hours after opening, whichever comes first[9].

The reconstituted vaccine should be administered IM into the deltoid in children. The RTS,S/AS01 vaccine should be provided in a 4-dose schedule in children from 5 months of age. The first 3 doses should be administered at one-month intervals, with a fourth dose given 18 months after the third dose[9].

Contraindications

Severe hypersensitivity to any of the vaccine components[9].

Adverse effects

The most commonly reported adverse reactions were fever, irritability and injection site reactions, such as pain and swelling. The incidence of generalised convulsive seizures within 7 days of RTS,S/AS01 booster was 2.2 per 1,000 doses in young infants and 2.5 per 1,000 doses in children[11].

Storage

2-8°C

Mpox vaccine

Introduction

Mpox is a viral zoonosis with symptoms similar to smallpox, although it is less contagious and causes less severe illness. Mpox virus is an enveloped, double-stranded DNA virus that belongs to the *Orthopoxvirus* genus of the *Poxviridae* family which also includes viruses such as vaccinia, cowpox, and variola. There are two distinct genetic clades of Mpox virus, Clade I (Central African or Congo basin) and Clade II (West African). Clade I clade has historically caused more severe disease and was thought to be more transmissible[14,15]. Mpox primarily occurs in rural Central and West Africa, often in proximity to tropical rainforests. Rodents are likely to be the natural reservoir of this virus with primates-including humans-being incidental hosts[15]. Animal-to-human transmission can occur from direct contact with the blood, bodily fluids, or cutaneous or mucosal lesions of infected animals. Eating inadequately cooked meat and other animal products of infected animals is a possible risk factor. However, the exact natural reservoir(s) and how the virus circulation is maintained in nature is still unknown[14].

On 23 July, 2022 WHO declared the global Mpox outbreak to be a public health emergency of international concern (PHEIC) as multiple clusters of cases (mostly Clade II) were identified in several non-endemic regions since May 2022 including Europe, the Americas, the Western Pacific, countries of the Eastern Mediterranean and in South East Asia[16].

Almost all (>95%) of cases were seen among men (median age of 38 years[15]), particularly men who have sex with men and those who have had recent sexual contact with a new partner or partners[16].

Human-to-human transmission can result from close contact with respiratory secretions, skin lesions of an infected person or recently contaminated objects. Transmission via droplet respiratory particles usually requires prolonged face-to-face contact. While close physical contact is a well-known risk factor for transmission, it is unclear at this time if monkeypox can be transmitted specifically through sexual transmission routes. Transmission can also occur via the placenta from mother to fetus or during close contact during and after birth. Vaccination against smallpox is about 85% effective in preventing monkeypox but today, young persons may be more susceptible to Mpox due to cessation of the smallpox eradication campaign[14].

The incubation period is 7 to 21 days. The rash begins within 1-3 days of fever onset and is centrifugal, i.e. more concentrated on the face and extremities rather than on the trunk. It affects the face (in 95% of cases), and palms of the hands and soles of the feet (in 75% of cases). Also affected are oral mucous membranes (in 70% of cases), genitalia (30%), and conjunctivae (20%), as well as the cornea. The rash evolves sequentially over a period of 2-4 weeks, from macules to papules, vesicles, pustules and crusts which dry up and fall off. The number of lesions varies from a few to several thousand. In severe cases, lesions can coalesce until large sections of skin slough off. Unlike smallpox, typical monkeypox infections are usually characterised by lymphadenopathy[14,15].

Mpox is usually a self-limited disease with symptoms lasting from 2 to 4 weeks. Severe cases occur more commonly among children. Complications include secondary infections, bronchopneumonia, sepsis, encephalitis, and infection of the cornea with ensuing loss of vision. The extent to which asymptomatic infection may occur is unknown. The case fatality rate of Mpox has ranges from 0 to 11% in the general population and is higher among young children. In recent times, the case fatality ratio has been around 3-6%[14].

Types of vaccine

Smallpox and monkeypox vaccines are developed in formulations based on the vaccinia virus due to cross-protection to other orthopoxviruses. First-generation smallpox vaccines are not available commercially or privately[15] but are held in strategic reserves in some countries. These first-generation smallpox vaccines are not recommended for monkeypox at this time, as they do not meet current safety and manufacturing standards[16]. Second generation smallpox vaccines use the same vaccinia virus vaccine strains employed for manufacture of first-generation vaccines. The term third generation refers to more attenuated smallpox vaccine strains specifically developed as safer vaccines by further passage in cell culture or animals[16]. Currently, there are three vaccines considered in the response to the ongoing monkeypox outbreak. All three vaccines were developed against smallpox, and evidence of their protection against monkeypox is limited[16].

Replication-competent vaccinia virus, second-generation (ACAM2000)

ACAM2000 is derived from a single clonal viral isolate from the first generation vaccine Dryvax that exhibited reduced neurovirulence in animal models. It is grown in cell culture rather than by the historical method of scarification on the sides of calves (*Bos taurus*). ACAM2000 is only licensed to prevent smallpox in the US[14].

Replication-deficient modified vaccinia ankara, third-generation (Modified Vaccinia Ankara-Bavarian Nordic; MVA-BN)

This is a third-generation vaccine based on the non-replicating modified vaccinia virus Ankara (MVA) strain with deletion of approximately 10% of its genome produced in chicken egg fibroblasts. It has been approved for the prevention of smallpox and monkeypox in the US in 2019[14].

Attenuated, minimally replication-competent vaccinia virus, third-generation (LC16m18, available in Japan)

LC16m8 is another third-generation vaccine containing a virus derived from the Lister strain used in first-generation vaccines subjected to multiple passages in tissue culture and selection for an attenuated phenotype. Vaccine is produced in cell culture using rabbit kidney cells. The vaccine received a full licence by Japanese regulatory authorities in 1980[15].

Efficacy

The real-world effectiveness of a single, subcutaneous dose of JYNNEOS, Modified Vaccinia Ankara-Bavarian Nordic; MVA-BN was evaluated in an observational, retrospective cohort study in 2022. The adjusted vaccine effectiveness was estimated at 86% (95% confidence interval, 59-95%)[17].

Indications

Mpox vaccination should be considered an additional measure to complement primary public health interventions. At an individual level, vaccination should not replace other protective measures[16]. Mass vaccination is not recommended for Mpox at this time[15,16].

Pre-exposure vaccination is recommended for individuals at high-risk of exposure. Persons at highest risk of exposure in the current multi-country outbreak are gay, bisexual or other men who have sex with men (MSM) with multiple sexual partners. Others at risk may include individuals with multiple casual sexual partners; sex workers; health workers at risk of repeated exposure, laboratory personnel working with orthopoxviruses; clinical laboratory and health care personnel performing diagnostic testing for monkeypox; and outbreak response team members[16].

Post-exposure preventive vaccination (PEPV) is recommended for contacts of cases (unprotected direct contact with an active ortho-poxvirus lesion or fluid or a contaminated item; being within 2m of an

individual with an active orthopoxvirus case for 3 h or more), ideally within four days of first exposure (and up to 14 days in the absence of symptoms)[16].

Dosage and administration

Replication-competent vaccinia virus, second-generation (ACAM2000) and Attenuated, minimally replication-competent vaccinia virus, third-generation (LC16m18, available in Japan)

Single percutaneous dose using the scarification method with a bifurcated needle

Replication-deficient modified vaccinia Ankara, third-generation (Modified Vaccinia Ankara-Bavarian Nordic; MVA-BN)

Two subcutaneous doses, 28 days apart. Because of a limited vaccine supply many countries have implemented a single-dose strategy or an intradermal 1/6th of a dose (injection volume of 0.1mL) to maximize vaccine availability[17].

Contraindications

Replication-competent vaccinia virus, second-generation (ACAM2000) is contraindicated in atopic dermatitis, active exfoliative skin conditions, immunosuppression, pregnancy, age <1 year, breastfeeding, serious vaccine component allergy, underlying heart disease, and ≥3 major cardiac risk factors[15].

Precautions

Replication-competent vaccinia virus, second-generation (ACAM2000) is a live vaccinia virus that can be transmitted to persons who have close contact with the vaccinee and the risks in contacts are the same as those stated for vaccines. Replication-deficient modified vaccinia Ankara, third-generation (Modified Vaccinia Ankara-Bavarian Nordic; MVA-BN) can be used in pregnant and lactating women when the

benefits of vaccination outweigh the potential risks and has obtained emergency use authorization in children in the USA. Attenuated, minimally replication-competent vaccinia virus, third-generation (LC16) has been authorized for children in Japan,

Adverse effects

ACAM2000 vaccination leaves a permanent scar (known as "take") at the injection site following successful inoculation[10]. Adverse effects common to all three vaccines include pruritus, lymphadenopathy, administration site soreness, fever, headache, myalgia, rash, fatigue, and bacterial infection at the site of administration[15]. Serious adverse events seen with replication-competent vaccinia virus, second-generation (ACAM2000) include myopericarditis and pericarditis, encephalitis, progressive vaccinia, erythema multiforme major, eczema, vaccinatum, generalised vaccinia, post-vaccinial encephalitis or encephalomyelitis, blindness due to autoinoculation, and fetal death in pregnant women[15].

Storage

Stored frozen between -25 and -15°C.

Zoster vaccine

Introduction

Reactivation of varicella virus causes herpes zoster. Highest incidence of reactivation is seen in the elderly and among immunocompromised individuals; persons with impaired cell mediated immune responses such as those with malignancy, organ transplant recipients and those on immunosuppressive treatment[18]. Herpes zoster affects up to 25% of human beings during their lifetime, with 50% of persons being aged 80 years or more. The most common complication of HZ, particularly in older persons, is post-herpetic neuralgia (PHN), which occurs in 10-13% of patients. PHN is the persisting debilitating pain weeks to months after resolution of HZ.

As the VZV vaccine is a live attenuated vaccine, the vaccine virus also establishes latency similar to the wild type virus. The prevalence of HZ among young adults who received the VZV vaccine 20 years ago was shown to be 0.9/1,000 person-years, which is significantly less than the prevalence of HZ following natural infection[19].

The currently recommended vaccine for prevention of herpes zoster and its complications is the zoster vaccine.

Types of vaccine

There are 2 types of zoster vaccines.

- Live, attenuated – contains the same VZV Oka strain used in varicella vaccine[20]. The vaccine is formulated with a higher potency of 19,400 PFU, as the target group will have been previously infected with varicella
- Recombinant – 50 μg of recombinant VZV glycoprotein E (gE) formulated with AS01B adjuvant

Efficacy

The vaccine was found to reduce the risk of zoster by 51.3% and PHN by 91.2%, three years following vaccination in those over 50 years of age[11]. However, the protection offered by this vaccine was shown to wane 5 years following vaccination[21,22].

Indications[20]

The vaccine is indicated for prevention of HZ, PHN and burden of illness (depending on country) in immunocompetent individuals aged ≥50 years who have been previously infected with varicella. The recombinant vaccine is indicated in addition, to adults aged 18 years and older who are or will be at increased risk of HZ due to immunodeficiency or immunosuppression caused by known disease or therapy.

Dosage and administration

- Live, attenuated – a single dose of 0.65 mL subcutaneous injection
- Recombinant – 2 doses IM, 2 to 6 months apart

Contraindications

- History of anaphylactic/anaphylactoid reaction to any component of the vaccine
- Immunosuppression or immunodeficiency
- Pregnancy

Adverse effects

HZ-like rash, erythema, pain/tenderness and swelling at the injection site, myalgia, fatigue, headache

Storage

2-8°C.

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CHAPTER 26
IMMUNIZATION IN PREGNANCY

Introduction

Pregnancy is a state of relative immunocompromise making a woman vulnerable for infections[1]. Some infections could affect the pregnancy significantly and could have serious consequences for maternal health. Some infections are harmful for the fetus and may result in fetal anomalies and even death. Immunization plays a major role in preventing and minimising the effects of these complications during pregnancy[2].

Recommendations for women planning pregnancy

It is important, as part of the pre-conceptional care to assess the need for vaccination against influenza, hepatitis B, measles, mumps, rubella and varicella. A thorough evaluation should be done to ascertain immunity or previous vaccination against these infections. This includes, taking a detailed history and review of previous immunization records. If there is a doubt about immunity, antibody testing could be offered, or administration of vaccines could be done. Women should refrain from getting pregnant at least for 4 weeks after vaccination with live-attenuated vaccines[2]. However, some of the live attenuated vaccine manufacturers advice against pregnancy for at least 3 months after administration.

Rubella

Rubella infection may result in serious consequences for the developing embryo. Infection with rubella virus causes the most severe damage in the first trimester. Pregnant women infected with rubella are at increased risk of miscarriages or still births and are at risk of severe congenital anomalies with devastating life-long consequences[3,4].

Congenital rubella syndrome (CRS)

Congenital rubella syndrome (CRS) could occur in the fetuses of women who are infected with rubella virus. Congenital anomalies with rubella infection in the first trimester, could be as high as 85%[3].

The most common birth defects from CRS include deafness, cataracts, heart defects and intellectual disabilities[4].

Vaccine recommendations

National Immunization Programme (NIP) recommends all women in the childbearing age group (15-44 years) should be vaccinated against rubella. MMR vaccine is an attenuated live virus vaccine and is contraindicated during pregnancy[2]. It is important to exclude pregnancy before vaccination. Women of childbearing age should avoid getting pregnant for at least 4 weeks after receiving MMR vaccine[5]. However, there are no reported cases of affected neonates due to inadvertent administration[6]. In this context, inadvertent administration of MMR vaccine is not considered as an indication for termination of pregnancy.

Pregnant women who are not vaccinated should be offered MMR vaccine soon after delivery.

Varicella (chickenpox)

Due to relative immunocompromised state, infection with varicella-zoster virus during pregnancy may cause serious maternal morbidity and though rare, even maternal mortality. In the fetus, it may lead to miscarriages, fetal varicella syndrome (FVS), varicella infection of the newborn and neonatal varicella[7].

Maternal effects

Incidence of pneumonia is increased to 5-14% in pregnancy[8]. Severe life-threatening pneumonia could occur during the third trimester due to gravid uterus compromising the respiratory function[9]. Antiviral therapy has reduced the case fatality rate significantly, though rare, maternal mortality is being reported yearly around the world[10].

Fetal effects

Spontaneous miscarriage does not appear to be increased if varicella occurs in the first trimester[11].

FVS is characterised by one or more of the following: skin scarring in a dermatomal distribution; eye defects (microphthalmia, chorioretinitis or cataracts); hypoplasia of the limbs; neurological abnormalities (microcephaly, cortical atrophy, mental retardation or dysfunction of bowel and bladder sphincters)[11]. It does not occur at the time of initial fetal infection but results from a subsequent herpes zoster reactivation in utero and only occurs in a minority of infected fetuses. Incidence before 20 weeks of gestation, appears to be 0.9%[9]. FVS has been reported to complicate maternal varicella occurring as early as 3 weeks and as late as 28 weeks of gestation[12]. There are no reported cases of FVS from varicella infection after 28th week of gestation.

Varicella infection of the newborn refers to varicella viral infection in early neonatal life. This could result from maternal infection near the time of delivery or immediately postpartum, or from contact with a person other than the mother with varicella or shingles during this time. The route of infection could be transplacental, ascending vaginal or result from direct contact with lesions during or after delivery. If maternal infection occurs 1-4 weeks before delivery, up to 50% of babies are infected and approximately 23% develop clinical varicella, despite high titres of passively acquired maternal antibody[7]. Severe varicella is most likely to occur if the infant is born within 5 days of onset of the mother's rash or if the mother develops the rash up to 2 days after delivery[13].

Vaccine recommendations

Currently, NIP does not recommend universal vaccination against varicella in the reproductive age. However, in pre-pregnancy, varicella vaccination could be given if the woman is found to be non-immune (no previous history of varicella or specific IgG negative)[7]. Pregnancy should be avoided for at least 4 weeks after vaccination after completing the two-dose schedule and to avoid contact with susceptible pregnant women

should a post-vaccination rash occur[7]. Nevertheless, no fetal anomalies have been reported with inadvertent administration while being pregnant[14].

Measles

Measles is a highly contagious viral infection. Infection during pregnancy could lead to severe infection of the mother, with increased risk of pneumonia and prolonged hospital stay[15]. Infection during pregnancy could also significantly affect the fetus and may lead to miscarriage, still birth, preterm labour and low birth weight[16].

Vaccine recommendations

Women in child-bearing age, who are found to be non-immune, should be vaccinated against measles with MMR vaccine[17]. Pregnancy should be avoided for at least 4 weeks after administration. Vaccination during pregnancy is contraindicated, however, there are no reported cases of affected neonates due to inadvertent administration[6]. In this context, inadvertent administration of MMR vaccine is not considered as an indication for termination.

Recommendations for pregnant women

All live attenuated vaccines are contraindicated in pregnancy due to theoretical risk of transmission to fetus, although there has been no evidence of adverse effects from inadvertent administration[2].

In Sri Lanka, tetanus toxoid is routinely administered as part of antenatal care. Seasonal influenza vaccination is recommended in most countries to prevent complications associated with influenza outbreaks. Many countries advocate vaccination against pertussis during third trimester to reduce neonatal infection.

Tetanus

Tetanus is a fatal infectious disease caused by toxigenic strains of *Clostridium tetani*. Tetanus and neonatal tetanus are major public health problems in many developing countries[18]. However, due to success of

the immunization programme in Sri Lanka, both tetanus and neonatal tetanus have reached elimination levels[19]. Nevertheless, NIP recommends immunization of pregnant women with tetanus toxoid.

Vaccine recommendations

Tetanus vaccine is derived from inactivated toxin which could induce antibodies against the tetanus toxin. In pregnancy, NIP recommends the following schedule for a monovalent tetanus vaccine[20].

Table. National immunization programme schedule for tetanus toxoid vaccination during pregnancy[20]

Pregnant women **with no documented evidence** of previous vaccination with tetanus toxoid containing vaccine.	Pregnant women **with documented evidence** of previous vaccination with tetanus toxoid containing vaccine.
• 1st dose – 1st pregnancy, after 12 weeks • 2nd dose – 1st pregnancy, 6-8 weeks after 1st dose • 3rd dose – 2nd pregnancy, after 12 weeks • 4th dose – 3rd pregnancy, after 12 weeks • 5th dose – 4th pregnancy, after 12 weeks	One booster dose tetanus toxoid is indicated during the 1st pregnancy, with a written evidence of previously being vaccinated with 6 doses of tetanus toxoid containing vaccination as per national immunization schedule during childhood and adolescence (3 doses of DTP in infancy + DTP at 18 months + DT at 5 years + aTD at 11 years) and a gap of 10 years or more after the last tetanus toxoid containing vaccination.
Tetanus toxoid vaccination is **not indicated** in the current pregnancy, if:	
• woman has already received 5 doses of tetanus toxoid during previous pregnancies. • woman has already had 6 doses of tetanus toxoid containing vaccination according to the national immunization schedule and the gap between the last vaccine is less than 10 years from the present pregnancy. • woman has already had 6 doses of tetanus toxoid containing vaccination according to the national immunization schedule and has had at least one booster dose during previous pregnancy or following trauma within the last 10 years.	

Influenza

Influenza could result in serious illness when it occurs during the antenatal or postpartum period. Studies have shown that pregnant women have a higher chance of progression to pneumonia, need for intensive care treatment and prolonged hospital stay, especially if they get influenza during the 3rd trimester[21]. During the 2014 H1N1 influenza outbreak, it became the leading cause of maternal mortality in many countries, including Sri Lanka[22].

Influenza vaccine protects pregnant women against strains circulating during the influenza season and protects babies born during the same time. Immunization during pregnancy has reduced the severity of the disease in addition to its role as a primary preventive measure[23]. There is reliable data showing vaccination during pregnancy also protects the newborn during the first few months of life[24].

The main challenge is to obtain seasonal influenza vaccine active against current strains during the season. However, since there is cross immunity against all strains, some protection is conferred, even when the vaccine does not contain the current strains.

Vaccine recommendations

The inactivated influenza vaccine is recommended during every pregnancy, at any gestation[25].

Pertussis (whooping cough)

Infants less than 3 months of age are susceptible to the more severe form of infection with pertussis. The majority of infants who succumb to pertussis are less than 6 weeks of age[26]. It has been shown that, more than 90% protection against severe infection, in infants less than 2 months, could be achieved by passive immunization from mother to fetus[27]. This could only be achieved through vaccination during pregnancy which leads to high levels of antibodies available for transfer to the fetus[27]. Therefore, vaccination during pregnancy is recommended in many countries.

Vaccine recommendations

Pertussis vaccination is recommended between 20 weeks to 32 weeks of gestation as a single dose in each pregnancy[28]. There has been no increased risk of adverse pregnancy outcomes, reported from vaccination during pregnancy[29]. Currently, pertussis vaccine is not included in the NIP for pregnancy.

Recommendations for post pregnancy

Women who are found to be non-immune for rubella or varicella should be offered vaccination in the immediate postpartum period before discharge from the hospital[2]. Breast feeding is safe and should be encouraged after vaccination[2].

Recommendations for COVID-19 infection

Pregnancy is considered as an independent risk factor for severe infection with COVID-19[30]. World Health Organisation, Centre for Disease Control and Prevention and almost all professional organizations worldwide including Sri Lanka College of Obstetricians and Gynaecologists strongly recommend a full course of vaccination of women pre-pregnancy, during pregnancy, post pregnancy and during breast feeding against COVID-19[31]. Two doses vaccine with a booster dose have shown to reduce the risk of severe infection during pregnancy by more than 80%[32]. Vaccination also reduces premature birth and severe disease of the new born.

All types of COVID-19 vaccines are recommended for immunization during pregnancy[33].

Pre-pregnancy

Women in the reproductive age group and planning to get pregnant are encouraged to get vaccinated against COVID-19. They should not avoid getting pregnant after vaccination. There is no evidence to suggest vaccination affects fertility adversely[34].

During pregnancy

A full course of vaccination is highly recommended during pregnancy if not already vaccinated. It is the best way to protect pregnant women and babies with known complications of COVID-19 infection in pregnancy.

Data from safety monitoring systems and other studies have not found any safety concerns from vaccination during pregnancy. There is no evidence so far of adverse pregnancy outcomes including miscarriages, still births, preterm birth, postpartum infection and thromboembolic complications after vaccination during pregnancy[35].

No increased risk of birth defects was detected by vaccination during first trimester[36].

Post-delivery and breast feeding

Breast feeding and post-delivery women are recommended to be vaccinated against COVID-19, if they have not been vaccinated prior to or during pregnancy[37]. They should not stop breast feeding after vaccination. Data regarding safety of vaccination during breast feeding are limited, however, available evidence indicates vaccination to be safe and effective during breast feeding and may even protect the newborn from severe disease[38].

Vaccine recommendations

Administration of vaccines should be similar to non-pregnant women and follow the recommended protocol according to the type of vaccine.

Details of different types of vaccines and their schedules of administration are discussed in chapter 6.

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CHAPTER 27

IMMUNIZATION FOR THE ELDERLY

Introduction

Ageing is one of the most intricate and complex biological phenomena. A person over the age of 65 years is considered elderly. The proportion of this group is gradually increasing due to advances in medical care and better living conditions[1]. Important cofactors for infection in older adults is the presence of comorbid conditions and advancing age which are predictors for worst outcomes[2].

Ageing is associated with dysregulation in the immune system even in the absence of comorbid diseases[2]. An age-associated progressive reduction in the ability to trigger effective antibody and cellular responses results in the vulnerability to infectious diseases and diminished responses to vaccinations in older adults. This phenomenon is called immuno-senescence. The hallmarks of immunosenescence include reduced ability to respond to new antigens, production of high affinity protective antibodies and defective T cell response contributing to dysregulated immune responses at multiple levels[3].

When compared to young adults, the severity of many infections is higher in the elderly and associated with long-term sequalae with impairment of activities and loss of independence. Therefore, prevention of infections is an important measure to ensure healthy ageing and to improve the quality of life[4].

Vaccines recommended for the elderly[1,4,5]

- Influenza vaccine
- Pneumococcal vaccine
- Tetanus, diphtheria and pertussis vaccine
- Varicella vaccine
- Zoster vaccine
- COVID-19 vaccine

Influenza

Influenza A and B viruses cause seasonal epidemics of influenza in humans. Adults aged >65 years have the highest risk for hospitalization, complications and death, resulting from influenza. The risk increases markedly in people over 85 years[1].

The standard-dose influenza vaccines are multivalent; trivalent or quadrivalent inactivated vaccines. Their composition is updated annually. In the over-65s, influenza vaccine reduced the risk of influenza from 6% to 2.4% and influenza-like illness (ILI) from 6% to 3.5% in comparison to placebo[6]. A systematic review and meta-analysis found that influenza-vaccinated populations demonstrated a 51% reduction in laboratory-confirmed influenza-related hospitalization rates in adults aged 18-65 years and a 37% reduction in those aged >65 years[6].

The standard-dose influenza vaccine has consistently shown a lower immunogenicity and efficacy in older adults than in young adults irrespective of their composition[1]. In contrast, the enhanced-trivalent vaccine has shown increased immunogenicity in older people than the standard-dose trivalent or quadrivalent vaccines. However, the efficacy of the enhanced-dose vaccine is still not known[1].

(Further reading, refer Chapter 13)

Pneumococcal disease

Invasive pneumococcal diseases (IPD) are more common in extremes of age with peaks at <2 years and >65 years[1,7]. Hospitalization for pneumonia increased from 1.5-3.9% per year from the age 65 to >85 years. Mortality increases substantially with age and is more than 2-5 folds grater among adults with underlying diseases than in healthy older adults[7]. Further, deaths from pneumococcal bacteraemia has remained constant with 5-10% despite advances in antimicrobial therapy[7]. The risk of multidrug-resistant infections is increasing in this group due to prolonged hospitalization and long-term antibiotic therapy[2].

Pneumococcal immunization is recommended in elderly. The efficacy of 23-valent pneumococcal polysaccharide vaccine (PPSV-23)

decreases as age increases above 65 years, especially for persons >85 years. A study from UK revealed, effectiveness of PPSV-23 is low among immunocompromised persons of >65 years than in immuno-competent aged 65-84 years. However, a significant serotype-specific vaccine efficacy was demonstrated against IPD in PPSV-23[1].

Impact of pneumococcal conjugate vaccine 13 (PCV13) followed by PPSV-23 in elderly was reviewed by the US Advisory Committee in Immunization Practices and concluded that no evidence was found in any increased reduction of IPD in older adults >65 years. An economic analysis revealed, unlike PCV13 immunization, PPSV-23 was cost effective especially in older adults aged >70 years[1].

(Further reading, refer Chapter 17)

Tetanus

Tetanus is a non-communicable disease due to a neurotoxin secreted by *Clostridium tetani* and is associated with substantial mortality and morbidity[8,9]. Patients ≥60 years of age are most likely to be fatal in approximately 11% of reported cases[8]. The disease normally affects unimmunized or partially immunized people and the risk increases with age. Antibody concentrations declined and are low in older adults >80 years. Titres of antibodies to tetanus are inadequate to ensure protection in 50% of adults >65 years[10]. Due to the extensive National Immunization program, tetanus cases are relatively low in Sri Lanka[9].

For older adults *Tdap or Td vaccines are recommended even if they have not completed the primary series of childhood vaccination. They have shown to be immunogenic and would provide protection for ≥65 years or older.[8] However, the antitoxin levels may decrease with time. As a result, routine boosters are recommended every 10 years or unless needed sooner as tetanus prophylaxis, as part of wound management[8].

(Further reading, refer Chapters 8, 21)

Diphtheria

Diphtheria is caused by the toxin-producing *C. diphtheriae* causing local and systemic manifestations of diphtheria[8,9].

Diphtheria toxoid is a combined vaccine with tetanus toxoid and pertussis; Tdap booster dose for older adults who have completed the recommended childhood DTP/DTaP vaccination series is recommended[9]. This vaccine available in Sri Lanka outside of the National Immunization Program. [Annex II, VI]

(Further reading, refer Chapter 8)

Pertussis

Pertussis is a highly contagious respiratory tract infection with a high secondary attack rate of 90%[9]. It could be easily transmitted to more vulnerable populations such as neonates and patients with chronic diseases. Waning immunity after infection or post vaccination in older adults are observed as the major source of infection for unvaccinated children and neonates[11]. Control of pertussis largely rests upon immunization.

Studies have revealed approximately 90% immune response after the administration of booster vaccination. The acellular pertussis booster vaccines are immunogenic and well-tolerated[11]. Tdap could be used for unimmunized adults[12].

**Tdap vaccine*; For the prevention of tetanus, diphtheria and pertussis diseases. Adults age ≥65 years, previously vaccinated or not, should get a booster dose. Persons should continue to receive Tdap every 10 years[8].

(Further reading, refer Chapter 08)

Varicella

Varicella zoster virus is highly contagious. Chickenpox tends to be more severe in adults than in children, and the adults have a higher risk of developing complications[1,12,13].

Varicella vaccine is recommended for susceptible persons without evidence of immunity to varicella[13].

Evidence of immunity includes,

- Documented age-appropriate varicella vaccination in childhood
- Laboratory evidence of immunity to varicella
- Diagnosis or verification of a history of varicella or herpes zoster by a healthcare provider; an epidemiological link to a typical varicella case or laboratory confirmed case

An adult with documented evidence of a single dose of varicella vaccine in the past, should be offered a single booster dose[12]. Single-antigen live-attenuated varicella vaccine is recommended for adults[13].

(Further reading, refer Chapter 23)

Herpes zoster

Herpes zoster is a condition due to reactivation of varicella zoster virus from a latent state in sensory ganglia following varicella[1,9]. Complications of herpes zoster increase with age and in immunocompromised states. Post herpetic neuralgia is the most frequent complication and increases in frequency, severity and duration with advancing age. It is not prevented by antiviral therapy and the pain is difficult to treat.

The live-attenuated herpes zoster vaccine (ZVL) is effective in preventing post herpetic neuralgia with statistically significant age-related vaccine efficacy. Vaccine efficacy decline significantly after 4-8 years of vaccination. The vaccine is recommended for immunocompetent adults aged ≥50 years[1]. ZVL prevent post herpetic neuralgia by 67% of vaccinees in over 70 years of age. Further, it attenuates the effects when HZ occurs, preserving the quality of life. In the UK, this vaccine is given for elderly in their National Immunization Programme[1].

Recombinant subunit herpes zoster vaccine (RZV) is more effective than the ZVL. It is also recommended in immunocompromised persons. RZV has a high vaccine efficacy of >90% in all age groups and against post-herpetic neuralgia. Vaccine efficacy remained same even with the presence of pre-morbid condition/s (rheumatoid arthritis, inflammatory bowel diseases etc.)[1]. This vaccine is not available in Sri Lanka.

(Further reading, refer Chapter 23)

COVID-19

Older adults have an increased risk of severe illness from COVID-19 infection. They are more prone for hospitalization, intensive care management including ventilator support. The risk increases in adults >60 years[5].

People >65 years, who received both doses of either Pfizer or Moderna vaccines have shown 94% reduced risks of COVID-19 related hospitalization[5].

For Sinovac and Sinopharm, WHO recommends that countries should consider offering an additional third dose of the vaccine for those aged above 60 years[14]. A study from Israel revealed that a fourth dose of Pfizer COVID-19 vaccine would increase the protection against severe illness and reduce hospitalization in people over the age of 60 years[15].

CDC recommends an additional booster dose for those aged 65 and above to reduce the risk for severe disease[16]. This should be given 4 months after the 3rd dose of the COVID-19 primary vaccination series.

(Further reading, refer Chapter 6)

- Refer the relevant chapters of the vaccines for further details and contraindications.
- CDC Adult Vaccine Schedule; https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html

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CHAPTER 28

IMMUNIZATIONS FOR COMPETITIVE SPORTSPERSONS

Introduction

There are significant numbers of Sri Lankans of all age groups, from children to senior citizens, who take part in competitive sports. They may be called upon to compete nationally or internationally and this may involve travel within the country as well as across many a continent, sometimes as individuals and at other times as a member of a team. Athletes are often exposed to crowded places (locker rooms, sports meetings, media conferences and sporting arenas) which increase the risk of airborne infection[1]. In contact sports (rugby, wrestling, gymnastics, martial arts etc.), there is an increased risk of airborne infection[1] as well as blood-borne transmission of infections. Vaccine-preventable diseases may interfere with the training schedules of athletes or with participation in competitions. Furthermore, there is a potential risk for some of these diseases to cause long-term problems as well.

Intense exercise alters the functions and quantity of circulating cells of both the innate and acquired immune systems (E.g. neutrophils, monocytes and natural killer cells). The reason for the decrease in the acquired immune response during intense physical exercise seems to be related to an increased release and circulation of stress hormones (cortisol and catecholamines) and the cytokine-mediated alteration of the balance of pro-inflammatory and anti-inflammatory activity[2]. This alteration of the immune response is called the 'open window' and it is responsible for higher risks of infection in athletes when exposed to microorganisms[2].

Administration of the National Immunization Programme (NIP) vaccines in Sri Lanka may not adequately meet the medical needs of sports-persons[1]. An enhanced benefit from preventing even mild diseases is important from the point of view of sports training and sports partici-

pation. A risk-benefit assessment has to be undertaken on an individual basis concerning immunization and the timing of vaccinations of sportspersons. Such risk-benefit analyses of vaccination in athletes differ significantly from that of the general population, providing the rationale for specific vaccination guidelines for sportspersons[3].

In the case of sportspersons, determination of antibody titres before vaccination is considered to be reasonable and essential for only very few diseases, mostly to avoid unnecessary vaccinations or to assess the immune status of an individual following vaccination. This is particularly relevant for measles, mumps, rubella, varicella, hepatitis B and hepatitis A. All necessary vaccinations for sportspersons need to be scheduled in a way that possible side effects are least likely to interfere with competition or training. At the same time, certain immunological concerns must be considered when the vaccination schedule is planned because vaccine administration during the 'open window' phase may be associated with a suboptimal immune response and reduced vaccine efficacy[2]. However, it is also necessary to appreciate that normally, vaccinations are quite well tolerated by athletes and the resulting antibody titres are no different to the levels in the general population[3].

In the case of children and adolescents involved in competitive sports, it is imperative to ensure that all the vaccines advocated by the NIP have been administered at the proper times. If deficiencies in their administration are detected, they should be promptly corrected. In addition, some vaccines that are not included in the NIP may need to be given to these young athletes.

In most situations, the vaccines recommended for all sportspersons are:

- Diphtheria, pertussis and tetanus
- Influenza
- Hepatitis A
- Hepatitis B
- Measles, mumps, rubella
- Varicella

Some of these vaccines are included in the NIP, with children and young adult sportspersons being already covered by the programme.

There are certain diseases for which vaccines are recommended under special circumstances and for epidemiological reasons. These are indicated for sportspersons who have to travel to certain countries in which these diseases are endemic (refer Chapter 28).

The recognised diseases that fall into this group are:

- Yellow fever
- Japanese encephalitis
- Poliomyelitis
- Typhoid
- Meningococcal disease
- Tick-borne encephalitis

There are other vaccines that are recommended when athletes have a co-morbid state or a significant underlying disorder or for athletes with different abilities or the elderly in the veterans' sports category.

The vaccines that are recommended for these categories are:

- Pneumococcal vaccine
- *Haemophilus influenzae* type b (Hib) vaccine

During the current era of the COVID-19 pandemic, vaccines against the SARS-CoV-2 need special consideration. There are several different vaccines and vaccination schedules that are used in Sri Lanka. These are changed through necessity from time to time, taking into account the developing scenarios of the pandemic. Comprehensive information regarding the commonly used COVID-19 vaccines and vaccination programmes are provided in Chapter 6.

Some important issues should be considered when one looks at the COVID-19 vaccination of sportspersons. It should be clearly understood that there is a real need to adequately immunize all sportspersons against COVID-19, especially because of the increased risks that sports participants run of contracting the virus during training and competition. There may be mandatory requirements for adequate and satisfactory

COVID-19 vaccinations for competitive sports participation nationally as well as internationally. In addition to the purely medical considerations, during international competitions held in different countries, there may be essential and obligatory requirements in COVID-19 vaccinations for international travel visa securement. These considerations are further complicated by the instances where the sportspersons have also contracted the disease previously. It is essential that when travelling abroad for sports training or competitions, the athletes are advised to carry all vaccination certificates as well as documents, if any, related to medical exemptions granted for COVID-19 vaccines.

It is important to note that because of the changing and challenging scenarios of the pandemic in Sri Lanka as well as in other parts of the world, it is not possible to lay down very specific recommendations regarding COVID-19 vaccinations for sportspersons. The requirements and the recommendations could vary quite significantly over time. It is in the best interests of sportspersons, for their sporting bodies, as well as Team Physicians, to find out the regulations prevalent at the time regarding COVID-19 vaccines before training and competitions, locally as well as overseas.

Additional information:

- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6116102/ doi: 10.1177/1941738118788279
- https://www.tandfonline.com/doi/full/10.1080/14760584.2017.1358092 https://doi.org/10.1080/14760584.2017.1358092
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- https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00082-5/fulltext https://doi.org/10.1016/S2213-2600(21)00082-5

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CHAPTER 29

IMMUNIZATION FOR INTERNATIONAL TRAVEL

Introduction

International traveller may be exposed to variety of health risks, depending on the travel destination, trip itinerary, duration of stay, travel activities and individual risk factors. It is important to protect the health of the individual traveller as well as the communities to which they return.

Pre-travel consultation

Pre-travel consultation is a major opportunity to review routine immunization, educate the traveller about health risks at the destination and how to mitigate them. Travel health advice should be personalized and require attention to the travellers' health status to determine the health risks, preventive measures including availability of vaccines. Ideally, all vaccinations should be completed at least two weeks before departure.

In considering immunization for travellers, the following information is important:

- general health such as age, allergies, medication, pregnancy and chronic diseases
- previous immunization history
- current information on vaccine-preventable diseases at travel destination
- activities planned during travel and at travel destination
- duration of stay
- time available before departure

Travel-related vaccination

It is categorized in to 3 groups[1,2].

- Routine immunization
- Vaccines recommended for certain destinations
- Vaccines demanded by certain countries

Routine immunization

Most of these vaccines are part of the National Immunization Programmes. They should be up-to-date regardless of travel [Annex 1].

Vaccines recommended for certain destinations

These vaccines are recommended to provide protection against diseases endemic to the country of origin or destination. They are intended to protect the traveller and to prevent disease spread within and between countries. Country requirements are subjected to change at any time. Travellers should check the relevant consulate or embassy of the destination country to ensure their requirement.

Yellow fever vaccine

Yellow fever vaccine is given for two reasons; to protect individuals in areas of high risk for yellow fever virus infection and to protect vulnerable countries from importation of the yellow fever virus. The vaccine is recommended to all travellers ≥9 months of age in countries where there is evidence of persistent or periodic yellow fever transmission.

The yellow fever vaccine is a live, attenuated highly effective vaccine. A single dose of the vaccine is sufficient to confer lifelong protective immunity against the disease.

In addition to vaccination, all travellers should take adequate measures against exposure to mosquito bites.

For persons travelling to endemic countries

Yellow fever vaccination is required for people travelling to endemic countries as per International Health Regulations (IHR)[1]. Currently, the endemicity of yellow fever is confined to certain countries in sub-Saharan Africa and tropical South America. The WHO provides updated information on yellow fever endemic countries from time to time.

For persons arriving from an endemic country

Countries protect themselves from the risk of importing or further spreading the yellow fever virus by establishing entry requirement on yellow fever vaccination for travellers.

Proof of vaccination is required from travellers arriving from countries with risk of yellow fever transmission and sometimes from travellers in transit through such countries; International Certificate of Vaccination and Prophylaxis (ICVP), on entry, for travellers arriving from endemic countries. Travellers arriving without a completed ICVP may be quarantined or refused entry.

If a physician concludes that a particular vaccination should not be administered for medical reasons, the travellers should be given a signed and dated statement of the reasons on the physician's letterhead. Under these conditions, the travellers should obtain specific advice from the embassy/consulate of the countries the person plans to visit.

How to obtain the certification of vaccination in Sri Lanka?

Yellow fever vaccines are produced by different manufacturers worldwide. For the purpose of international travel, a WHO-approved vaccine must be given and it should be administered at an approved yellow fever vaccination center in the country.

The only authorized centre in Sri Lanka is the Assistant Port Health office located at the Medical Research Institute, Colombo 8. The traveller should receive a completed ICVP, signed and validated with the official stamp. The certificate is valid for life, from 10 days after vaccination.

Official address;

The Assistant Port Health Officer,
Assistant Port Health Office,
Dr. Danister de Silva Mawatha
Colombo 08, Sri Lanka
Telephone: +94 112 675 182
Working hours: Week days 9 am to 4 pm

(Further reading, refer Chapter 24)

Meningococcal vaccine

The risk of meningococcal disease in travellers is generally low. Travellers to sub-Saharan meningitis belt may be exposed to outbreaks, most commonly by serogroup A and serogroup W135. Incidence rates are high during the dry season from December to June[2].

Pilgrims to Mecca are at high risk of invasive meningococcal disease. Vaccination is required by the government of Saudi Arabia for travellers performing Hajj or arriving for employment. In some countries meningococcal vaccine is given in their National Immunization Programmes (E.g. UK, USA)[2,3].

Meningococcal vaccine is recommended for students who travel to countries that are endemic for meningococcal disease if they plan to live in dormitories or residence halls.

(Further reading, refer Chapter 16)

Polio vaccine

International spread of wild poliovirus is a public health emergency under the IHR[1]. The South East Asia Region was declared polio free in 2014. However, until the declaration of Global Polio Eradication, the risk of transmission to polio-free countries will remain[1].

The World Health Organization recommends travellers across all age groups visiting polio-infected countries to have completed age-appropriate polio vaccine doses recommended in the National Immunization

Programme of the country. Travellers to polio-infected countries who completed an oral polio vaccine (OPV)/inactivated polio virus (IPV) vaccine series >12 months previously, should be given another booster dose.

Travellers residing in polio-infected countries (those with active transmission of wild or vaccine-derived poliovirus) and long-term visitors to such countries (who will spend more than four weeks in the country) should have completed a full course of polio vaccination in compliance with the National Immunization Programme. Travellers from infected countries should receive an additional dose of OPV/IPV within 4 weeks to 12 months before departure. All travellers should carry a written vaccination record or ICVP[1].

Some polio-free countries (E.g. Saudi Arabia) require resident travellers and long-term visitors from polio-infected countries to provide documentation of recent vaccination to obtain entry visa or they may require travellers to receive an additional dose of polio vaccine on arrival.

An up-to-date list of polio-affected countries is available at World Health Organization (WHO) Global Polio Eradication Initiative website (www.polioeradication.org)

(Further reading, refer Chapter 18)

Varicella vaccine

Vaccination against varicella is not a requirement for entry into any country, but people who do not have evidence of immunity and are at risk of varicella should consider vaccination prior to international travel.

(Further reading, refer Chapter 23)

Hepatitis B vaccine

Vaccination to prevent hepatitis B should be considered for all international travellers, regardless of the destination. Unvaccinated people travelling to areas with intermediate to high prevalence of chronic HBV infection (HBsAg ≥2%) such as in the WHO Western Pacific and African regions need special consideration[1,2].

Ideally, vaccination should begin ≥1 month before travel to complete the primary series before departure. Optimal protection is not conferred until after the vaccine series is completed. An approved, accelerated vaccination schedule could be used in an emergency situation[1,2]. All travellers should be counseled and given information on the risks for hepatitis B.

(Further reading, refer Chapter 11)

Pneumococcal vaccine

Travel itself does not increase the risk of acquiring pneumococcal disease. Vaccine is advisable when travelling to countries with limited medical resources, children <2 years, adults ≥65 years and adults considered to be at risk of serious disease[1,2]. Protection occurs 14 days after vaccination.

(Further reading, refer Chapter 17)

Hepatitis A vaccine

All susceptible persons travelling to or working in countries that have high or intermediate hepatitis A endemicity should be vaccinated, and age-appropriate doses should be administered. The first dose of hepatitis A vaccine should be administered as soon as travel is considered and a second dose should be administered after 6-12 months for long term protection.

One dose of single-antigen hepatitis A vaccine administered at any time before departure can provide adequate protection for most healthy persons. More than 95% of vaccinated persons develop protective antibodies one month after the first dose[2].

(Further reading, refer Chapter 10)

Typhoid vaccine

The vaccine is recommended to travellers to countries with recognized risk of exposure to typhoid fever. Vaccinated travellers should follow recommended food and water precautions.

(Further reading, refer Chapter 22)

Rabies vaccine

Travellers to rabies-endemic countries should be warned about the risk of rabies exposure and educated to avoid animal bites. Pre-exposure rabies vaccination (PrEP) is recommended for international travellers based on the prevalence of animal rabies in the country of destination, intended activities and the duration of stay. A decision to receive pre-exposure rabies immunization may be based on the likelihood of repeat travel to at-risk destinations or long-term travel.

(Further reading, refer Chapter 19)

Japanese encephalitis (JE) vaccine

Travellers to JE-endemic countries should be advised of the risks of JE and the importance of personal protective measures to reduce the risk of mosquito bites. Evaluation of a traveller's risk should consider travel location, duration, activities, accommodation and seasonal patterns of disease in the areas to be visited.

The risk of JE is high in different seasons and certain areas in Australia, China, Korea and other South East Asian countries.

(Further reading, refer Chapter 14)

Influenza vaccine

Travellers are at risk in any country during the influenza season. In the tropics, influenza could occur throughout the year, while in the temperate regions' disease activity occurs during the winter. The elderly, people with pre-existing chronic diseases and young children are most susceptible to complications. High risk travellers, travelling to countries where influenza activity is on-going should consider influenza vaccination ≥2 weeks before departure. Travellers should be advised on preventive health measures such as avoiding close contact with sick persons and frequent hand hygiene during travel.

The requirements of the destination country should be considered before administering the vaccine. The seasonal influenza vaccines do not provide protection against human infection with influenza viruses of animal-origin.

(Further reading, refer Chapter 13)

Vaccines demanded by certain countries

- Polio vaccine – see above
- Yellow fever vaccine – see above
- Meningococcal vaccine – see above
- COVID-19 vaccine

COVID-19 vaccine

Countries may change entry requirements and travel advice for COVID-19 vaccination at very short notice. Travellers must ensure they are up to date regarding the current requirements of the destination country. Some countries request proof of vaccination status from international travellers. Travellers should follow the advice of the destination country and the airline regulations.

In many countries, criteria for 'fully vaccinated' status is that a person should be vaccinated with two doses followed by a booster dose with an accepted COVID-19 vaccine. This may differ by country and periodically.

WHO recommends an additional booster dose for those aged 60 and above[5]. CDC recommends an additional booster dose for those aged 65 and above to reduce the risk for severe disease[6]. It should be given 4 months after the 3rd dose of the COVID-19 primary vaccination series.

Travellers should check the accepted vaccine list and the criteria for 'fully vaccinated' status of the destination country before travel.

(Further reading, refer Chapter 6)

Special groups

Long stay travellers

Persons who travel for long term stay such as for education and employment should inquire regarding vaccination requirements of the host country from the respective organizations, e.g. educational institutes or employing organizations, well before travel. This will facilitate completion of vaccination prior to travel.

Long stay travellers to India, Bangladesh, Nepal, Pakistan and China should consider vaccination against hepatitis A, hepatitis B, typhoid fever, meningococcal disease and Japanese encephalitis. Students who travel to UK, Europe, USA may require meningococcal, MMR and varicella vaccinations.

Last-minute travellers

Although travellers are encouraged to access vaccination services one month prior to travel, this may not be possible in some instances. In such situations, it is important to consider travel itinerary and risk of infection at the destination. They should be advised on preventive behaviors as they may not be protected adequately by the travel date.

Combined vaccines should not be used for any accelerated schedule.

It is important to use single dose vaccines to initiate protection, e.g. hepatitis A (monovalent), typhoid (injectable), Japanese encephalitis (live). Travellers who have not received a documented dose of polio vaccine within previous 12 months should receive a single dose of OPV prior to departure.

Immunocompromised travellers

In the case of an immunocompromised traveller, vaccination must be considered from the following perspectives:

- safety in the context of the underlying illness and concurrent medication
- the possibility of decreased effectiveness of the vaccine

The medical officer should explain to the traveller, the risks and benefits of immunization. As a general rule, live attenuated vaccines should be avoided in immunocompromised travellers, including those taking immunomodulators, calcineurin inhibitors, cytotoxic agents, antimetabolites and high-dose steroids.

(Further reading, refer Chapter 32)

Elderly travellers

Elderly travellers who have never been vaccinated should be offered a complete primary course of vaccination against diphtheria, tetanus, poliomyelitis and hepatitis B. Hepatitis A vaccine is recommended depending on the destination country.

Since the elderly are at risk of severe and complicated influenza, regular annual vaccination is recommended. Those who arrive before the influenza season and planning to stay for more than 2-3 weeks, should receive the vaccination after arrival. Pneumococcal polysaccharide vaccine may be considered in view of the risk of pneumococcal pneumonia following influenza infection.

Adult travellers without a history of varicella, who travel from tropical countries to temperate climates may be at increased risk and should consider vaccination.

(Further reading, refer Chapter 27)

Special situations

- Hajj mass gatherings
- Simultaneous vaccinations*
- Antibody containing blood products and vaccination*
- Antimicrobial therapy and vaccination*

  (*refer Chapter 3)

Hajj

Hajj is a religious pilgrimage to Mecca and Madina in Saudi Arabia. More than 2 million Muslims from all over the world gather here as an act of religious devotion. The potential of spread of infectious diseases associated with this pilgrimage has long been recognized. Extensive outbreaks have prompted the Saudi Arabian health authorities to introduce mandatory vaccination for meningococcal disease. Other vaccines recommended include, polio, hepatitis A and influenza vaccines.

Travellers and clinicians could stay updated of new developments by visiting the official U.S. government website for travel (http://www.cdc.gov/travel) and the WHO website (www.who.int).

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CHAPTER 30

IMMUNIZATION IN DISASTERS, PANDEMICS, EPIDEMICS AND OUTBREAKS

Disasters

A disaster is defined as a sudden accident or a natural catastrophe that causes great damage or loss of life. It is classified as natural (E.g. tsunami, floods etc.) or man-made (E.g. war). Natural disasters are mostly inevitable as well as unpredictable in time and location. During the non-disaster period the 'epidemiological triad' which consists of 'environment, agent and host' is in equilibrium. But due to many reasons, this equilibrium gets disturbed during a disaster which leads to communicable diseases among victims.

Overcrowding and poor sanitary facilities in camp settings, inadequate food and water supply, climate changes and breakdown of routine health care services are some environmental factors which could disturb the equilibrium and drive towards causation of communicable diseases.

Changes in the host factors also make people vulnerable to communicable diseases. This includes a decrease in immunity due to poor nutrition and psychological and physical distress. This could be worsened in already immunocompromised persons. Disasters could relocate individuals to new areas either temporarily or permanently. The local disease pattern in the new area may be different and they could become more susceptible to these locally endemic infections.

However, with proper and timely healthcare delivery, infections could be minimized to a great extent following a disaster. Rapid situation assessment, setting up a disease surveillance system among the disaster victims and immediate commencement of preventive activities are the key strategies to control communicable diseases following a disaster.

Preventive activities could be divided into general and specific measures. General measures include the provision of appropriate shelter, clean water supply, regular and adequate food supply, waste management, provision of sanitary facilities, vector control activities, and provision of basic clinical services. Specific measures depend on the nature of the disaster (E.g. chemoprophylaxis with doxycycline to prevent leptospirosis following floods). Immunization is considered as one of the important measures to prevent disease following disasters.

Sri Lanka has a well-established public health system which makes the country a high-performing state in health indicators at a relatively low cost. Further, it has been globally recognized for its childhood immunization programme, which helped to control/eliminate several communicable diseases from the country. Sri Lanka maintains a high vaccine coverage and a high age-appropriate vaccination in all the districts[1,2]. These achievements are mainly due to the existing public health infrastructure in the country and well-trained public health staff.

Therefore, following disaster situations, mass immunization campaigns with childhood vaccines are not indicated in the Sri Lankan setting as sustainable high National Immunization Programme (NIP) vaccination coverage has been observed at all levels over the years.

However, following a disaster situation, age-appropriate vaccination could be compromised in the victims. This could be due to service delivery issues as well as issues related to recipients. The extent of damage to the system depends on the magnitude of the disaster situation.

Service delivery issues (delay in re-establishment of the immunization services)

- Destruction of immunization centres
- Difficulty in the transportation of vaccines
- Difficulty in the storage of vaccines due to electricity failures
- Lack of trained staff as they also may become victims of the disaster

The recipient factors

- Illness following the disaster
- Loss of immunization records
- Inability to take the child to the immunization clinic if parents were victims of the disaster

It is important to resume routine vaccination services at the earliest to provide age-appropriate vaccinations. The Medical Officer of Health of the area and his team are responsible for the early re-establishment of immunization services. They should identify,

- unvaccinated children
- children with delayed vaccination
- children who require age-appropriate vaccination and plan the vaccination sessions accordingly.

If the Child Health Development Record (CHDR) / immunization record is available with the child, routine immunization guidelines should be followed. If the CHDR / immunization record is not available, evidence of vaccination should be traced through the existing documents (B portion of the CHDR which is available with the Public Health Midwife of the area)/ history provided by the parent or guardian and routine immunization continued.

In the absence of valid information on immunization, the vaccination schedule should be tailor-made according to the situation, considering background factors, by the responsible authorities in the Ministry of Health.

Recommended vaccines

Tetanus-containing vaccines should be administered to people who have open wounds and penetrating injuries, according to the national guidelines[3].

Tetanus toxoid for pregnant women needs to be administered according to the national guideline. The protocol differs with the number and the

documented evidence of tetanus-containing vaccines received previously. Please refer to chapter 4 of the Immunization Handbook[4].

Other optional vaccines include hepatitis A, varicella, MMR, influenza and typhoid. The decision regarding the administration of the optional vaccines needs to be taken after careful consideration of the epidemiology of the disease, risk profile of the victims, surveillance data, vaccine-related data, and alternative preventive methods.

Pandemics, epidemics and outbreaks

Epidemics are defined as a sudden increase of a disease above the normally expected number for a given population in each period. Outbreak carries the same meaning with an extra sense of urgency to act. When the disease spreads world-wide, it is named as pandemic.

The methods to control outbreaks are usually classified as general and specific. Enhancement of surveillance activities, quarantine, source identification and control and risk communication are a few general measures. Vaccination is an example of a specific measure, and it will cost-effectively prevent death and disability.

Routine immunization services could be disrupted during epidemics/ pandemics. It is important to restart the immunization clinics as early as possible to prevent a resurgence of vaccine-preventable diseases. It has been shown that deaths prevented by sustaining routine vaccination outweigh the excess risk of COVID-19 deaths associated with vaccination clinic visits[5]. When and how to re-start the immunization services, needs to be done following careful analysis of the risks and benefits to the children by the responsible authorities.

Since the vaccine coverage in Sri Lanka is high (>90% at the national as well as at the district level)[1], the occurrence of large-scale epidemics from diseases prevented by NIP vaccines is less likely. However, there could be epidemics in specific categories that need to be closely monitored.

Epidemics could occur from diseases which are not covered by the routine NIP schedule (E.g. influenza, varicella, hepatitis A and typhoid).

In both instances, the use of vaccines must be decided after careful evaluation of the epidemiology of the disease, host factors, vaccine factors, cost-effectiveness etc. by the relevant authorities.

COVID-19 outbreak and vaccination

Sri Lanka reported the first COVID-19 patient on 28th January 2020, who was a foreigner, and on 11th March 2020 reported the first locally infected person. The well-established public health network was a blessing in controlling the outbreak and especially their role was important in contact tracing, quarantine and educating the public about the prevention methods.

The National Influenza Pandemic Preparedness Plan was activated in the wake of the global pandemic, which provided the initial directives for a coordinated national response to COVID-19. The already available infrastructure for communicable disease surveillance was further strengthened and utilised for the surveillance of COVID-19.

Sri Lanka used 5 different types of COVID vaccines, namely, AstraZeneca/Covishield, Sinopharm, Moderna, Sputnik-V and Pfizer. The Covishield vaccination programme was started on 29th January 2021 after a detailed circular[6] was issued by the Ministry of Health. Later, the other vaccine types were also launched with guidance from the Ministry of Health[7,8,9]. The total number of doses used was around 40 million. Two dose regime was administered in AstraZeneca, Sinopharm, Moderna, and Sputnik V, for primary vaccination while the Pfizer vaccine was predominantly used as the first and second boosters. The country had high COVID-19 vaccination coverages which helped immensely to control the outbreak.

Routine vaccination during the COVID-19 outbreak

The routine childhood vaccination programme was carried out with enormous difficulties amidst the pandemic while adhering to all the protocols. The public health field staff were re-tasked to support the pandemic control activities.

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CHAPTER 31

IMMUNIZATION OF TRANSPLANT RECIPIENTS

Transplantation includes both solid organs such as kidney, liver, heart and lung transplants, and bone marrow or stem cell transplants.

Solid organ transplantation

Solid organ transplant (SOT) recipients are at increased risk of infections. This is mainly due to the type and dose of immunosuppression used to prevent rejection[1,2]. In addition, anatomical changes that occur with the transplanted organ may also increase the risk[2]. Infections may be responsible for graft failure as well as other effects. Influenza infection can result in graft rejection. Hepatitis B infection, from the donor, as well as from transfusions may lead to fulminant hepatic failure[2]. A 20-100-fold increase in carcinoma in situ due to human papillomavirus infection following transplantation has been noted[3]. Disseminated varicella infection, measles encephalitis and pneumonitis and interstitial nephritis due to mumps infection in renal transplant recipients may increase mortality[2].

The humoral and cellular responses after transplantation are decreased compared to normal people or even transplant candidates with organ dysfunction[4,5]. As organ failure reduces the 'take' of vaccines, immunization should be provided early in the disease process, if possible before transplantation. All patients with chronic or end stage kidney, liver, heart and lung disease should be given age appropriate vaccines[5]. Serological tests should be done to evaluate whether some vaccines are necessary[4]. If overseas travel is planned after transplantation, travel related vaccines, especially live vaccines, should be administered before transplantation[4]. Live vaccines should be given at least 4 weeks before transplantation[1,2]. They are generally not recommended after transplantation due to the risk of vaccine induced infection. Inactivated vaccines can be given up

to 2 weeks before transplantation[2]. They can be given 3-6 months after transplantation, if not administered pre-transplantation[1]. Vaccination should be followed by checking antibody responses 4 weeks later.

Donor immunization

Live donors should have been immunized according to the current immunization schedule. Vaccination of donors solely for the recipient's benefit is not recommended[5]. Live vaccines should be avoided in the 4 weeks before organ donation[5].

Immunization of close contacts and health care personnel

Household and close contacts and health care personnel may be a source of infection. Ideally, they should be given yearly influenza vaccines, as well as the measles, mumps and rubella (MMR) and varicella vaccines, if indicated. However, they should not be given the oral polio vaccine (OPV). Rotavirus vaccines also pose a threat and viral antigen can be detected in stool in 50-90% of infants up to 2 weeks after the first dose. Therefore, good hand-washing practices should be used after diaper changes of the infant[6]. Pets should also be fully immunized. There is little or no risk of transmission following immunization of pets with live vaccines[1].

Influenza vaccine

The inactivated influenza vaccine should be administered annually[7]. While earlier studies showed immunization before 6 months after transplantation to be poorly immunogenic[1], a study showed that vaccination at 1 month was safe and immunogenic[8]. Guidelines from the Kidney Disease Improving Global Outcomes (KDIGO) recommend giving the influenza vaccine 1 month after transplantation[1]. The Infectious Diseases Society of America (IDSA) suggests vaccination at one month post transplantation during an epidemic[5].

MMR vaccine

The MMR vaccine is contraindicated after transplantation. If the vaccine is given inadvertently or the patient is exposed to wild type measles, passive immunization with pooled immunoglobulin (HNIG) should be administered[5]. The MMR vaccine should be administered at least 4 weeks before transplantation. The NIP recommends the MMR vaccine at 9 months, but it can be given at 6 months[1]. If the infant has not been transplanted by the age of 1 year, a second dose can be administered, provided transplantation is scheduled after at least 4 weeks[1]. All children should complete a two-dose MMR series, if possible, with at least 4 weeks between doses[1]. It should also be given to sero-negative adults and sero-conversion tested. If the patient is still sero-negative, a further dose is recommended if time permits[1].

Herpes zoster vaccine

Two vaccines are currently available, a live-attenuated zoster vaccine (ZVL) and a recombinant subunit zoster vaccine (RZV)[1]. While both vaccines prevent shingles and post herpetic neuralgia in adults over 50 years of age, the recombinant vaccine is more efficacious and is recommended over the live attenuated vaccine[1]. Transplant candidates aged ≥50 years who are not severely immune-compromised could receive the live vaccine up to 4 weeks before transplantation, regardless of varicella zoster immunity[4]. However, the effectiveness of the vaccines in this population is not known. The live vaccine is contraindicated post-transplant. The recombinant vaccine has been administered to kidney transplant patients without an increase in rejection rates[1]. The zoster vaccines are not available at present in Sri Lanka.

Human papillomavirus vaccine (HPV)

It was observed in a review of transplant recipients, that there was an increase in vulval and penile cancers compared to the general population[9]. The incidence of invasive cervical cancer was not increased whereas carcinoma-in-situ was increased[9]. This is probably due to increased surveillance in this population[9]. The quadrivalent HPV vaccine is

recommended for persons from 9-45 years in females, and 9-26 years in males[5]. It is recommended to give the quadrivalent vaccine to transplant candidates and recipients in the standard 3 dose schedule. If the full course could not be given before transplantation, the course can be completed 3-6 months post transplantation. However, as the immunogenicity may be impaired, it is recommended that yearly cervical screening is performed[5].

Hepatitis B vaccine

Sero-negative candidates should receive the Hepatitis B vaccine series. The usual schedule (0, 1, 6 months) is more immunogenic than accelerated schedules (E.g. 0, 1, 2 months) in patients undergoing liver transplants[10]. Those who are on hemodialysis and aged ≥20 years should receive the high-dose (40 µg or 2 adult doses) vaccine. If a post – vaccination anti-HBs concentration of ≥10 mIU/mL is not attained, a second 3-dose series of Hepatitis B vaccine should be administered, using standard dose or adult dose (20 µg) for children and high dose (40 µg) for adolescents and adults[5]. Alternatively, a single dose of vaccine could be administered after which anti-HBs is tested, and if negative, the full course should be administered. Intradermal vaccination has been successful in some of those who do not sero-convert following repeated vaccinations[11]. In addition, the anti-hepatitis B titres should be checked annually in patients on haemodialysis, and those with titres <10 mIU/mL should be revaccinated[4,5]. Non-responders should be counselled, and given post exposure prophylaxis with hepatitis B immune globulin.

Pneumococcal vaccine

The risk of pneumococcal disease is 13 times more in the transplanted population compared to the general population[11]. The conjugated 7 valent vaccine evoked a better response rate compared to the 23 valent polysaccharide vaccine (PPSV23). Theoretically, administering the 13 valent vaccine followed 8 weeks later by the PPSV23 vaccine leads to a prime boost response: i.e. the T and B cell responses evoked by the conjugate vaccine are further boosted by the PPSV 23, which augments the memory B cells produced by the conjugate vaccine, as well as providing additional sero-type specific immunity. However, while

theoretically sound, the booster response did not occur in a study of liver transplant recipients, and gave conflicting results in the paediatric SOT recipients[1]. A second dose of the PPSV23 should be given 5 years after the first dose[1]. The 13 valent vaccine is not available in Sri Lanka at present, and the 10 valent vaccine can be substituted, instead.

Meningococcal vaccine

All patients at risk of invasive disease (i.e. after splenectomy, congenital or acquired asplenia, complement deficiency) or on complement inhibitors such as eculizumab should be given the quadrivalent conjugated meningococcal vaccine[1,5]. The meningococcal B vaccine is recommended in patients at risk of invasive disease or during meningococcal B outbreaks[1].

Varicella vaccine[1,5]

Varicella vaccine should be administered ≥4 weeks before transplantation for children over 12 months of age, with 2 doses, ideally 3 months apart, even though it can be given 4 weeks apart[1]. Sero-negative adults should be given 1 dose, and a second dose can be administered in those who do not sero-convert, if time permits[1]. Non-responders should be given varicella zoster immune globulin after exposure.

COVID-19 vaccine

Mortality rates following COVID-19 in SOT recipients is higher than in healthy individuals[12]. In addition, immune responses, especially antibody responses, are lower than in healthy individuals. mRNA vaccines (mRNA-1273 (Moderna) and BNT162b2 (Pfizer) have shown better antibody responses in SOT recipients, compared to ChAdOx1 nCoV (AstraZeneca/Covishield) vaccines[12]. While there is no evidence to recommend specific vaccine schedules, the initial vaccination should be completed at least 2 weeks before transplant. If the primary course was not completed, the next dose should be given 1 month after transplantation, or 3-6 months if B/T cell reducing agents (anti-thymocyte globulin/rituximab) was given for induction. For those not given the vaccine pre-transplant, vaccination should commence 1 month after surgery, 3 months after T cell depletion or 6 months after B cell depletion therapy[12].

Transplant recipients ≥12 years should be given a primary series of 3 doses, the 3rd dose 8 weeks after the 2nd, with 2 boosters, the first at least 3 months after the primary series, and the 2nd booster at least 6 months later. In the UK, transplant recipients aged 5-11 years are administered the primary 3 dose schedule as well. The UK guidelines give preference for the mRNA vaccines for transplant recipients (30 µg of Pfizer BioNTech or 100 µg of Moderna) ≥18 years, and 30 µg of Pfizer BioNTech from 12-17 years[13].

Household contacts of SOT should receive the primary series as well as one dose of the booster, at least 3 months later[13].

Table 1. Recommended vaccines (paediatric and adult) adapted from[1,2,4,5,12,13]

Vaccine*	Inactivated (I) or live (L)	Before trans-plantation	After trans-plantation	Monitor titre
Influenza*	I	Yes	Yes	No
Hepatitis B**	I	Yes	Yes[a]	Yes[a]
Hepatitis A[b]*	I	Yes	Yes	Yes
DTP (paediatric <7 years)* Tdap (>7 years and adult)*	I	Yes	Yes	For tetanus
Inactivated polio*	I	Yes	Yes	No
H. influenza type b*	I	Yes	Yes	Yes[c]
S. pneumoniae conjugate (PCV)[d]	I	Yes	Yes	Yes[e]
S. pneumoniae polysaccharide (PPSV23)[d]	I	Yes	Yes	Yes[5]
N. meningitides[f] *	I	Yes	Yes	No
Human papillomavirus (HPV)[g]*	I	Yes	Yes	No
Rabies[h]*	I	Yes	Yes	Yes[i]
Varicella*[j]	L	Yes	No	Yes
MMR*[j]	L	Yes	No	Yes
Recombinant zoster vaccine[k]	I	Yes	Yes	No
Live zoster vaccine	L	Yes	No	No
Japanese encephalitis	I	Yes	Yes	No
COVID-19 vaccine[l]	mRNA	Yes	Yes	No

[*] Follow National Guidelines for dosage

[**] Refer text

[a]Routine vaccine schedule recommended prior to transplant and as early in the course of disease as possible; vaccine poorly immunogenic after transplantation, and accelerated schedules may be less immunogenic. Serial hepatitis B surface antibody titres should be assessed both before and every 12 months after transplantation to assess ongoing immunity.

[b]For children, routine recommendation for all transplant candidates and recipients, if unvaccinated, under vaccinated or sero-negative[6]. In adults, it is routinely recommended for liver transplant candidates and recipients.

[c]Serologic assessment recommended if available. *H. influenzae* type b titre greater than 0.15 mg/L is considered protective in the general population. Test not available in Sri Lanka.

[d]Children older than 5 years of age and adults should receive.

- one dose of PCV followed by one dose of PPSV23 8 weeks later, with a second dose of PPSV23 after 5 years.

Children aged 2-5 years

- who have taken a full course of PCV, should be given one dose of PPSV23. A second dose of PPSV23 after 5 years.
- who have taken a partial course, or are un vaccinated, should be given 2 doses of PCV with an interval of 8 weeks, and one dose of PPSV23, 8 weeks after the last dose of PCV. A second dose of PPSV23 should be given after 5 years.

Children less than 2 years of age should receive

- two doses of PCV with a gap of 8 weeks, with a dose of PPSV23 at 2 years of age, at least 8 weeks after last dose of PCV.

[e]However, the absolute protective titre for pneumococcus is unknown and may vary by serotype. Assay not available in Sri Lanka.

[f] Travellers to high-risk areas, properdin deficient, terminal complement component deficient, those with functional or anatomic asplenia and those on ecluzimab should be vaccinated.

[g]Recommended for all females aged 9-45 years, males 9-26 years. See text. FDA has approved the use of the 9 valent vaccine for both men and women from 9-45 years[14] (https://www.fda.gov/vaccines-blood-biologics/vaccines/gardasil-9 Accessed on 29th December, 2022).

[h]Recommended for exposures or potential exposures to rabies. IM schedule to be administered. Intra dermal vaccination is not recommended.

[i] Checking the titre post vaccination is recommended in high-risk patients (DGHS/Circular/2016-127 (MRI-ARPET)[15]

[j] See text

[k]Vaccine is indicated for persons ≥50 years[4]. However, studies on the herpes zoster vaccine in the pre and post-transplant setting are limited[1]

[l]See text

Hematopoietic stem cell transplantation (HSCT)

HSCT includes autologous and allogeneic (heterologous) transplants. Allogeneic transplants include matched related, haplo-identical, matched unrelated and cord blood derived transplants. Following HSCT, delayed immune reconstitution leads to increased morbidity and mortality, especially due to infection. Generally, innate immunity recovers first, in the first few months, whereas specific immune reconstitution may take 1-2 years[16]. T cell immunity depends on donor memory cell expansion in the periphery, which occurs in the first few months, followed by de novo T cell expansion of donor hematopoietic precursors after thymic selection[16,17]. The risk of post-transplant infections is dependent on the CD4 count[16]. Generally, immune recovery is more rapid with autologous transplants, and less when there is T cell depletion.

B-cell counts recover 3-12 months after HSCT, even though class switching and production of functional antibody takes 1-2 years post-transplant[17]. Ability to produce anti-polysaccharide antibody takes even longer[17]. CD4 counts normalize 6-9 months post HSCT in paediatric recipients, and twice as long in adult patients resulting in a decreased response to vaccines[16]. Antibody titers to vaccine-preventable diseases decline during the first decade unless revaccinated, after autologous or allogeneic HSCT[16,18,19]. Immunity to pertussis, pneumococcus and *H. influenzae* will be lost after transplantation, and most patients will be susceptible to tetanus by 2 years, even if sero-positive at transplantation[18]. HSCT recipients are at increased risk for infections, particularly with certain organisms such as *S. pneumoniae, H. influenzae* type b (Hib), measles, varicella and influenza[16,18].

The IDSA recommends considering patients undergoing HSCT as never vaccinated, and therefore requiring full immunization depending on the age and epidemiology of the country[5]. While immune reconstitution after HSCT depends on source of cells and immune suppressants used, guidelines for immunization are based on timing after HSCT. Thus, delayed immune reconstitution due to donor (cord blood), conditioning regimes, age, T cell depletion, use of rituximab, graft vs host disease

(GVHD) and use of immune-modulatory agents are not considered[19]. Inactivated vaccines and toxoids are administered 3-6 months post-transplant, irrespective of immune status[19]. Live vaccines are delayed for 24 months, based on insufficient safety and efficacy data on earlier immunization[16]. Inactivated vaccines can be given during immune suppression, and with ongoing GVHD, whereas live vaccines are contraindicated. The response to polysaccharide vaccines is inadequate, probably due to poor antigen presenting cell or B cell activity to T cell independent antigens[19].

Immunization prior to HSCT[5]

Candidates should receive vaccines appropriate for immune-competent people, provided they are not immunosuppressed. Live vaccines should be administered 4 weeks prior to the conditioning regime, whereas killed vaccine could be administered up to 2 weeks before the conditioning regime. Children ≥12 months should receive the varicella vaccine, with a 2nd dose if time permits.

Donor immunization

There is emerging evidence that immunization of donor or recipient before transplantation is beneficial[20]. However, the IDSA guidelines recommend against immunizing the donor solely for the benefit of the recipient[5]. Live vaccines should be avoided within 4 weeks of stem cell harvest[5].

Table 2. Vaccinations recommended for autologous and allogeneic HSCT recipients adapted from[5*,19**,21***, 22]

Vaccine recommended for use after HSCT	Earliest time post-HSCT to initiate vaccine	No. of doses[a]	Improved by donor vaccination (practicable only in related-donor setting)
Pneumococcal conjugate (PCV)	3-6 months	3-4[b]	Yes; may be considered when the recipient is at high risk for chronic GvHD
Tetanus, diphtheria, acellular pertussis[c]	6-12 months	3	Tetanus: likely Diphtheria: likely Pertussis: unknown
H. influenzae type [b]	3-6 months	3	Yes
Meningococcal[d]	6-12 months	2	Unknown
Hepatitis B[e]	6-12 months	3	Likely
Inactivated influenza[f]	6 months, yearly thereafter	1-2[g]	Unknown
MMR[h]	24 months	2	Unknown
Inactivated polio[j]	6-12 months	3	Unknown
COVID-19[j]	3 months	3 followed by 2 boosters	Unknown

*2013 Infectious Diseases Society of America (IDSA) Clinical Practice Guideline for Vaccination of the Immunocompromised Host (2014)

** Based on Guidelines from European Group of Blood and Marrow Transplantation (EBMT), Centers for Disease Control (CDC), IDSA and American Society for Blood and Marrow Transplantation (ASBMT) (2009)

***Guidelines of the 2017 European Conference on Infections in Leukaemia (ECIL 7) (2017)

[a] A uniform specific interval between doses cannot be recommended, as various intervals have been used in studies. As a general guideline, a minimum of 1 month between doses may be reasonable

[b] Following the primary series of three PCV doses, a dose of the PPSV23 should be given 12 months after HSCT (provided patient is ≥2 years) to broaden the immune response. For patients with chronic GvHD who are likely to respond poorly to PPSV23, a fourth dose of the PCV should be considered instead of PPSV23. For patients with GvHD, prior rituximab therapy or hypogammaglobulinaemia (IgG <300 mg/dL), antibiotics or IVIG may be beneficial[21]

[c] DTaP is preferred (even though not licensed for adults) as it gives better responses[21]. If only Tdap is available administer Tdap. Acellular pertussis vaccine is preferred, but the whole-cell pertussis vaccine should be used if it is the only pertussis vaccine available.

[d] Men A, C, W, Y conjugate vaccine 3 months apart. Recommended for persons aged 11-18 years, with a booster at 16-18 years. Meningococcal B vaccines should additionally be administered to HSCT recipients aged 10-25 years with at-risk conditions (asplenia, terminal complement deficiency, laboratory workers, travellers, outbreaks)[21].

[e] Patients who were negative for HBV antibody before transplantation and patients who were vaccinated before transplant but lost their immunity should be vaccinated at 6 months post transplantation[21]. If a post-vaccination anti-HBs concentration of ≥10 mIU/mL is not attained, a second 3-dose series of Hep B vaccine, with an adult dose (20 µg) for children and high dose (40 µg) for adolescents and adults, should be administered[5]. As an alternative, give one dose and test for antibodies 1 month later; if there is no seroconversion, the full course should be completed. However, the benefit of higher antigen doses in HSCT recipients is not clear[21].

An anti-HBc positive donor could transmit HBV to the recipient, even if negative in nucleic-acid testing. For recipients who receive stem cells from donors who are anti-HBc positive, immunization of the patient before transplantation is recommended, along with hepatitis B immunoglobulin, due to the risk of HBV transmission[21].

Patients infected with HBV before HSCT (HBsAg negative and anti-HBc positive) should be assessed regularly for anti-HBs antibody titres and should be vaccinated if they do not have protective titres[21].

[f] Starting at 3 months post-transplant, in an outbreak of influenza[21].

[g] For children aged 6 months to <9 years, who are receiving influenza vaccine for the first time, 2 doses should be administered ≥4 weeks apart[5]. In children older than 9 years and adults, a second dose of vaccine after 4 weeks could be considered in patients with severe GvHD or low lymphocyte counts[21].

In the setting of a community outbreak, inactivated influenza vaccine (IIV) could be administered 3 months after transplantation, in which case, a second dose administered 4 weeks later is likely to be beneficial[21].

[h] After 24 months post-transplant, if sero-negative for measles, without GvHD and not on immunosuppressives, without disease recurrence and 8-11 months after intravenous immunoglobulin (or earlier if there is a measles outbreak). A gap of at least 4 weeks between the two doses.

[i] Due to a higher risk for losing polio immunity in the years after initial vaccination for patients transplanted before the age of 10 years, a regular assessment of anti-polio antibody titres to assess persistent immunity is recommended and boosters should be considered[19].

[j] According to UK guidelines, transplant recipients ≥12 years should be given a primary series of 3 doses, the 3rd dose 8 weeks after the 2nd, with 2 boosters, the first at least 3 months after the primary series, and the 2nd booster at least 6 months later. In the UK, transplant recipients aged 5-11 years are administered the primary 3 dose schedule. The UK guidelines give preference for the mRNA vaccines for transplant recipients (30 µg of Pfizer BioNTech or 100 µg of Moderna) ≥18 years, and 30 µg of Pfizer BioNTech from 12-17 years[13]. The American Society of Hematology and American Society of Transplantation and Cellular Therapy have suggested that immunization should commence at 3 months.

Table 3. Optional vaccines (adapted from[5,21])

Vaccine	Recommendations for use
Hepatitis A	Follow recommendations for general population Two doses given at 6-12-month intervals commencing at 6 months HNIG should be administered to hepatitis A-susceptible HSCT recipients for post-exposure prophylaxis
Varicella	Limited data regarding safety and efficacy 2 dose schedule 6-8 weeks apart For varicella sero-negatives, >24 months after transplantation, without disease recurrence, without active GvHD and not on immunosuppressives and 8-11 months (or earlier if there is a varicella outbreak) after intravenous immunoglobulin. Anti-virals if a VZV vesicular rash appears following immunization
Zoster vaccine	Inactivated vaccine to be used in patients ≥50 years, who are not severely immunosuppressed
Human papillomavirus	6-12 months after transplantation No data exists regarding the time after HSCT when vaccination could be expected to induce an immune response The Food and Drugs Administration (FDA) of the US has extended the age to 9-46 years[14]
Rabies[a]	Anti-rabies vaccine should be given intra muscularly. The intradermal route is not recommended after HSCT Pre-exposure rabies vaccination should probably be delayed until 12-24 months after HSCT Post-exposure administration – rabies immunoglobulin should be given when indicated, irrespective of the severity of the exposure followed by a course of vaccine. Post vaccination antibody titres should be measured[b]

Yellow fever	It is generally not recommended Proof of vaccine receipt may be required for entry to certain destinations. If YFV cannot be given safely, a waiver letter can be granted from certified YFV providers. Risks of disease at destination versus benefits of travel should be discussed[23] Yellow fever vaccine should be considered cautiously and only administered to patients with no active GvHD and no immunosuppressive drugs, and if the patient cannot avoid travelling to endemic areas[21] A recent study demonstrated immunogenicity and safety in a cohort of 21 allogeneic HSCT recipients who were immunized with the yellow fever vaccine, a median of 33 months after HSCT[24]
Japanese encephalitis	Inactivated vaccine[25]

[a]ACIP and American Academy of Pediatrics guidelines for post-exposure human rabies immunoglobulin and vaccine administration should be followed, which include administering five doses of rabies vaccine intramuscularly (IM) on days 0, 3, 7, 14 and 30 post-exposure

[b] Checking the titre post vaccination is recommended in high-risk patients[15] (DGHS/Circular/2016-127 (MRI-ARPET)

The following vaccines are contraindicated in HSCT patients.

- Bacillus Calmette-Guérin (BCG)
- Oral polio vaccine (OPV)
- Live attenuated influenza vaccine
- Rotavirus vaccine
- Zoster vaccine (live)

Table 4. Vaccinations for family, close contacts and health-care workers (HCW) of HSCT recipients

(Vaccination should ideally be completed at least 4 weeks before transplantation)

Vaccine	Recommendation
Hepatitis A	Routine vaccination is recommended for: • Children >12 months of age • Persons at increased risk for hepatitis A
Inactivated influenza[a]	**Family and close contacts** Vaccination with inactivated vaccine is strongly recommended annually during each influenza season, beginning in the season before the transplant and continuing as long as there is contact with an HSCT recipient **HCW** Annual vaccination with inactivated influenza vaccine is strongly recommended during each influenza season
Polio[b]	Inactivated polio vaccine should be administered when indicated Oral polio vaccine (OPV) is contraindicated
Rotavirus	Vaccination is not contraindicated in contacts of HSCT transplant patients. HSCT recipients should have no contact with the stools or diapers of the infants within 4 weeks of vaccination because there is a risk of contracting the vaccine virus[22].
MMR	Vaccination is recommended for all susceptible persons who are not pregnant or immuno-compromised No evidence exists that live-attenuated vaccine-strain viruses in MMR vaccine are transmitted from person-to-person
Pertussis	Vaccination with DTaP is recommended for children <7 years and Tdap for adolescents and adults
Varicella[c]	Vaccination should be administered to susceptibles >12 months old, who are not pregnant or immune-compromised[d]

[a] Children aged 6 months to 9 years, who are receiving influenza vaccination for the first time require two doses one month apart and those who have received only one dose in the first year should receive two doses the following year.

[b] Vaccine-strain poliovirus in the OPV could be transmitted from person-to-person; therefore, OPV administration is contraindicated among household contacts of immunocompromised persons. If OPV is inadvertently administered to a household contact of an HSCT recipient, minimize close contact with the immunocompromised person for 4-6 weeks after vaccination.

[c] HCW, family members, close contacts and visitors who do not have a documented history of varicella-zoster infection or who are seronegative should receive varicella vaccine before being allowed to visit or have direct contact with an HSCT recipient. Ideally, varicella-zoster-susceptible HCW, family members, household contacts and potential visitors of immunocompromised HSCT recipients should be vaccinated as soon as the decision to perform an HSCT is made. The vaccination should be completed 4 weeks before the conditioning regimen begins or 6 weeks (42 days) before contact with the HSCT recipient is planned. If a varicella vaccinee develops a post-vaccination rash within 42 days of vaccination, the vaccinee should avoid contact with HSCT recipients until all lesions are crusted or the rash has resolved.

[d] Children 12 months to 12 years should receive two doses at least 3 months apart; adolescents >13 years and adults should receive two doses at least 4 weeks apart.

The following vaccines are contraindicated in family, close contacts and HCW of HSCT recipients[23]

- Live attenuated influenza vaccine
- Oral polio vaccine

Special considerations

- Anti CD20 therapy (rituximab) – Such patients lose B lymphocytes. Therefore, a gap of at least 6 months should be kept before initiating immunization[24].
- Chimeric antigen receptor therapy (CAR) T-cell therapy – T lymphocytes with genetically engineered receptors targeting B lymphocytes have been developed for acute lymphoblastic leukaemia and B cell lymphoma. As B cells (normal and malignant) are destroyed, the effectiveness of vaccination is unknown[24]

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CHAPTER 32

IMMUNIZATION OF THE IMMUNOCOMPROMISED

Immunodeficiency is classified as primary or secondary. Primary immunodeficiencies or inborn errors in immunity are due to an inherent absence or deficiency in the immune system. In contrast, secondary immunodeficiencies are acquired as a result of a disease process or its therapy[1].

Vaccination of persons with immunodeficiency is important as they are at a higher risk of vaccine preventable diseases[1,2]. However, the decision to vaccinate should be taken depending on the answer to two pertinent questions[2];

- Can vaccination harm the patient (i.e. safety)?
- Is the patient able to make a sufficient immune response to justify the use of the vaccine (i.e. effectiveness)?

Inborn errors of immunity (IEI)

Although there are more than 400 distinct IEI, vaccine recommendations are generally based on the type of immune deficiency. Namely, combined immunodeficiencies, antibody deficiencies, phagocytic defects, complement deficiencies, innate immune defects and asplenia[3,4].

Immunodeficiencies may be undiagnosed in young children and it is an important consideration in infants receiving live vaccines, as there is a risk of disease due to vaccine strains. The live vaccines administered during infancy are BCG, OPV, MMR, JE and rotavirus. Clues pointing to the presence of a significant immunodeficiency include family history of unexplained early infant deaths, failure to thrive, recurrent or prolonged oral candidiasis despite treatment and recurrent severe infections such as pneumonia or sepsis[2]. **Neonates/ infants with these clinical features should not receive live vaccines till their immune status is determined**.

All patients with IEI could receive any of the routinely recommended killed or subunit vaccines, provided they have the ability to respond to the vaccine[3,4].

Refer Table 1 for recommendation in each condition.

These recommendations must be seen as generalisations and expert advice should be sought before vaccinating children with rare defects.

Table 1. Vaccination of persons with IEI[1, 2, 3, 4, 5,6]

Category	Specific Immunodeficiency	Contraindicated vaccines[a]	Risk-specific recommended vaccines[a,b]	Effectiveness and comments
Humoral immuno-deficiency	Severe antibody deficiency E.g. X linked agammaglo-bulinaemia (XLA), common variable immunodeficiency (CVID)	All live vaccines	Annual inactivated influenza HPV	Most patients require lifelong immunoglobulin, which provides protection against common infections. Immunocompetent household members should be encouraged to receive vaccines according to standard schedule with the exception of the oral polio vaccine.
	Less severe antibody deficiency E.g. Selective IgA deficiency, IgG subclass deficiencies, specific antibody deficiency and ataxia telangiectasia	BCG Live influenza OPV Yellow fever[c]	Hib (children <5 years)[d] Pneumococcal[e]	Other live virus vaccines appear to be safe. However, IVIG/SCIG may interfere with the response to measles, mumps, rubella vaccines and possibly varicella containing vaccines. All inactivated vaccines are safe and likely to be effective and should be administered, although immune response might be suboptimal.

Category	Specific Immunodeficiency	Contraindicated vaccines[a]	Risk-specific recommended vaccines[a,b]	Effectiveness and comments
Combined T and B cell immuno-deficiencies and syndromes	E.g. Severe combined immunodeficiency (SCID), complete Di George syndrome (Chr22q 11.2 deletion), other combined immunodeficiencies with CD3 T cell counts <500 cells/mL, Wiskott-Aldrich syndrome, class switch recombination defects/hyper IgM syndromes	All live vaccines		All inactivated vaccines are probably ineffective Annual inactivated influenza is the only vaccine administered routinely to patients on immunoglobulin replacement therapy, when there is residual antibody producing capacity
Combined immuno-deficiency	E.g. Partial Di George syndrome (Chr22q11.2 deletion) or other combined immunodeficiencies with CD3 T cells ≥500 cells/μL, CD8 T cells ≥200 cells/μL and a normal T cell function test	All live vaccines	Hib (children <5 years)[d] Meningococcal Pneumococcal[e]	All other inactivated vaccines are safe, maybe effective depending on the degree of immune defect and should be administered MMR vaccine and varicella vaccine could be considered

Category	Specific Immunodeficiency	Contraindicated vaccines[a]	Risk-specific recommended vaccines[a,b]	Effectiveness and comments
Immune dysregulation	E.g. Familial predisposition to haemophagocytic lymphohistiocytosis (HLH), x-linked lymphoproliferative syndrome (XLP), Chediak-Higashi	Live vaccines		All inactivated vaccines in the standard schedule are safe, likely to be effective and should be administered
Phagocytic dysfunction	E.g. Chronic granulomatous disease (CGD), neutropaenia	All live bacterial vaccines	Influenza vaccine	All inactivated and live viral vaccines in the standard schedule are safe, likely to be effective and should be administered
	Leukocyte adhesion defects, cytotoxic granule defects (myeloperoxidase deficiency)	All live vaccines	Hib (children <5 years)[d] Pneumococcal[e]	All inactivated vaccines in the standard schedule are safe, likely to be effective and should be administered
Complemente deficiency	E.g. Persistent complement component, properdin or factor B deficiency	None	Hib (children <5 years)[d] Meningococcal Pneumococcal[e]	Patients with classical complement path defects are at a higher risk of infection with *S. pneumoniae* and *H. influenzae* type b and terminal or alternative path defects with *N. meningitides*

Category	Specific Immunodeficiency	Contraindicated vaccines[a]	Risk-specific recommended vaccines[a,b]	Effectiveness and comments
				All inactivated vaccines on the standard schedule are safe, likely to be effective and should be administered Live vaccines other than influenza and oral typhoid may be given
Innate defects	Interferon alpha, Interferon gamma; Interleukin 12 axis deficiencies (Mendelian susceptibility to mycobacterial disease – MSMD) STAT I deficiency	All live-bacterial vaccines and YF vaccine; other live virus vaccines if severely lymphopaenic		All inactivated vaccines are safe, likely to be effective and should be administered Inactivated typhoid vaccine should be considered for people living in areas with endemic typhoid

[a.] Other vaccines that are universally or routinely recommended should be given if not contraindicated.

[b.] In suspected exposure to rabies virus, rabies immunoglobulin should be administered followed by intramuscular rabies vaccine for patients with antibody deficiency, combined immunodeficiency and complement deficiency (refer chapter 18). There are no data on rabies post exposure prophylaxis for patients with phagocytic dysfunction and innate immune defects.

[c.] There are no data to support IgA deficiency as a contraindication for yellow fever vaccine.

[d.] Hib or Hib containing vaccines given at 2, 4, 6 months is considered a complete primary series of the vaccine. Children <5 years: if unimmunized or received only 1 dose of Hib administered before 12 months of age, should receive 2 doses of Hib, 8 weeks apart; if received 2 or more doses before 12 months of age, should receive 1 dose of Hib 8 weeks after the last dose; if completed a primary series and received a booster dose at 12 months of age or older, no additional Hib doses are recommended.

[e.] PPSV23 is begun at ≥2 years of age. If pneumococcal conjugate vaccine is required (i.e. for children <2 years who have not received all required doses, and for those ≥2 years of age who have never received pneumococcal conjugate vaccine) conjugate vaccine must be administered first, followed by PPSV23 at least 8 weeks later; a second dose of PPSV23 is administered 5 years after the first.

Persons with asplenia or functional asplenia

Asplenia or complete loss of splenic function may result from, congenital asplenia, surgical removal following trauma or for therapeutic reasons and functional asplenia due to medical conditions such as sickle cell anaemia.

All children, adolescents and adults with asplenia, irrespective of the cause, have an increased risk of fulminant septicaemia. Risk of infection and mortality is higher with encapsulated bacteria, especially *S. pneumoniae, N. meningitidis,* and *H. influenzae* type b[3].

When surgical splenectomy is planned, all indicated vaccines should be completed at least 14 days before the surgery. All incomplete schedules may be resumed 14 days after splenectomy.

In case of emergency splenectomy, all indicated vaccines should be initiated as soon as possible ≥2 weeks after surgery[3]. For those who require chemotherapy or other immunosuppressive treatment, vaccination is usually resumed approximately three months after completing treatment[3].

Asplenia by itself is not a contraindication for any of the live or inactivated vaccines[3]. Therefore, asplenic persons should receive all recommended vaccines according to the standard schedules.

Table 2. Vaccination in asplenia[1,3,4,7,8]

Category	Vaccine	Primary series	Revaccination (booster)
Children	Pneumococcal conjugate vaccine (PCV)	All children should receive an age-appropriate series of pneumococcal conjugate vaccines • Unvaccinated children 2 months-1 year – 2 doses 8 weeks apart and a booster at 1 year with an additional booster after 8 weeks • Unvaccinated children 1-2 years – 2 doses 8 weeks apart and a booster at least 6 months after the last dose • Children ≥2 years – single dose if they have not received a dose previously	
	PPSV23	Children aged ≥2 years – 1 dose of PPSV23 ≥8 weeks after completing all recommended doses of the conjugate vaccine	A single dose of PPSV23 vaccine should be given 5 years after the initial dose
	H. influenzae type b	Should initiate at 2 months of age as per standard schedule Children ≤5 years, • Unvaccinated or who have received only one dose before 12 months of age – 2 doses 8 weeks apart • Those who have received ≥2 doses before 12 months of age – one additional dose[3] Unimmunised children ≥5 years – single dose	None

Category	Vaccine	Primary series	Revaccination (booster)
	Meningococcal serotype ACWY conjugate vaccine	Children <1 year – 2 doses at least 4 weeks apart Children ≥1 year – single dose	Booster dose at 1 year of age Booster dose every 5 years
	Meningococcal serotype B[a]	Primary series according to manufacturer's advice starting from 10 years of age	Currently no recommendations
	Seasonal influenza vaccine	1 dose annually at the start of influenza season (children 6 months – 9 years receiving the vaccine for the 1st time – 2 doses one month apart)	Repeat annually at the start of influenza season
Adult	Pneumococcal conjugate vaccine (PCV) PPSV23	If a primary series is not received, 1 dose of conjugate vaccine followed by 1 dose of PPSV23 vaccine 8 weeks later Patients who have previously received PPSV23, administer a dose of PCV 1 year later Patients who have previously received PCV, 1 dose of PPSV23 ≥8 weeks later	A single dose of PPSV23 vaccine should be given 5 years after the initial dose Another dose should be given after completing 65 years of age, timed ≥ 5 years after the previous dose
	H. influenzae type b	Single dose regardless of previous vaccine status	None
	Meningococcal serotype ACWY conjugate vaccine	Single dose	Booster dose every 5 years
	Meningococcal serotype B[a]	2 doses administered at least 2 months apart or primary series according to manufacturer's advice	None
	Seasonal influenza vaccine	1 dose annually at the start of influenza season	Repeat annually at the start of influenza season

[a]This vaccine is currently not available in Sri Lanka

Persons on corticosteroid therapy

The immunosuppressive effects of steroids may vary. However, daily corticosteroid therapy with a dose ≥20 mg (or >2 mg/kg/day for patients who weigh <10 kg) of prednisolone or equivalent for ≥14 days is considered to cause high level immunosuppression[1,3,4,9,10].

Live virus vaccines should be deferred for at least 4 weeks after discontinuation of high level immunosuppression. When immunosuppressive therapy needs to be restarted following vaccination, it should be done at least 4 weeks after a live vaccine and 2 weeks after an inactivated vaccine. However, if patients require therapy for chronic inflammatory conditions, this therapy should not be delayed because of past administration of vaccines[3]. Inactivated vaccine should be given at least 2 weeks before initiating therapy or should be deferred until after stopping treatment[3].

Live viral vaccines may be given immediately after discontinuation of therapy when high doses of systemic corticosteroids (≥20 mg or >2 mg/kg/day for patients who weigh <10 kg) are given daily or on alternate days for fewer than 14 days. However, some experts delay this by 2 weeks[4].

Short term (i.e. <14 days); low to moderate doses; long-term, alternate day treatment with short acting preparations (E.g. hydrocortisone); maintenance physiologic doses (replacement therapy); topical (skin or eyes), inhaled, intra-articular, bursal, or tendon injections are not considered contraindications for live viral vaccines[1]. Vaccines should be administered as scheduled for normal subjects[1, 2, 3]. However, children with an immunosuppressive disease (E.g. systemic lupus erythematosus) or those on immunosuppressive medication other than corticosteroids should not receive live-virus vaccines during therapy, even when the dose of systemic corticosteroid is low or moderate (<20 mg of prednisolone or equivalent per day or <2mg/kg body weight per day for a young child) or it is locally administered. Exceptions could be made in special circumstances during which the potential benefit of protection and the risk of adverse reaction are weighed[4].

Vaccination of patients receiving disease-modifying anti-rheumatic drugs (DMARDS)

Vaccines remain an important aspect in the management of patients requiring treatment with DMARDS. These patients are likely to be at a higher risk of infection due to the underlying disease, comorbidities and immunosuppressive therapy. Additional vaccinations may be required when there are specific infection risks, whereas live-attenuated vaccines might be contraindicated in specific circumstances.

Immunosuppressive doses of DMARDS in paediatric patients, cyclosporine >2.5 mg/kg/day, azathioprine ≥3 mg/kg/day, cyclophosphamide orally >2.0 mg/kg/day, leflunomide ≥0.5 mg/kg/day, mycophenolate mofetil ≥30 mg/kg/day or >1000 mg/day, methotrexate ≥15 mg/m^2/week or ≥25 mg/week and tacrolimus >1.5 mg/day[9]. In adults, immunosuppressive doses are described for methotrexate, azathioprine and -mercaptopurine (methotrexate ≥0.4 mg/kg/week, azathioprine ≥3.0 mg/kg/day and 6-mercaptopurine ≥1.5 mg/kg/day)[10].

Live vaccines are contraindicated during immunosuppressive therapy and should be administered at least 4 weeks prior to initiating therapy[7,9,10,11].

Duration taken for immune reconstitution varies greatly according to type and intensity of immunosuppression. Hence, administration of live vaccines after discontinuation of therapy may need to be assessed individually[1,11]. Generally, live vaccines should not be given at least 4 weeks after discontinuation of DMARDS. This interval may extend if combination immunosuppressive therapy is used.

Response to inactivated vaccines may also be impaired during immunosuppression. Therefore, immunization with inactivated vaccines should be completed at least 2 weeks prior to starting therapy. If vaccination is carried out during therapy, they should not be considered valid doses unless protective antibodies are documented[3,4].

Sulfasalazine and hydroxychloroquine do not affect the immune response and are not regarded as immunosuppressive therapy[11].

Vaccination in patients with autoimmune inflammatory rheumatic diseases (AIIRD) should preferably be administered during quiescent disease. Refer Table 3 for recommended vaccines for patients with AIIRD.

Table 3. Recommendations for vaccination of patients with AIIRD[7, 9, 10,11]

Vaccine	Recommendations
Influenza	Non-live seasonal influenza vaccination Two doses 4 weeks apart for the 1st year and then one dose annually[a,b]
Pneumococcal[c]	Refer table 2 for doses
Hepatitis B	Should be administered only to patients at risk (seronegative travellers to endemic countries, medical personnel, household contacts or sexual partners of known persons with chronic HBV infection, intravenous drug users, men who have sex with men).
Vaccine naive	3 doses; (0,1,6 months) For patients receiving immunosuppressive therapy, 3 double doses (0, 1, 6 months)
Previously vaccinated	
• HBs antibody titre <100 IU/mL	Double dose given only once
• HBs antibody titre ≥100 IU/mL	None
Varicella zoster	Should be considered in VZV naive patients on methotrexate as well as in patients treated with TNFi, anti-IL1, anti-IL6 and low-dose glucocorticosteroids. Refer chapter for doses
Herpes zoster	Consider in those aged ≥50 years with AIIRD Inactivated vaccine is preferred. Two doses should be given 2- 6 months apart. Re-vaccination interval unclear

Diphtheria, tetanus, pertussis (TdaP)	In ≥50 years without booster in the last 10 years – One dose. Booster dose probably every 10 years
HPV	Patients with AIIRD, in particular patients with SLE, should receive vaccinations against HPV in accordance with recommendations for the general population. Refer chapter for doses

[a.] Vaccination should be delayed as much as possible after a dose of rituximab.

[b.] Hold methotrexate for 2 weeks after vaccination if the disease activity allows. Give influenza vaccination on schedule. Delay any subsequent rituximab dosing for at least 2 weeks after influenza vaccination if disease activity allows.

[c.] Avoid the PPSV-23 in patients with cryopyrin associated periodic syndromes due to safety reasons.

Biologics

Biologics are protein molecules that target specific points in the inflammatory cascade. They are currently used widely in the treatment of many autoimmune diseases.

All patients on biologics are considered immunosuppressed and vaccination should precede immunosuppressive therapy to produce an optimal response. However, initiation of treatment should not be delayed until vaccination is completed where therapy is indicated[9].

Some of the commonly used biologics and the intervals for administration of live-attenuated virus vaccines are shown in table 4.

Since IgG crosses the placenta during the third trimester, anti-TNF biologics, except certolizumab pegol, are detectable until 6 months after birth in newborns born to mothers who received such treatment. Children who have been exposed to biologics after the 22nd week of gestation, should not receive live vaccines including BCG at least until 6 months of age. Whenever available, measurement of child's serum levels of the biologic in question could guide the decision for or against administering a live vaccine[9].

Non-live vaccines could be administered to patients with AIIRD on biologics except B cell depleting therapy where it should be withheld for 6 months after completion of therapy. However, to avoid suboptimal response to vaccines, wherever possible inactivated vaccines should be administered at least 2 weeks before the commencement of immuno-suppressive therapy without delaying the treatment[8].

In case of major and or contaminated wounds in patients who received rituximab within the last 24 weeks, passive immunization with tetanus immunoglobulin should be carried out[11]. Patients who need to be immunised against rabies should receive both RIG as well as the ARV using the IM schedule.

Immunocompetent household members should be encouraged to receive vaccines according to standard schedule except for the oral polio vaccine.

Refer Table 3 for recommended vaccines in AIIRD. The vaccination status and indications for further vaccination in patients with AIIRD should be assessed annually by the rheumatology team[9].

Table 4. Recommendations for vaccination of patients on biologics for live vaccines

Mechanism of action	Agent	Interval for administration of live-attenuated vaccine after biologics	Interval for administering biologics after live-attenuated vaccine
JAK inhibitors	Tofacitinib	1 week	4 weeks
Tumor necrosis factor inhibitors	etanercept adalimumab infliximab certolizumab pegol golimumab	1 dosing interval[a]	4 weeks
Interleukin-17A inhibition	secukinumab	1 dosing interval[a]	4 weeks
Interleukin 12/23 inhibition	ustekinumab	1 dosing interval[a]	4 weeks
BAFF/BLyS inhibitors	Belimumab	1 dosing interval[a]	4 weeks
Interleukin-6 receptor inhibition	Tocilizumab	1 dosing interval[b]	4 weeks
IL1 inhibitors	anakinra rilonacept canakinumab	1 dosing interval[b]	4 weeks 4 weeks 4 weeks

T-lymphocyte co-stimulation blockade	Abatacept	1 dosing interval[a]	4 weeks
Type I interferon receptor antagonist	Anifrolumab	1 dosing interval[a]	4 weeks
B-lymphocyte depletion	Rituximab	6 months[c]	4 weeks

[a] For medications with more than one approved dosing interval, the longest interval should be chosen (E.g. hold subcutaneous adalimumab for 2 weeks although it can be dosed every 1 or every 2 weeks).

[b] In children with autoinflammatory disorders or systemic juvenile idiopathic arthritis in whom the risk of disease flare if biologic DMARDs are held is very high, shorter hold times can be considered if live-attenuated vaccination is critical.

[c] Some experts recommend vaccines to be withheld for up to 1 year after completion or until B cell counts return to normal levels[1,8,11]. Vaccination may be considered in some cases, taking into consideration a potential suboptimal response to vaccine[9].

Patients with malignancies

Patients with malignancies are at increased risk of serious infection. The degree of risk varies depending on the underlying malignancy and type of immunosuppressive treatment used.

Patients with haematologic malignancies, such as chronic lymphocytic leukaemia (CLL), Hodgkin lymphoma and multiple myeloma are generally more immunocompromised than those with solid tumours. However, patients with solid tumours are also at risk of infection due to debility, malnutrition and anatomic obstruction that may interfere with innate immune mechanisms.

Risk of infection

Patients with haematologic malignancies, particularly B cell malignancies such as CLL, Hodgkin and multiple myeloma are prone to infections due to pneumococci. The morbidity resulting from infection with influenza is also high. Patients are more likely to die during hospitalisation for influenza, especially the elderly and patients with comorbidities[13]. Among patients with solid tumours, patients with lung cancer have a high case fatality rate following influenza[13]. In addition, influenza may also lead to interruptions in chemotherapy leading to a negative impact on the ultimate disease outcome.

The protection against tetanus, diphtheria and polio is frequently low in children undergoing chemotherapy. In one report, only 59% of patients undergoing treatment for acute leukaemia were protected against tetanus. In contrast, treatment with radioimmunotherapy for non-Hodgkin lymphoma in children did not influence their specific immunity to tetanus[13].

Severe infections due to *H. influenzae* is rare. However, patients with Hodgkin and multiple myeloma may benefit from vaccination.

Although the mortality due to chickenpox has decreased due to the wider use of acyclovir for prophylaxis and treatment, immunization with varicella vaccine is indicated in seronegative individuals. However, interrupting maintenance chemotherapy in order to vaccinate is not indicated[13]. The mortality rate remains high in cancer patients who are infected with measles[13].

Timing of immunization

All live vaccines are contraindicated in cancer patients receiving immunosuppressive therapy and/or who have poorly controlled malignant disease. Live vaccines should be given ≥4 weeks prior to initiation of chemotherapy. In seronegative persons, vaccines should be administered at least 3 months after completion of chemotherapy, provided the underlying malignancy is in remission. However, it should be deferred for at least 6 months after therapy with anti-CD20 therapy (E.g. rituximab). MMR or varicella containing vaccines should be deferred accordingly in patients receiving blood products or immunoglobulin (refer Chapter 34).

The response to inactivated vaccines may be impaired during chemotherapy. Therefore, immunization is recommended at least 2 weeks prior to the start of chemotherapy, radiation, splenectomy or other immunosuppressive drugs or when immunosuppressive therapy is at the lowest level. An exception could be made if the risk of imminent exposure to the pathogen is high[12]. Revaccination, preferably 3 months after completion of treatment should be considered unless an adequate antibody response is demonstrated.

In patients receiving radiation therapy involving an arm or hemithorax, vaccines should be given on the opposite side.

Vaccines should not be administered during severe neutropaenia (apart from children with primary autoimmune neutropaenia) where the absolute neutrophil count is $<0.5 \times 10^3$/L, to avoid precipitating an acute febrile episode.

Patients on combination checkpoint inhibitors (E.g. ipilumumab plus nivolumab) should not receive any vaccines because of the significant increased incidence of immune-related adverse reactions.

Vaccines

It is important to offer routine or catch-up vaccination during chemotherapy for children and adults who have not completed a primary vaccination schedule before diagnosis, adhering to the general principles discussed above[2,12,13].

Table 5. Vaccination of persons with malignancies[13]

Vaccine	Children and adults who have not completed a primary vaccination schedule before diagnosis	Children and adults who completed primary vaccination schedule and cancer therapy
Inactivated influenza	All cancer patients above 6 months of age. Two doses 4 weeks apart for the 1st year and annually[a]	Single dose annually
Diphtheria, tetanus, pertussis	Age appropriate primary series	Single booster dose following intense chemotherapy could be considered to retain long-term immunity <10 years of age – DTaP ≥10 years of age – aTd or Tdap
Hib	Age appropriate primary series	Single dose, especially for patients with Hodgkin disease
IPV	Age appropriate primary series	Single dose
Hepatitis B vaccines	Age appropriate primary series	Single dose[b]
Pneumococcal vaccine	Age appropriate primary series of PCV and PPSV23 if previous age-appropriate doses not received	Single dose each of both vaccines, especially for patients with lymphoma, CLL

HPV vaccine	Age appropriate primary series	Age >9 years, previously completed a primary course – single dose not received previously – primary course (refer Chapter 12)
MMR	Contraindicated during immunosuppression, active disease	Single dose[c] – defer accordingly if blood products or IVIG/ SCIG have been administered (refer Chapter 34) and at least 6 months after anti-CD20 therapy
Varicella vaccine	Contraindicated during immunosuppression, active disease	Seronegative persons should be given a 2-dose schedule at least 6 months after chemotherapy

[a.] Caution advised for patients on checkpoint inhibitors (ipilumumab plus nivolumab)

[b] Check antibody status 4 weeks after vaccination

[c.] Check antibody status 6-8 weeks after vaccination

Booster vaccination is recommended for children and adults who have completed cancer therapy and a primary vaccination schedule before diagnosis. This should be carried out once the person is well and in remission, 6 months after chemotherapy. Most vaccines could be administered without checking antibody titres beforehand, and could be given at the same time[2,12,13].

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CHAPTER 33
IMMUNIZATION OF HIV INFECTED PERSONS

Immunization is an important measure to protect people living with HIV/AIDS (PLHIV) against certain vaccine-preventable diseases. PLHIV often have an increased risk of infection and they could experience more severe diseases compared to uninfected persons. However, as HIV infection alters immune function, vaccination of PLHIV may not confer the same degree of protection gained by immuno-competent persons. The antibody response is frequently impaired in PLHIV, as the virus attacks the CD4 T cell, which is important in antibody formation. However, many of these vaccines still afford protection but the immunity may remain lower and decline more rapidly compared to HIV-negative individuals. To overcome this issue, some vaccines could be administered with a modified schedule such as more frequent doses and a higher antigen content which improves the immunogenicity[1]. Certain vaccines enhance HIV virus replication and transiently increase HIV viral load, but this does not preclude vaccination[2].

Ideally for PLHIV, the vaccine should be given before the immune status of the patient is suppressed. Persons with severe immuno-deficiency* may have impaired humoral response and may not respond to vaccines or they may require supplemental doses to develop serological evidence of protection. If possible, vaccines should be administered before the CD4 count decreases to <200 cells/µL.

In general, all inactivated vaccines could be administered safely to persons with altered immunocompetence[3]. However, live vaccines may pose a risk to PLHIV. Nevertheless, antiretroviral therapy (ART) induced immune restoration reduces the possibility of having adverse effects and shifts the risk-benefit ratio in favour of vaccination. Therefore, live

vaccines such as varicella (VZV), yellow fever and MMR could be considered for individuals whose immunity is not severely compromised or is restored with ART (children <5 years with CD4 T lymphocyte cell percentage ≥15% and those aged >5 years with CD4 counts ≥200 cells/μL)[3]. Before administering live vaccines, consultation with an immunologist or a vaccinologist is advised.

* HIV-infected persons >5 years of age with CD4 counts <200 cells/μL. Children ≤5 years of age with CD4 percentage <15% are considered to have severe immunosuppression

General principles of immunization in HIV-infected children

Vaccines may be less effective in HIV-infected children. However, these children also have an increased risk of infectious diseases and may have more severe illnesses. Therefore, HIV-infected children should be protected from vaccine-preventable diseases. Hence completing immunization is important, but consideration should be given to the most appropriate time for immunization. It is important to immunize the HIV-infected children prior to the impairment of their immune system or after immune reconstitution occurs with ART.

Table 1. Immunization schedule for HIV infected children**

Age	Standard schedule	Child with HIV	Remarks
0-4 weeks	BCG	If vaccinated with BCG at birth are at increased risk of developing disseminated BCG disease. Therefore, BCG vaccination should be delayed until ART has been started and the infant is confirmed to be immunologically stable (CD4 >25%)[4]	Neonates born to women of unknown HIV status should be vaccinated as the benefits of BCG vaccination outweigh the risks[4] Neonates of unknown HIV status born to HIV-infected women should be vaccinated if they have no clinical evidence suggestive of HIV infection, regardless of whether the mother is receiving ART[4] However, if the mother is having a detectable viral load at the time of delivery it is better to postpone BCG till HIV is excluded in the infant. Exclusion of HIV in infants will take 4-6 months
On completion of			
2 months	Pentavalent (DTP-Hep B-Hib) and OPV (1st dose)	Pentavalent (DTP-Hep B-Hib)+inactivated polio vaccine***(1st dose)	OPV and fIPV are not recommended in infants with HIV infection
	fIPV (fractional IPV) (1st dose)	Pneumococal conjugate vaccine (PCV) 1st dose	

4 months	Pentavalent (DTP-Hep B-Hib) and OPV (2nd dose)	Pentavalent (DTP-Hep B-Hib)+ inactivated polio vaccine*** (2nd dose)	OPV and fIPV are not recommended in infants with HIV infection
	fIPV (fractional IPV) (2nd dose)	PCV 2nd dose	
6 months	Pentavalent (DTP-Hep B-Hib) OPV and (3rd dose)	Pentavalent (DTP-Hep B-Hib)+ inactivated polio vaccine*** (3rd dose)	OPV is not recommended in infants with HIV infection
		PCV 3rd dose	
9 months	MMR	MMR	Should be postponed in severe immunodeficiency
12 months	Live JE	Inactivated JE vaccine, if available	Live JE is not recommended for HIV infected children
		Hep A 1st dose (2nd dose 6-12 months later)	Children with severe immunosuppression may have a suboptimal response to Hep A vaccine
13-15 months		Varicella 2 doses 3 months apart[3]	Patients who are severely immunosuppressed should not receive the vaccine
		PCV booster dose	

18 months	DTP and OPV (4^{th} dose)	DTP+inactivated Polio vaccine***	OPV is not recommended for children with HIV infection
3 years	MMR 2^{nd} dose	MMR 2^{nd} dose	Patients who are severely immunosuppressed should not receive the vaccine
5 years	DT+OPV	DT+inactivated polio***	OPV is not recommended for children with HIV infection
		Pneumococcal polysaccharide vaccine[3]	
10-15 years	HPV (quadrivalent) 2 doses (females) (0, 6 months)	HPV (quadrivalent) 3 doses (both females and males) (0, 2, 6 months)	
10-15 years	aTd Tdap	aTd Tdap	

** Adapted from national immunization schedule

*** IPV dose and route – 0.5mL intramuscular

COVID-19 vaccination for children with HIV infection[5]

Children aged 16-17 years

Children aged 16 to 17 years with HIV infection should receive two doses of the COVID-19 vaccine at an interval of at least eight weeks. Those who have severe immunosuppression with a CD4 count of <200 cells/μL should receive a third primary dose of the COVID-19 vaccine. The third dose should be given ideally at least 8 weeks after the second dose. A booster dose should then be given at least three months later.

Children aged 12-15 years

Children aged 12 to 15 years with HIV infection should receive two doses of Pfizer BioNTech vaccine at an interval of at least eight weeks. Children aged 12 years and over with immunosuppression due to HIV/AIDS with a current CD4 count of <200 cells/μL should receive a third primary dose of COVID-19 vaccine at least 8 weeks after the second dose. A booster dose should then be given at least three months later.

Children aged 5-11 years

Children aged 5 to 11 years with HIV should receive two doses of the paediatric dose (10 micrograms) of the Pfizer BioNTech vaccine at an interval of at least eight weeks. The third dose should be given ideally at least 8 weeks after the second dose.

General principles of immunization in HIV infected adults

Live vaccines

- Persons with symptomatic HIV infection or CD4 counts <200 cells/μL should not be given live vaccines. Vaccination may be reconsidered when immune restoration occurs with ART[1].

- HIV infected adults with a CD4 count of 200-300 cells/μL have a moderate immunodeficiency[1]. When administering live vaccines for them it is important to weigh the risk and benefits before vaccination.
- Co-administration of multiple live vaccines to HIV-infected individuals is not recommended due to issues related to safety, immunogenicity and efficacy. It is recommended to have at least an interval of four weeks between vaccinations[1].

Inactivated vaccines

- In persons with CD4 counts <200 cells/μL, the response to inactivated vaccines is reduced[1]. Delaying vaccination till immune restoration could be considered in these patients. However, if the risk of exposure is high, vaccination could be done. If indicated, vaccination could be repeated following immune restoration on ART.

Table 2. Vaccination of adults with HIV

Vaccine	Indication	Primary course	Boosting	Remarks
COVID-19 vaccines	All people living with HIV should be prioritized for early vaccination regardless of their CD4 count	All COVID vaccine doses recommended for people without HIV are recommended for PLHIV with a current CD4 count >200 cells/μL. For the people with a CD4 count of <200 cells/μL, an additional vaccine dose should be administered as part of the extended primary	A booster dose can be taken 4 to 6 months after the completion of the primary vaccination series	Completion of the vaccine series is recommended to improve the response

		series and should be given 1-3 months after the second dose		
H. influenzae type b (Hib)	At risk	Single dose	None	Could be given regardless of the CD4 cell count
Hepatitis A	At risk	Two or three doses	Every ten years if at risk	Three doses at 0,1 and 6 months if the CD4 cell count is <350 cells/µL and two doses at 0 and 6 months if the CD4 cell count is >350 cells/µL
Hepatitis B	All non-immune	Four doses**** (at 0, 1, 2, 6 months)	If HBsAb ≥10 – <100 IU/L – need one booster dose and retesting If HBsAb ≤10 IU/L need three further vaccine doses and retesting	Could be given regardless of the CD4 cell count. Screen HBsAb levels according to initial response
Human papillo-mavirus	Age and gender related	Three doses of quadrivalent vaccine 0, 2 and 6 months apart	None	Could be given regardless of the CD4 cell count
Inactivated polio	To all non-immune	Five doses (at 0,1,2 months, 5 years and 10 years)	Every ten years if at risk	Could be given regardless of the CD4 cell count
Influenza	For all	Single dose	Annually	Could be given regardless of the CD4 cell count

Japanese encephalitis inactivated Vero cell derived	At risk	Two doses 1 month apart	One booster dose 1 to 2 years later for those at continued risk with a further boost after 10 years	Could be given regardless of the CD4 cell count
Meningo-coccal (conjugated)	At risk	Two doses 2 months apart	Every five years if at risk	Could be given regardless of the CD4 cell count
MMR	To all non-immune	Two doses at least 1 month apart	None	Could be given when the CD4 cell count is >200 cells/μL
Pneumo-coccal (polysac-charide) PPSV23 and pneu-mococcal (conjugate) – PCV 13/10 is preferred	For all	One dose of PCV13/10 followed by one dose of PPSV23 at least 8 weeks later. Second dose of PPSV23 at least 5 years after the previous dose. One final PPSV23 at 65 years or older	None	Could be given regardless of the CD4 cell count
Rabies vaccine	For exposed non-immune	Rabies immunoglobulin + five doses of the vaccine IM at 0, 3, 7, 14 and 30 days	None	Could be given regardless of the CD4 cell count
Tetanus-diphtheria (aTd)	To all non-immune	Five doses at 0, 1, 2 months, 5 years and 10 years	Every ten years	Could be given regardless of the CD4 count
Tetanus toxoid	To all non-immune	Five doses at 0, 1, 2 months, 5 years and 10 years	Every ten years	Could be given regardless of the CD4 count

Typhoid Vi capsular polysac -charide	At risk	Single dose	Every three years if at risk	Could be given regardless of the CD4 count
Varicella	All non-immune	Two doses 3 months Apart	None	Could be given when the CD4 cells count is >200 cells/µL
Yellow fever	At-risk age <60 years and the CD4 cell count is >200 cells/µL	Single dose	Every ten years if at risk	Age >60 years, CD4 cell count is <200cells/µL and pregnant women should not receive the vaccine

[***]Yeast based vaccine 40 µg/dose or 2 doses of 20 µg/dose vaccine

Recommendation for pre-exposure vaccination in HIV-infected adults[1]

COVID-19 vaccine

People infected with HIV at any CD4 cell count are at increased risk for severe outcomes and death due to COVID-19 complications compared with people without HIV[9]. Furthermore, many people living with HIV have one or more comorbidities that may put them at increased risk for a more severe COVID-19.

Latest studies have revealed that HIV infection is a significant independent risk factor for severe COVID-19 presentation at hospital admission. These studies have also found that the risk of developing severe or fatal COVID-19 was 30% greater in PLHIV compared to people without HIV infection[7]. Therefore, the individuals infected with HIV should receive all the doses of vaccines recommended for COVID regardless of their treatment status, nadir, current CD4 cell count, and current viral load.

Despite the differences in the efficacy of the vaccines, still, there are not enough data to recommend one vaccine type over another for people with HIV[9]. Therefore, it is recommended to accept the first vaccine that is offered. People with HIV should be informed about the side effects of the vaccine and there is no indication at present for doing antibody testing either pre- or post-vaccination to evaluate the vaccine response. It is recommended that in people with acute illnesses, including COVID-19, vaccination should be deferred until clinical recovery and to around 4 weeks after the first onset of symptoms or first positive RNA test.

PLHIV should be informed that the onset of protection after the first dose requires 2-3 weeks and that completion of the recommended vaccine series is needed to achieve better protection. Even after vaccination, PLHIV should follow the general guidance to reduce the risk of future infection.

H. influenzae type b vaccine (Hib)

The vaccine has been shown to produce protective antibodies in HIV-infected individuals, but the response can vary with the CD4 cell count. It is recommended that HIV-positive individuals with the following conditions who are at risk of having an infection, should receive one dose of a Hib-containing vaccine whether or not they were immunized previously and regardless of CD4 count, ART use and viral load[1].

- Asplenia
- Splenic dysfunction
- Complement deficiency

Hepatitis A vaccine

It is recommended to perform pre-vaccination screening for hepatitis A immunity in HIV-positive adults who are at risk of hepatitis A. The following categories could be considered as at risk for hepatitis A infection.

- Close contacts with Hepatitis A
- Men who have sex with men

- Injecting and non-injecting drug users
- Persons who have chronic liver disease or conditions that could lead to chronic liver disease
- Those with occupational exposure to Hepatitis A
- Persons who require frequent blood /blood product transfusions
- Persons with special needs living in residential institutions and their carers
- Persons who travel to countries with high or intermediate endemicity of infection

If serologically negative for hepatitis A, they should be offered a monovalent hepatitis A vaccine. The immune response to the hepatitis A vaccine is generally reduced in HIV-positive individuals compared to HIV-negative individuals. But the response improves with increasing CD4 cell counts and viral load suppression on ART. If the CD4 count is less than 200 cells/µL, or when the patient is having symptomatic HIV infection, it is preferable to defer vaccination until several months after initiation of ART and an improvement of the CD4 count. However, it should not be deferred in patients who are clinically unlikely to achieve increased CD4 cell count.

HAV IgG should be performed at least 1 month after the last dose of vaccination to identify the non-responders[6]. Non-responders should be revaccinated. The vaccine is safe and well-tolerated in HIV-positive individuals including those who receive three doses over 6 months.

Hepatitis B vaccine

HIV infection affects the response to the hepatitis B vaccine and the HBsAb seroconversion strongly correlates with CD4 cell count and viral load. Revaccination of non-responders once the CD4 count is >350 cells/µL, suppression of viral load with ART, and the use of higher and more frequent vaccine doses are some of the strategies available to improve the vaccine response among HIV infected individuals. Duration of vaccine-induced protection is unknown in HIV-positive individuals and in general, post-vaccination antibody levels are lower and disappear more quickly than in HIV uninfected individuals.

When using recombinant vaccines, a high dose (40 µg i.e. 2 doses of 20 µg/mL vaccine) vaccination should be offered. Four vaccine doses should be given at 0, 1, 2 and 6 months[1]. It is recommended to measure the HBsAb levels 4-8 weeks after the last dose of vaccine.

Antibody level >100 IU/L is regarded as ideal, whereas a level <10 IU/L is classified as non-responsive. It is recommended that individuals with HBsAb levels ≥10 but <100 IU/L should receive one booster dose[1]. If retesting of HBsAb shows that it is between 10-100 IU/L regular annual HBsAb testing is needed to guide subsequent boosting requirements.

Individuals who have HBsAb levels <10 IU/L after the primary vaccine course should receive three further vaccine doses at monthly intervals. It is better to delay the revaccination until the viral load is suppressed on ART and the CD4 count has increased >350 cells/µL.

Screening of HBsAb levels with longer intervals (2-4 yearly) is indicated for individuals with initial HBsAb levels >100 IU/L, CD4 count >350 cells/µL, and viral load suppression on ART. Other individuals should undergo yearly HBsAb screening.

Human papillomavirus vaccine

HIV-infected individuals are at higher risk of HPV acquisition, persistence and at increased risk of HPV-related malignancies. The response to the vaccine is highest in those receiving ART and showing high CD4 cell counts and suppressed viral load. Studies are still ongoing to demonstrate the duration of vaccine-induced protection. Even though younger individuals are more likely to benefit from the vaccine, older men and women may continue to have at least a partial benefit from vaccination.

It is recommended that previously unvaccinated HIV-infected men and women aged up to 26 years should be offered HPV vaccination regardless of CD4 count, ART use, and viral load. Previously unvaccinated HIV-positive men having sex with men aged up to 45 years should be offered HPV vaccination regardless of CD4 count, ART use, and viral load[5].

It may be useful to offer HPV vaccination for previously unvaccinated HIV-positive women aged up to 40 years regardless of CD4 count, ART use, and viral load[1]. In ART naive patients with CD4 cell count <200 cells/μL, vaccination may be postponed until the patient is established on ART.

It is recommended that three doses of the quadrivalent vaccine need to be administered at 0, 2 and 6 months to HIV-infected individuals[1]. If the schedule is interrupted, the vaccine series need to be completed rather than restarted. Nonavalent (9vHPV) can replace quadrivalent vaccine for both men and women once available[1].

Inactivated polio vaccine

Inactivated polio vaccine could produce neutralizing antibodies in HIV positive adults and children and in patients with CD4 count <300 cell/μL. It is safe and well tolerated. It is recommended that individuals who are unvaccinated should receive 3 doses of vaccine at monthly intervals followed by 2 reinforcing doses after 5 and 10 years[1]. Fully vaccinated individuals should receive booster doses every 10 years if at risk of exposure. Fractionated intradermal IPV is not recommended.

Inactivated influenza vaccine

HIV infected individuals are at 4-8-fold risk of influenza and are 1.5 times more likely to die compared to HIV uninfected individuals[8]. Vaccination against influenza has been identified as an effective preventive strategy.

Vaccine response is lower compared to HIV negative individuals and correlates with CD4 cell count and viral load. Vaccine may have a low immune response especially when the CD4 count is less than 200 cells/μL. However, as the vaccine is still effective in preventing and reducing complications in patients with HIV infection, it is recommended to offer an annual inactivated influenza vaccine to all HIV infected individuals, especially for HIV infected pregnant women.

Japanese encephalitis vaccine

Live JE vaccine is not recommended in HIV-infected patients. There is insufficient evidence on the safety, immunogenicity, and clinical efficacy of JE vaccination in HIV-positive adults. However, it is recommended that HIV-infected individuals be offered an inactivated Vero cell-derived JE vaccine with two doses given 1 month apart. A booster dose could be given 1-2 years later for those at continued risk with a further booster planned after 10 years[1]. This vaccine is not available in Sri Lanka at present.

Meningococcal vaccine

Patients with HIV infection are at higher risk of invasive meningococcal infection especially those with CD4 cell count <200 cells/µL and viral load >400 copies/mL. However, HIV infection alone is not currently an indication for the meningococcal vaccine. It is recommended that HIV-positive individuals should follow the general indications for meningococcal vaccination and should be offered the vaccination as needed. Individuals who are in close contact with patients with meningococcal disease should be offered antibiotic prophylaxis and appropriate vaccination. Two doses of conjugated vaccine given at an interval of two months are recommended for individuals with HIV infection[1]. The individuals who received MenACWY should be offered a booster dose every five years if there is an ongoing risk[1].

MMR vaccine

The prognosis of rubella and mumps does not show much difference between HIV-infected individuals and the general population. However, measles could be life-threatening in persons with advanced HIV infection. Therefore, it is recommended to offer two doses of MMR vaccine at least 1 month apart to measles seronegative HIV-infected patients with CD4 cell counts >200 cells/µL. However, based on the likelihood of exposure, vaccination may be postponed in patients with CD4 cell count >200 cells/µL who have not started on ART.

After a significant exposure to measles, HIV-infected individuals should be screened for measles IgG within 3 days regardless of a history of previous vaccination. After a risk assessment about the need and the mode of post-exposure prophylaxis, measles seronegative adults:

- with CD4 count >200 cells/μL preferably on ART with a stable viral load could receive MMR vaccine within 3 days of contact or IM preparation of human immunoglobulin (HNIG) within 6 days of contact[1]
- with CD4 counts <200 cells/μL could be given HNIG within 6 days[1]

However, the protection afforded with HNIG/IVIG will be short-lived.

It is also recommended to give MMR vaccine to rubella seronegative HIV-positive women of childbearing age provided their CD4 count is >200cells/μL and they are not pregnant. Vaccine responses are reduced in HIV-infected individuals, but effective ART can improve the response.

Pneumococcal vaccine

HIV-infected individuals are at higher risk of developing pneumococcal disease and show an increased risk of mortality. Studies conducted on the clinical efficacy of the pneumococcal polysaccharide vaccine (PPSV23) in HIV-positive adults have shown inconsistent findings. However, serological studies conducted on the pneumococcal conjugate (PCV) vaccine have shown immunogenicity in HIV-infected persons[1]. With both vaccines, the response is low in HIV-positive individuals compared to HIV-negative individuals. However, the PCV vaccine has demonstrated superiority with certain serotypes over PPSV in serological studies[1].

It is recommended to give both the pneumococcal vaccines to HIV-infected individuals irrespective of the CD4 cell count, ART use, and viral load.

One dose of PCV 13/10 should be administered followed by one dose of PPSV23 at least 8 weeks later. The second dose of PPSV23 should be administered at least 5 years after the previous dose. One final dose of PPSV23 should be administered at 65 years or older. This dose should be given at least 5 years after the most recent dose of PPSV23[9].

Rabies vaccine

When giving post exposure prophylaxis, each case should be assessed individually. The following categories should be considered non-immune for rabies and should be given rabies immunoglobulin (RIG) and five doses of cell culture derived vaccine intramuscularly at 0,3,7,14 and 30 days[1]. Intradermal ARV is not recommended for these patients.

- Unvaccinated
- Partially vaccinated (<3 doses)
- Given a complete course of vaccination (5 doses) but without serological evidence of an adequate antibody response
- Uncertain vaccination history
- CD4 cells<500 cells/μL and not receiving ART

In patients who previously received 5 doses of the vaccine and had adequate antibody response with a CD4 count >500 cells/μL, viral suppression (>6 months) and on ART may be managed with 2 intramuscular doses given at 0 and 3-7 days without RIG[1].

After the full course of vaccination, all patients should undergo serological testing 2 weeks after the last vaccine dose, and non-responders are offered a double dose or more frequent vaccine doses after obtaining specialist advice.

Tetanus-diphtheria vaccine (aTd)

The HIV-infected adults who require vaccination against tetanus and diphtheria could be given aTd vaccine regardless of CD4 cell count, ART use, and viral load. It is recommended to give three vaccine doses at 1 month intervals, followed by 2 reinforcing doses after 5 and 10 years[1].

Tetanus toxoid

The vaccine has been shown to be immunogenic in HIV-infected individuals even though the response is less compared to HIV non-infected individuals. However, the immunity improves following successful ART.

If the patient is unvaccinated for tetanus, it is recommended to give the adult tetanus vaccine regardless of CD4 count, ART use, and viral load in three vaccine doses given at 1 month intervals, followed by two reinforcing doses after 5 and 10 years. Fully vaccinated individuals should receive a booster dose every 10 years.

Following a potential exposure

- Individuals with uncertain or incomplete vaccination, 3 vaccine doses at monthly intervals should be given regardless of the type of wound and level of risk.
- Individuals who have previously received three vaccine doses with a clean wound and negligible risk should receive one dose if the last dose received was >10 years previously.
- Individuals who received at least three vaccine doses with tetanus prone wounds should receive tetanus immunoglobulin and 1 dose of vaccine if the last dose received was >10 years previously.

Typhoid vaccine

HIV-infected individuals are at higher risk of developing infections with salmonella and are more likely to develop complications. It is recommended to offer Vi capsular polysaccharide vaccine to HIV-infected individuals who are likely to be exposed to poor sanitary conditions. The vaccine should be given at least 2 weeks before the expected exposure. The booster dose could be given every 3 years for those who remain at risk.

Varicella zoster vaccine

HIV-infected individuals who acquire chickenpox are at higher risk of developing severe and fulminant disease. In addition, they are at increased risk of developing VZV reactivation especially with low CD4 counts and with a viral load of >400 copies/mL. Even with ART, the disease burden is 3-5 times higher compared to HIV-negative individuals.

The chickenpox vaccine was shown to be safe and immunogenic in children with asymptomatic or mildly symptomatic HIV infection. However, only limited data are available on HIV-positive adults[1].

Two doses of the varicella vaccine 3 months apart are recommended for varicella seronegative patients who have CD4 cell count >200 cells/ µL and are on ART[1].

Post exposure prophylaxis

Varicella-zoster immune globulin is recommended for HIV infected individuals following a significant exposure to VZV. Following a close contact with a patient who has active VZV infection, HIV infected individuals specially with <200 cells/ µL and are susceptible for VZV infection, should receive VariZIG as soon as possible preferably within 96 hours, but up to 10 days after exposure. Due to the high cost of VariZIG, it is reasonable to check VZV serology before administering VariZIG to people who do not have a clinical history of chickenpox or shingles and no documentation of varicella vaccination. The efficacy of post-exposure varicella vaccination for people with HIV has not been studied and is not recommended[10].

Yellow fever vaccine

It is recommended that HIV-infected individuals aged <60 years and with CD4 cell count >200 cells/µL who are planning to travel to countries in which there is a risk of exposure should be offered the vaccination after counselling on the benefits and risks of vaccination. One vaccine dose at least 2 weeks before travel is recommended[1]. Higher CD4 counts and a suppressed viral load on ART are likely to maximize the safety and efficacy of vaccination.

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CHAPTER 34

IMMUNIZATION IN OTHER SPECIAL CLINICAL CIRCUMSTANCES

Preterm and low birth weight infants

Preterm infants and infants of low birth weight (lower than 2500g) should receive routinely recommended childhood vaccines at the same chronological age as term infants. Vaccine doses should not be reduced when given to preterm and low birth weight infants. Babies born prematurely should receive the BCG vaccine when they are discharged from hospital[1]. All immunizations recommended at 2 months of age could be administered to preterm or low birth weight infants. The rotavirus vaccine may be given if the infant is at least 6 weeks of postnatal age and is clinically stable; it should be deferred until the infant is discharged from the hospital to prevent potential spread of this live vaccine virus[2].

Patients requiring repeated blood transfusions/ blood products

A wide range of infections could be transmitted by blood transfusions. These include HIV, hepatitis A, B and C, syphilis, malaria, human T cell lymphotropic virus types 1 and 2, cytomegalovirus, Epstein-Barr virus and parvovirus B19. Since immunization is at present available only for hepatitis A and B, all patients requiring repeated transfusions should be immunized with these vaccines prior to commencement of transfusions. Administration of the MMR or varicella vaccine should be delayed by 3-11 months after infusion of blood or blood products, including plasma, IVIG or platelets depending on the blood product given (Table 1). Low levels of antibodies present in the blood product may impair the immune response to the live vaccine[3].

Table 1[3]. Recommended intervals between immunoglobulins or blood products, and measles-mumps-rubella, measles-mumps-rubella-varicella or varicella vaccination

Immunoglobulin/ blood product	Route	Dose (IU or mL)	Dose (estimated mg IgG/kg)	Interval (months)
Blood transfusion: washed red blood cells	IV	10 mL/kg	Negligible	0
Blood transfusion: red blood cells, adenine-saline added	IV	10 mL/kg	10	3
Blood transfusion: packed red blood cells	IV	10 mL/kg	20-60	5
Blood transfusion: whole blood	IV	10 mL/kg	80-100	6
Cytomegalovirus immunoglobulin	IV	3 mL/kg	150	6
Hepatitis B immuno-globulin as hepatitis B prophylaxis	IM	100 IU or 400 IU	10	3
NHIG (intravenous) for treatment of idiopathic thrombo-cytopenic purpura	IV	NA	400	8
NHIG (intravenous) for treatment of idiopathic thrombocytopenic purpura	IV	NA	1000	10
NHIG (intravenous) for treatment of idiopathic thrombocytopenic purpura or Kawasaki disease	IV	NA	1600-2000	11
NHIG as hepatitis A prophylaxis	IM	0.5 mL (<25 kg), 1.0 mL (25-50 kg), 2.0 mL (>50 kg)	NA	3

NHIG as measles prophylaxis: standard	IM	0.2 mL/kg (maximum dose 15 mL)	NA	5
NHIG as measles prophylaxis: immunocompromised	IM	0.5 mL/kg (maximum dose 15 mL)	NA	6
Plasma or platelet products	IV	10 mL/kg	160	7
Human rabies immunoglobulin as rabies prophylaxis	IM	20 IU/kg	22	4
Replacement (or therapy) of immune deficiencies as NHIG (intravenous), various doses	IV	NA	300-400	9
Rh (D) immunoglobulin (anti-D)	IM	NA	NA	0
Tetanus immunoglobulin (intramuscular use) as tetanus prophylaxis	IM	250 IU (given within 24 hours of injury)	10	3
Tetanus immunoglobulin (intra-muscular use) as tetanus prophylaxis	IM	500 IU (>24 hours after injury)	20	3
Zoster immunoglobulin as varicella prophylaxis	IM	200 IU (0-10 kg), 400 IU (11-30 kg), 600 IU (>30 kg)	NA	5

IM = intramuscular; IU = international units; IV = intravenous; NA = not applicable; NHIG = normal human immunoglobulin

Patients with chronic diseases

Some chronic diseases make persons susceptible to severe manifestations and complications of common infections. In general, immunizations recommended for healthy individuals should be given to such persons with the exception of those with immunological disorders. Such patients should also receive certain additional vaccines according to their underlying disease. Clinical evidence indicates that vaccines are not triggers of diseases or flare up of existing diseases and therefore, should not be withheld because of this concern[2].

Children with cardiac disease

Children with underlying cardiac disease (particularly cyanotic congenital heart disease and cardiac failure) are at increased risk of vaccine preventable diseases when compared to healthy children. This includes influenza and invasive pneumococcal disease with those at highest risk being children with cyanotic heart disease or cardiac failure.

Vaccine recommendations:

- Routine childhood vaccines according to the National Immunization Programme
- If they have received blood products and/or immunoglobulin, parenteral live virus vaccines should be delayed (refer Table 1)
- Vaccines should be given within recommended time frames unless contraindicated due to medical treatment, including surgery
- Recommended time intervals for vaccination before and after surgery[3]
    - Before surgery – 1 week for inactivated vaccines; 3 weeks for live vaccines (E.g. MMR, varicella)
    - After surgery – delay vaccination for one week

Additional vaccines

- Influenza vaccine: All cardiac patients are recommended to receive influenza vaccine annually from 6 months of age[4]
- Pneumococcal vaccine (refer Table 2): For children who have not received all doses of the pneumococcal vaccine, in either the recommended series or an age-appropriate catch-up series, the missed doses should be given. When both PCV and PPSV23 are indicated, PCV should be administered first

Table 2. Pneumococcal vaccination in special circumstances (adapted from[5])

	Chronic heart disease, chronic lungdisease, diabetes mellitus	Chronic renal failure, nephrotic syndrome	Cerebrospinal fluid leak, cochlear implant
2 months-2 years	2 doses of PCV 8 weeks apart, and 1 booster 6 months after the 2nd dose		
2-5 years	2 doses PCV 8 weeks apart 1 dose PPSV23 8 weeks later	2 doses PCV 8 weeks apart 1 dose PPSV23 8 weeks later, 2nd dose 5 years after 1st dose	2 doses PCV 8 weeks apart 1 dose PPSV23 8 weeks later
6-18 years	1 dose PCV 1 dose PPSV23 8 weeks later	1 dose PCV 1 dose PPSV23 8 weeks later, 2nd dose 5 years after 1st dose	1 dose PPSV1 dose PPSV23 8 weeks later
19-64 years	**For those who have not previously received any pneumococcal vaccine** Give 1 dose of PCV 1 dose of PPSV23 at least one year later. The minimum interval is 8 weeks and could be considered in adults with an immunocompromising condition, cochlear implant or cerebrospinal fluid leak **For those who have only received PPSV23** May give 1 dose of PCV at least 1 year after PPSV23 **For those who have received PCV with or without PPSV23** Give PPSV23 5 years after last dose of PPSV23		
>64 years	**65 years or older who have not previously received any pneumococcal vaccine** 1 dose of PCV 1 dose of PPSV23 at least one year later. The minimum interval is 8 weeks and can be considered in adults with an immunocompromising condition, cochlear implant or cerebrospinal fluid leak. **For adults 65 years or older who have only received PPSV23** 1 dose of PCV **For adults 65 years or older who have only received PCV** 1 dose of PPSV23		

Infants with severe congenital heart disease[6]

Severe congenital heart disease is not a known contraindication for vaccination. However, the vaccine or the vaccination process may trigger events (E.g hypotension, tachycardia) which may lead to deterioration of the underlying disease, which may be fatal. Therefore, it is recommended that all infants with severe congenital heart diseases listed below should be admitted to a hospital where a paediatrician's service is available for vaccination and be observed for a minimum period of 24 hours after vaccination.

Infants with severe congenital heart disease who need hospitalization for vaccination are as follows:

- Cyanotic defects:
  - Tetralogy of Fallot
  - Pulmonary atresia with duct dependent pulmonary circulation
  - Univentricular heart with pulmonary stenosis
  - Tricuspid atresia
  - Any other condition with significant cyanosis (SaO_2<85%)
- Any cardiac condition with significant left ventricular (LV) hypertrophy
  - Hypertrophic cardiomyopathy
  - Significant valvular, supravalvular or subvalvular aortic stenosis
- Any condition with significant LV dysfunction (ejection fraction <45%)
  - Dilated cardiomyopathy
  - Any other cardiac condition with significant LV dysfunction
- Any patient with moderate/severe pulmonary hypertension
- Cyanotic congenital heart defects palliated with systemic to pulmonary artery shunts and pulmonary artery banding

It is recommended that cardiac monitoring (pulse, BP and SaO_2) of these infants be carried out preferably for 24 hours after vaccination.

All children with significant cyanosis should be kept well hydrated before and after vaccination. Blood pressure should be monitored in the event of hypotension due to fever or vasodilatation; appropriate fluid administration along with other therapeutic measures is indicated.

Adults with chronic heart disease

Vaccine preventable diseases, especially influenza, can increase the risk of cardiovascular complications, in patients with chronic heart disease[7]. The American Heart Association/American College of Cardiology and the European Society of Cardiology recommend the influenza vaccine annually for patients with established coronary vascular disease (CVD)[7,8]. While the efficacy of the pneumococcal vaccine in CVD is not well established due to the absence of prospective randomized control trials, the consensus is to vaccinate this group[7].

- Influenza vaccine – recommended annually[4,7,8]
- Pneumococcal vaccine (refer Table 2)

Patients with chronic lung disease

Patients with chronic lung diseases (E.g. asthma, chronic pulmonary dysplasia, chronic obstructive pulmonary diseases (COPD) or cystic fibrosis), are at increased risk of complications of influenza and pneumococcal infection[9]. Those with cystic fibrosis are also at increased risk of complications from varicella infection[9], which may cause a transient worsening of lung function. Smoking also impairs mucociliary clearance and predisposes to pneumococcal disease.

Annual influenza vaccination is recommended for all children (over 6 months of age) and adults who have chronic pulmonary disease (including asthma)[4]. Adults with chronic lung disease should receive the varicella vaccine. The pneumococcal vaccine should be administered according to the normal schedule.

For children who have not received all doses of the pneumococcal vaccine, in either the recommended series or an age-appropriate catch-up series, the missing doses should be given. When both PCV and PPSV23 are indicated, PCV should be administered first (refer Table 2).

Patients with cerebrospinal fluid (CSF) leaks

Cranial CSF leaks usually involve communication with the central nervous system and the oropharynx and nasopharynx which are

colonized with bacteria, often inclusive of pneumococcal strains. For this reason, these patients have a higher risk of meningitis as compared with the general population and those who have not received all doses of the pneumococcal vaccine, in either the recommended series or an age-appropriate catch-up series should receive pneumococcal vaccination to reduce the risk of pneumococcal meningitis. When both PCV and PPSV23 are indicated, PCV should be administered first (refer Table 2).

Patients with spinal CSF leaks do not need the pneumococcal vaccine in the absence of other indications. There is no evidence of increased risk of meningitis in patients with spinal CSF leaks because the vast majority has no anatomical communication with sites colonized with bacteria (oropharynx, nasopharynx, GI tract, respiratory tract, skin).

Patients with cochlear implants

Infection is an important complication of cochlear implants and the type of infection varies with age. Surgical site infections are more common in adults whereas meningitis and the complications of acute otitis media (such as mastoiditis and meningitis) are more common in children.

Vaccines for children

- The increased risk of bacterial meningitis, particularly pneumococcal meningitis has led to the administration of PCV and the *H. influenzae* type b (Hib) vaccine according to the routine schedule. (For pneumococcal vaccination, refer Table 2). For maximum benefit, children should receive the PCV series, followed by a single dose of PPSV23 prior to surgery if over 2 years of age.
- Children less than 5 years of age should be vaccinated with Hib vaccine according to the routine schedule, with a booster after 1 year of age. Incompletely immunized individuals 5 years of age and older do not require a dose[10].
- Since cochlear implant recipients do not appear to be at increased risk of invasive meningococcal disease, they should receive the meningococcal vaccine only if they have a specific indication.

- Annual influenza immunization is recommended for all children more than 6 months of age and is particularly important for cochlear implant recipients and their household contacts in order to reduce the incidence of otitis media due to secondary bacterial infection[4].

Vaccines for adults

- Adult cochlear implant candidates and recipients should receive all routine vaccines. They should be vaccinated against the pneumococcus with both the PCV and the PPSV23 vaccines (refer Table 2).
- Annual influenza vaccination is recommended for cochlear implant recipients and their household contacts[4]

Patients with chronic renal disease and patients requiring renal dialysis

Recommendations for children

Patients with chronic kidney disease (CKD) and those on dialysis may have impaired innate and acquired immune function[11]. In addition, they may be on immunosuppressives due to treatment of glomerulopathies. Patients on dialysis may have disruption of protective cutaneous barriers[11]. By virtue of their immunosuppressed state, CKD patients are at risk for many infections, particularly hepatitis B, pneumococcus and influenza. In addition, the effectiveness of vaccines is also impaired. It is therefore recommended that immunization is commenced early in the disease process[11].

Children should receive all routine immunizations according to the schedule for healthy children. An exception being, withholding live virus vaccines in children with CKD related to glomerulonephritis during treatment with immunosuppressive medications. It is important, however, to make every attempt to administer live virus vaccines (MMR and varicella) before kidney transplantation. These vaccines are not advised for use in immunosuppressed patients.

- Hepatitis B – Patients should receive 3 doses of hepatitis B vaccine as early in the course of the disease as possible. A higher vaccine dose is recommended[9]. For children <16 years, double the routine dose should be administered[12]. The HBs antibody titre should be assessed 1-2 months after the primary course. Revaccination with a full course is recommended for patients who do not develop protective antibody titres (<10 mIU/mL)[13]. In CKD, an anti-HBs titre of above 100 mIU/mL is regarded as protective. Patients with titres between 10 and 100 mIU/mL may be at risk of acquiring HBV infection, especially when exposed to a high inoculum of HBV[13]. Patients on haemodialysis should be tested annually, and a booster given if the titre falls <10 mIU/mL[13].
- Pneumococcal vaccine (refer Table 2) – Patients with renal failure have an increased risk for pneumococcal infections. The efficacy of pneumococcal vaccination may be lower for some of these patients. They may require repeat vaccinations or an increased dose of vaccine.
- DTaP, Hib, hepatitis A, Japanese encephalitis, MMR, meningococcal, IPV, typhoid, varicella and inactivated influenza vaccines should be administered prior to commencement of dialysis, if not routinely administered earlier.

Recommendations for adults (refer Chapter 31)

- Hepatitis A, pneumococcal, inactivated influenza, Tdap vaccines should be administered.
- Hepatitis B immunization

  The standard HBV vaccination regimen for CKD patients is double the standard dose (40 μg instead of 20 μg) given at 0, 1 and 6 months intramuscularly. The HBs antibody titre should be assessed 1-2 months after the primary course. Revaccination with a full course is recommended for patients who do not develop protective antibody titres (<10 mIU/mL)[13]. In general, an anti-HBs titre of above 100 mIU/mL is regarded as protective. Patients with titres between 10 and 100 mIU/mL may be at risk of acquiring HBV infection, especially when exposed to a high inoculum of HBV[13]. Patients on haemodialysis should be tested annually, and a booster given if the titre falls <10 mIU/mL[13].

- MMR and varicella vaccines are given if there is no evidence of immunity. Two doses of MMR at least 4 weeks apart and 2 doses of varicella vaccines 4-8 weeks apart will have to be administered if not previously received.

Children with nephrotic syndrome[14]

To reduce the risk of serious infections in children with nephrotic syndrome (NS), it is recommended to give the full pneumococcal vaccination (with PCV and PPSV23 vaccines) and the annual influenza vaccination to the child and their household contacts. Defer vaccination with live vaccines for at least 1 month after stoppage of prednisolone if the prednisolone dose is 2 mg/kg day for >2 weeks in children weighing less than 10 kg or the dose is >20 mg/day for 2 weeks or more (refer Chapter 32). Live virus vaccines are also contraindicated in children receiving corticosteroid-sparing agents such as cyclophosphamide or cyclosporine. After treatment of the first episode of steroid sensitive NS, non-immunized children should be vaccinated with live vaccines as soon as possible, especially varicella zoster virus[14]. Following close contact with varicella infection, non-immune children on immuno-suppressive agents should be given varicella-zoster immunoglobulin if available. Immunize healthy household contacts with live vaccines to minimize the risk of transfer of infection to the immunosuppressed child. Direct exposure of the child to gastrointestinal or respiratory secretions of vaccinated contacts should be avoided for 3-6 weeks after vaccination.

Patients with chronic liver disease

Dysfunction of the innate and acquired immune system could occur as a result of chronic liver disease, especially in cirrhosis, which could lead to hypo responsiveness to vaccines[15]. Infection with vaccine preventable diseases, such as hepatitis A and B, pneumococcal disease, influenza and COVID-19 could lead to hepatic decompensation[15]. The Advisory Committee on Infectious Diseases (ACIP) advises giving the hepatitis A and B vaccines to all sero-negative patients with chronic liver disease[16] (disease lasting more than 6 months), including, but not limited to, those

with cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis and an ALT or AST level greater than twice the upper limit of normal[17]. As the sero-conversion rates for both vaccines are lower in patients with severe liver disease, it is recommended that the patient is vaccinated before the onset of decompensation[15]. Patients who have previously been immunized against HBV should undergo testing to confirm their immunity. An anti-HBs level of 10 mIU/mL or greater is protective and indicates that no additional doses of hepatitis B vaccine are needed[15]. For hepatitis A, the vaccine should be given as a 2-dose series[16], or 3 doses if given as a combined vaccine with hepatitis B. The inactivated influenza vaccine is recommended for use in patients with hepatic dysfunction[4].

The pneumococcal vaccine is also recommended (refer Table 2).

Diabetes mellitus

Routine vaccination should be provided for all diabetics. Individuals with diabetes have a higher risk of hepatitis B with transmission occurring from inappropriate use of blood glucose meters or infected needles. Adults with diabetes have a 60% higher prevalence of past or present HBV infection and twice the odds of acquiring acute HBV, compared to non-diabetic adults[18]. The fatality rate following acute hepatitis infection is also higher in the diabetic population[18]. The hepatitis B vaccination is recommended for persons with diabetes aged 19-59 years; immunization for patients with diabetes aged ≥60 years are at the discretion of the treating clinician[18]. Yearly influenza vaccination significantly reduces infection and diabetes-related hospital admissions[4]. Annual influenza vaccine to all children (over 6 months of age) and adults with diabetes is recommended[4].

The pneumococcal vaccine is also recommended (refer Table 2).

Diabetics have a higher risk of experiencing herpes zoster[19]. Individuals over 50 years of age should receive the recombinant zoster vaccine[20]. The vaccine is given as 2 doses separated by 2 to 6 months. Patients should be immunized even if they have had zoster or have an unknown chickenpox history.

Table 3[21]. Recommended child and adolescent immunization schedule by medical indication

Vaccine	Indication					
	Kidney failure, end stage renal failure or on haemodialysis	**Heart disease or chronic lung disease**	**CSF leaks or cochlear implants**	**Asplenia or persistent complement component deficiencies**	**Chronic liver disease**	**Diabetes**
Hepatitis B						
Rotavirus						
Diphtheria, tetanus, acellular pertussis (DTap) for <7 years and Tdap for ≥7 years						
H. influenzae type b (Hib)						
Pneumococcal conjugate						
Inactivated poliovirus						
Influenza (inactivated)						
OR Influenza (live attenuated)		Asthma, wheezing 2-4 years*				
Measles, mumps, rubella (MMR)						
Varicella						
Hepatitis A						
Human papillomavirus						
Meningococcal ACWY						
Meningococcal B						
Pneumococcal polysaccharide						


Vaccination according to the routine schedule recommended


Vaccination is recommended, and additional doses may be necessary based on medical condition


Precaution – vaccine might be indicated if benefit of protection outweighs risk of adverse reaction


Not recommended/Contraindicated – vaccine should not be administered


Recommended for persons with an additional risk factor for which the vaccine would be indicated

Retrieved from: https://www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf

Children with a personal or family history of seizures

Infants and children with a history of seizures should be given routine immunization except Japanese encephalitis vaccine. Japanese encephalitis vaccine should be given one year after the last seizure, provided there is no progressive neurological disorder. If a seizure follows the first dose of any vaccine, that vaccine should not be repeated. Pertussis immunization in infants with a history of recent seizures should be deferred until a progressive neurological disorder has been excluded or cause of the earlier seizure has been determined[2] (refer Chapter 8).

A family history of seizures is not a contraindication or reason to defer any immunization[2].

Healthcare personnel

Healthcare personnel should protect themselves, their families and patients by ensuring that they have received all appropriate immunizations. All those without evidence of immunity should receive vaccines that were not given in the primary immunization programme when they were children.

A course of hepatitis B vaccine should be given and seroconversion determined in all personnel who are likely to be exposed to blood and body fluids. MMR and varicella vaccine for susceptible individuals and annual influenza vaccination should be considered for healthcare workers[2].

Adolescents and young adults

Adolescents and young adults may not be protected against all vaccine preventable diseases because they have escaped natural infection and they have not received all recommended vaccines. Rarely persons who have received immunizations according to the routine schedules, may not be immune. To ensure age-appropriate immunization, all children should have a routine appointment at 11 to 12 years of age for administration of appropriate vaccines.

Tdap or aTd and HPV vaccines should be administered at 11 to 12 years of age.

During adolescent visits, immunization status should be reviewed and deficiencies rectified. It is imperative that adolescents and young adults intending to travel abroad should have their immunization status reviewed according to their travel plans at least 2-6 months prior to departure, to allow time to administer required vaccines[2].

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CHAPTER 35
PASSIVE IMMUNIZATION

Introduction

Passive immunization is the transfer of antibody from a human or an animal to another individual to provide immediate, albeit temporary, immunity. Transplacental transfer of antibody from the mother to the fetus is the commonest form of passive immunity. This occurs primarily during the last 1 to 2 months of pregnancy. Transferred antibodies will protect a term infant from certain diseases within the first few months after birth.

Passive immunization may be used in the following circumstances to prevent or ameliorate infectious diseases[2].

- For replacement – In congenital or acquired immunodeficiencies, where the patient cannot produce antibodies sufficiently (E.g. X-linked agammaglobulinaemia, common variable immunodeficiency, severe combined immunodeficiency, following treatment with immunosuppressive drugs)
- Prophylactically – Following or during high risk of exposure to a specific infectious agent, where severe consequences are anticipated or when time does not permit adequate protection by active immunization alone (E.g. rabies, varicella zoster, hepatitis B)
- Therapeutically – To ameliorate or suppress the effects of toxins (e.g. botulism, diphtheria, tetanus) and clinical disease (e.g. anthrax, post-transplantation hepatitis B) or to suppress inflammatory responses (e.g. Kawasaki disease, Guillain-Barre syndrome)

Choice of the product used to induce passive immunity depends mainly on the availability, type of antibody desired, route of administration and timing of administration[3].

Types of products

Human normal immunoglobulin/Intramuscular immunoglobulin/ HNIG[2,3]

HNIG is a concentrated blood product (approximately 16.5% or 165 mg/mL) containing antibodies that reflect the infectious and immunization experiences of the donor population. Immunoglobulin from 1,000 to 60,000 donors per lot are included in order to expand the spectrum of antibodies contained in the final product. More than 90% is IgG with trace amounts of IgA and IgM. HNIG should be administered into a large muscle mass such as the gluteal muscle in adults and adolescents and lateral thigh in children. Up to 5 mL could be administered to a single site in adults and adolescents, whereas 1-3 mL could be administered per site in a smaller child. Peak serum concentrations are achieved within 2-3 days. **HNIG should not be given by any other route**.

Uses

- Hepatitis A prophylaxis[2,4]

  HNIG could be used as both pre-exposure and post-exposure prophylaxis.

  HNIG alone is used for,

  - infants younger than 12 months for post-exposure prophylaxis and younger than 6 months for pre-exposure prophylaxis
  - individuals in whom the vaccine is contraindicated (life-threatening allergic reaction to a previous dose of hepatitis A vaccine, or allergy to any vaccine component)

For persons older than 40 years, immunocompromised patients of all ages and patients with chronic liver disease or other chronic medical conditions, HNIG may be administered as pre or post-exposure prophylaxis in addition to hepatitis A vaccine depending on the risk assessment. For travellers, HNIG is considered for pre-exposure prophylaxis if the travel is in <2 weeks' time.

Although effectiveness is greater when administered soon after exposure, HNIG could be given up to 2 weeks. A single dose of 0.1 mg/kg usually offers protection for a month and longer duration of protection requires higher doses or repeated doses.

This product is not available in Sri Lanka at present. (refer Chapter 10 Hepatitis A vaccine)

- Measles prophylaxis[3,5,6]

  HNIG could be used following exposure to measles in infants less than 6 months of age and infants aged 6-8 months with household exposure. It could also be used in mild to moderately immuno-compromised children with HIV who lack immunity to measles virus. Use is limited by the body weight as maximum dose recommended per person is 15 mL and higher doses are needed for patients who weigh >30 kg. Although it can be administered up to 6 days following exposure, effectiveness is higher when carried out within the first 72 hours. Infants aged 6-8 months who have exposures to non-household contacts may be managed with the MMR vaccine rather than HNIG.

  Children who received HNIG should subsequently receive the MMR vaccine, provided there is no contraindication for live vaccines. Vaccination should not be carried out earlier than 5 months following HNIG.

- Rubella prophylaxis[3]

  Usefulness of HNIG in prevention of rubella is uncertain.

Hyperimmune globulins/specific immunoglobulins

This can be either homologous or heterologous[1].

Homologous hyperimmune globulins: this is made from donated plasma of humans with high levels of the specific antibody. It could also contain other antibodies in lesser quantities. Hyperimmune globulins are used for postexposure prophylaxis for several diseases, including hepatitis B, rabies, tetanus and varicella.

- Hepatitis B immunoglobulin (HBIG)

  HBIG is prepared from the plasma of donors with high concentrations of hepatitis B antibody. It is used mainly to augment protection until a response to vaccination is achieved. For non-responders, HBIG is the primary means of protection following exposure. It is administered intramuscularly and protection generally lasts 3-6 months[7]. (refer Chapter 11 Hepatitis B vaccine)

- Rabies immunoglobulin – (refer Chapter 19 Rabies vaccine)

- Tetanus immunoglobulin (TIG)

  TIG should be considered in individuals, who have incomplete vaccination or unknown vaccine status, presenting with[8],

  - wounds contaminated with dirt, faeces, soil or saliva
  - puncture wounds
  - avulsions
  - wounds resulting from missiles, crush injuries, burns or frostbite

  Tetanus toxoid or tetanus toxoid containing vaccine should be commenced at the same time at another site using a separate syringe. Persons with HIV infection or severe immunodeficiency who have tetanus-prone wounds should also receive TIG, regardless of their history of tetanus immunizations. TIG is administered intramuscularly at a dose of 250 IU[3]. The circulating half-life of TIG is approximately 28 days.

  TIG could be used in treatment of tetanus as well. A single IM dose of 500 IU is recommended by experts[3]. However, an optimal therapeutic dose has not been established and doses ranging from 3,000-6,000 IU have been used[3]. Infiltration of part of the dose locally around the wound is recommended, although the efficacy of this approach is uncertain.

- Varicella zoster immunoglobulin (VZIG)

  The decision to administer VZIG depends on 3 factors[2,9,10],

  - likelihood that the exposed person has no evidence of immunity to varicella

- probability of an infection following exposure
- likelihood of complications of varicella in the individual

In chickenpox, the infectious period is usually from 48 hours before until all the lesions have crusted. Whereas in zoster, it is from the onset of rash until all the lesions have crusted.

Indications for VZIG following a significant exposure:

- children with congenital or acquired immunodeficiency (E.g. leukaemia, lymphoma and other malignant neoplasms affecting the bone marrow or lymphatic system, receiving high-level immunosuppression, HIV, haematopoietic stem cell transplant recipients). Individuals receiving regular IVIG do not require VZIG, if the last dose was given within 3 weeks
- newborn of a mother who had chickenpox (not zoster) within 5 days before or within 48 hours after delivery
- preterm infants born at <28 week of gestation or <1000g birthweight, less than 4 weeks of age who lack evidence of immunity to varicella (found to be VZV antibody-negative by a qualitative assay or <150 mIU/mL by a quantitative assay)
- pregnant women who do not have a history of chickenpox and are varicella IgG negative. VZIG should only be offered if the person is unable to take oral antivirals due to malabsorption or renal toxicity
- neonates exposed to chickenpox or zoster in the first 7 days of life from a person other than the mother, if the mother lacks immunity to varicella

VZIG should be given as early as possible within 10 days, according to the manufacturer's instruction.

Any person who receives VZIG and does not develop the infection, should receive varicella vaccine subsequently, provided there are no contraindications for live vaccines. Immunization should be delayed until 5 months after VZIG.

Heterologous hyperimmune globulin: this is also known as antitoxin, is produced in animals and contains antibodies to only a single type of antigen. Serum sickness could occur in the recipients due to the presence of animal proteins in the product[1].

- Rabies immunoglobulin/ ERIG — (refer Chapter 19 Rabies vaccine)
- Botulism antitoxin

Equine derived heptavalent botulism antitoxin contains antitoxin to all 7 types (A-G) of the toxin. It could be used to treat paediatric and adult botulism[2]. Since botulinum neurotoxin is internalized in the nerve endings, antitoxin does not reverse paralysis. However, early administration ideally within 24 hours, ends the toxaemia and stops further uptake. As a result, disease progression is arrested and duration of dependence on mechanical ventilation decreases[3].

- Diphtheria antitoxin

As patients with pharyngeal or laryngeal diphtheria could deteriorate rapidly, a single dose of equine antitoxin could be administered on clinical suspicion. Intravenous route is preferred for rapid action. Hypersensitivity reactions could occur in about 5-20% of the recipients. However, once universally recommended skin prick testing prior to infusion is no longer recommended[11]. The standard adult dose is one vial, whereas the paediatric dose is based on weight[11]. Antitoxin probably is of no value in cutaneous disease[3].

Intravenous immunoglobulin (IVIG)

Similar to HNIG, IVIG is extracted from pooled plasma of 1,000 to 60,000 qualified adult donors. Approximately 95% of the final product contains IgG with trace amounts of IgA and IgM. Final concentration of IgG could vary from 3-12% (300-1,200 mg/mL) depending on the product[2,3]. All IVIG products must have a minimum concentration of antibodies to measles virus, *Corynebacterium diphtheriae* toxoid, poliovirus and hepatitis B virus. However, antibody concentration against other pathogens vary between products and lots of the same product[2].

Uses

- Replacement therapy in primary or secondary immunodeficiency
- Measles post-exposure prophylaxis[5,6]

  IVIG could be used for prevention of measles in immunocompromised patients, following exposure. It could also be used when HNIG is not available or when the dose required is difficult to be administered intramuscularly (for >30 kg body weight).

  Patients who have received a HSCT within the past 12 months and patients with severe primary immunodeficiency needs to be provided IVIG as soon as possible after exposure, ideally within 72 hours. However, patients on regular IVIG therapy generally do not require additional doses if they have received the most recent dose within 3 weeks of the exposure.

  Patients who have the following conditions require IVIG in the absence of a documented **positive measles IgG test since diagnosis or treatment end or found to be IgG positive within 72 hours of exposure**,

  - Patients on or after completion of immunosuppressive chemotherapy for acute lymphoblastic leukaemia (ALL)
  - Patients with lymphoproliferative disorders
  - Patients who have received a solid organ transplant
  - Patients more than 12 months after receiving a haematopoietic stem cell transplant (HSCT)
  - Patients receiving or within 6 months of completing biological therapies (E.g. monoclonal antibodies such as alemtuzumab and rituximab, cytokine inhibitors such as etanercept) alone or in combination with steroids
  - Patients with a diagnosis of acquired immunodeficiency syndrome (AIDs).

All other immunocompromised patients who have a positive measles IgG test at any time, either prior to or since diagnosis or treatment or at

the time of exposure do not require IVIG. In the absence of a IgG test an assessment of susceptibility needs to be undertaken based on the individual's age, history of measles infection and vaccine status in order to determine the need for IVIG.

Although the effectiveness is higher following administration within the first 72 hours following exposure, IVIG could be given up to 6 days. A single dose of 150 mg/kg is considered adequate to achieve a minimum protective dose of approximately 11 IU/kg measles antibody[5]. Where a second exposure occurs more than 3 weeks after a first dose of immunoglobulin, a further dose of immunoglobulin need to be considered.

Individuals who receive IVIG should subsequently receive MMR vaccine, provided there are no contraindications for live vaccines. Interval between IVIG and MMR vaccine should be more than 6 months. For those who were pregnant at the time of IVIG, MMR should be given following delivery maintaining a minimum interval of 5 months between IVIG and MMR vaccine.

- Tetanus

  IVIG could be given at a dose of 200-400 mg/kg for treatment of tetanus when hyperimmune globulin is not available[2]. However, there may be lot-to-lot variation in antitetanus antibody concentration in IVIG.

- Toxic shock syndrome[3]

  Use of IVIG early in the clinical course as an adjunct to antimicrobials may be beneficial in patients with severe staphylococcal and streptococcal toxic shock syndrome and necrotizing fasciitis.

  - IVIG should be strongly considered as adjunctive therapy for streptococcal toxic shock syndrome or necrotizing fasciitis if the patient is moderately to severely ill, although its use is supported by limited data. IVIG 1 g/kg on day 1 followed by 0.5 g/kg on 1-2 subsequent days has been used. However, the optimal regimen is unknown[2]
  - Staphylococcal toxic shock syndrome – Data on the usefulness is limited. It could be useful in critically ill children with shock who

are unresponsive to fluid resuscitation, presence of an undrainable focus, persistent oliguria with pulmonary oedema. Although the optimal regimen is unknown, 150-400 mg/kg per day for 5 days or a single dose of 1-2 g/kg has been used[3]

- Varicella zoster

  A single 400 mg/kg dose of IVIG could be used in indicated individuals (see indications for VZIG) with bleeding disorders who cannot be given an intramuscular injection, cannot receive antivirals or when VZIG is not available[9]. However, IVIG is not routinely tested for varicella antibodies and the effectiveness in post-exposure prophylaxis is uncertain[3].

Subcutaneous immunoglobulin (SCIG)

Immunoglobulin for subcutaneous administration is also available. However, the use is limited to replacement therapy in primary and secondary immunodeficiencies, as slower absorption and lower bioavailability is inadequate for prophylactic or therapeutic use in acute infections[1].

Monoclonal antibodies (mAb)

Monoclonal antibodies are derived from a single type/clone of antibody producing cells. Therefore, it is specific to a single antigen or closely related group of antigens. A humanized monoclonal antibody product known as palivizumab is available for the prevention of respiratory syncytial virus (RSV) infection. It is given intramuscularly, as prophylaxis during the RSV season to children who are at a higher risk of severe disease such as preterm infants born before 29 weeks of gestation; infants born with certain congenital heart defects; and certain infants with chronic lung disease of prematurity or haemodynamically significant heart disease[2]. Unlike other immunoglobulins used for passive immunity, palivizumab contains antibody only to RSV and will not interfere with the response to live virus vaccines[1,2]. It is administered intramuscularly at a dose of 15 mg/kg, once every 30 days. Children who qualify for palivizumab prophylaxis should receive the first dose at the onset of the RSV season.

Adverse effects[3]

- HNIG
  - Pain and discomfort at the site of administration is common. This could be lessened if the product is at room temperature at the time of use[3].
  - Less frequently, flushing, headache, nausea and vomiting may occur.
- IVIG
  - Flushing, headache, nausea and vomiting could occur in as many as 25% of patients. It is often related to the rate of IVIG infusion.
  - Patients with selective IgA deficiency may develop anaphylaxis as a result of immune response to trace amounts of IgA in the product.
  - Other potentially life threatening reactions are thrombosis, isoimmune haemolysis, renal insufficiency and failure, aseptic meningitis, non-cardiogenic pulmonary oedema and transfusion related lung injuries.
- SCIG
  - Most common adverse effects are infusion-site reactions, including local swelling, redness, itching, soreness, induration, and local heat, both mild and severe systemic reactions are substantially less frequent with SCIG.
  - Commonest systemic reaction is headaches.

Precautions[3]

- Immunoglobulins should be administered cautiously to individuals with a past history of adverse reactions to the same product. Some experts recommend administering a test dose of 1-10% of the intended dose prior to the full dose.
- Although systemic reactions are rare, administration should be carried out in units with resuscitation facilities and with healthcare professionals who have training in emergency care.

- The intramuscular route should not be used in individuals with thrombocytopenia and coagulation disorders.

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CHAPTER 36
ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI)

Immunization is considered as one of the most cost-effective public health interventions for protecting the individual and the public from vaccine-preventable diseases (VPDs). Immunization has saved millions of lives globally. Modern vaccines used in the national immunization programmes are safe and effective.

Vaccines are biological substances that are administered to individuals to elicit immunity (protection) against specific diseases. Such products are formulated together with adjuvants and/or excipients, and like all medicinal products, may cause adverse events following their administration to some individuals. Despite the fact that such adverse events following immunization (AEFI) are mostly mild and very rarely severe, measures need to be put in place to monitor and prevent their occurrence, taking appropriate regulatory action(s) on the products themselves[1].

In the majority of serious cases, these events are mere coincidences. In others, these are caused by the vaccine or by an error in the process of administration or handling of the vaccine. Most of the time, there is no causal relationship between the vaccine and the reported adverse events.

Irrespective of the cause, when AEFI occur, people may lose confidence and refuse further immunization of their children, making them susceptible to VPDs which are more disabling and life-threatening. Surveillance of AEFI, i.e. systematic collection of data on events following immunization, provides valuable information to help, plan and take necessary actions in order to sustain public confidence and ensure the smooth functioning of the programme.

Vaccine pharmacovigilance, which includes surveillance of AEFI, should be part of all immunization programmes, as this helps sustain public confidence in the programme. It facilitates proper management of AEFI and avoids inappropriate responses. In order to increase acceptance of immunization and improve the quality of services, surveillance of AEFI must become an integral part of both public and private sector immunization services in the country[1].

Definition of AEFI

An AEFI is defined as any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, symptom, disease or abnormal laboratory finding. Reported adverse events could either be true adverse events, resulting from the vaccine or immunization process or coincidental events that are not due to the vaccine or immunization process, but are temporally associated with immunization[2]. The five categories of AEFI as defined by the Council for International Organizations of Medical Sciences (CIOMS) and WHO based on the cause are described in Table 1.

Table 1. Cause-specific categorization of adverse events following immunization (CIOMS/WHO, 2012)

Cause-specific type of AEFI	Definition
Vaccine product-related reaction	An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product
Vaccine quality defect-related reaction	An AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product, including its administration device as provided by the manufacturer
Immunization error-related reaction (formerly "programme error")	An AEFI that is caused by inappropriate vaccine handling, prescribing or administration and thus by its nature, is preventable
Immunization anxiety-related reaction	An AEFI arising from anxiety about the immunization
Coincidental event	An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety

Vaccine reactions

Vaccine reactions may be classified into minor reactions which are common and serious reactions which are rare[2]. Most vaccine reactions are minor and subside on their own. Serious reactions are very rare and in general, do not result in death or long-term disability[1].

Minor vaccine reactions

These are caused when the recipient's immune system reacts to antigens or components of the vaccine (E.g. aluminium adjuvant, stabilizers or preservatives). Minor AEFI could be local or systemic. Local reactions include pain, swelling and redness at the injection site. Systemic reactions include fever, irritability and malaise. A safe and good quality vaccine reduces these reactions to a minimum while producing the best possible immunity[1]. The occurrence of minor vaccine reactions is expected and observed with all vaccines. The expected rates of vaccine reactions are available in medical literature[3].

Severe and serious vaccine reactions

They are caused by the body's reaction to a particular component of a vaccine. The term "severe" is used to describe the intensity of a specific event (as in mild, moderate or severe). Severe AEFI could be disabling but is rarely life-threatening. Some examples are seizures, thrombo-cytopaenia, hypotonic hyporesponsive episodes (HHE), inconsolable crying and anaphylaxis.

Severe AEFI are considered serious by definition if they:

- result in death
- are life-threatening
- require hospitalization
- result in prolongation of existing hospitalization
- result in persistent or significant disability/incapacity
- result in a congenital anomaly/birth defect

Vaccine adverse reactions previously unknown or partially known are called 'signals'. All signals need a comprehensive scientific evaluation to establish causality.

Surveillance of AEFI

All AEFI should be reported to the Epidemiology Unit, with copies to MOH and Regional Epidemiologist of the patients' area of residence, irrespective of its being detected by the public or private sector services[4]. Refer to the list of AEFI which need to be notified (Annex 1V).

AEFI may be detected in medical institutions when affected patients seek treatment. The OPD of these institutions, paediatric wards and surgical wards are the potential places to detect AEFI. Therefore, it is important that relevant health workers in both public and private hospitals are made aware of AEFI and the notification process. AEFI notification is the responsibility of a treating clinician. For the reporting of AEFI, the Epidemiology Unit has developed a Notification Form (Annex V, available at www.epid.gov.lk). All healthcare institutions (public and private) and clinicians are expected to use this format to notify[4].

It is important that all AEFI are recorded in the relevant cage of the Child Health Development Record (CHDR) by the treating medical officer/medical specialist and notified to the MOH of the area where the patient resides, with copies to Regional Epidemiologist and Epidemiology Unit using AEFI Notification Form 1 (Annex V).

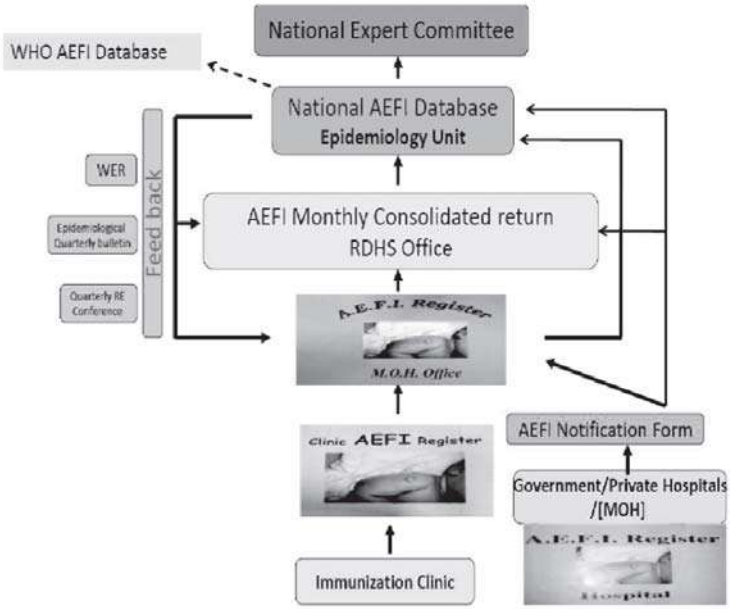

Figure: AEFI surveillance system in Sri Lanka[4]

All suspected AEFI-related deaths need to be notified to the Epidemiology Unit immediately, by the treating clinician or the health care institution by telephone (011 269 5112) or fax (011 269 6583). All deaths suspected to be linked with immunization require a post-mortem investigation performed by the consultant JMO[5].

Anaphylaxis reactions following immunization need to be reported to the Epidemiology Unit with copies to MOH and Regional Epidemiologist of patients' residential area using a separate anaphylaxis reporting form (Annex VI).

All reported serious cases of AEFI should be investigated by the respective MOH. The Epidemiology Unit with the collaboration of the Regional Epidemiologist will investigate all deaths linked to immunization. All AEFI-related deaths and selected serious AEFI will be referred to the National AEFI Expert Committee for causality assessment.

For vaccines used only in the private sector: All AEFI following administration of these vaccines should be reported to the National Medicines Regulatory Authority (NMRA) with copies to MOH and Regional Epidemiologist of the patient's area of residence and to the Epidemiology Unit by the healthcare provider and local agent of the relevant vaccine. Any death following administration of such vaccine should be reported to both NMRA and the Epidemiology Unit, within 24 hours[4].

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CHAPTER 37

MANAGEMENT OF ANAPHYLAXIS FOLLOWING IMMUNIZATION

Introduction

Anaphylaxis is defined by the World Allergy Organization as "a serious systemic hypersensitivity reaction that is usually rapid in onset and may cause death"[1]. It is potentially life threatening. The clinical features lie along a spectrum of severity, from mild objective breathing difficulty (mild wheezing) to circulatory "shock" and/or collapse (anaphylactic "shock")[2]. The incidence of anaphylaxis following immunization is rare, estimated to be 1-10 cases per million doses[3]. The onset is generally within an hour after immunization, but may be delayed for up to 12 hours[3].

Anaphylaxis following immunization is usually due to allergy to excipients. These include egg (yellow fever vaccine), gelatin (usually MMR, varicella, live JE and yellow fever vaccines)[4] and bovine serum albumin (BSA) (MMR, varicella, live JE, rabies vaccines)[5]. Patients with allergy to cow's milk or red meats may be allergic to vaccines containing gelatin or BSA[4,5]. Recently, allergy to galactose-a-1, 3-galactose (alpha-gal), resulting in delayed allergy to red meats, was implicated in allergy to vaccines (MMR and varicella)[6]. Anaphylaxis following administration of the Pfizer-BioNTech SARS-CoV-2 vaccine, reported to be 11.1 cases per million doses, was believed to be due to polyethylene glycol 2000, whereas anaphylaxis to the Astra Zeneca vaccine was thought to be due to polysorbate 80, both of which are excipients[7]. It is also possible that the reactions to the Pfizer BionTech vaccine was due to PEGylated lipid nanoparticles surrounding the mRNA or is non IgE mediated where complement activation related pseudo allergy (CARPA), with IgG or IgM antibody directed against PEG activating complement resulting in the symptoms[8].

Anaphylaxis following routine vaccination is rare but could be fatal[9]. Hence, immunization service providers must be able to recognize the symptoms and signs of anaphylaxis. A fainting attack (vasovagal episode) maybe mistakenly diagnosed as anaphylaxis. The features useful in differentiating a fainting attack from anaphylaxis are given in Table 1[10].

Table 1. Differences between a fainting attack and anaphylaxis[10]

Clinical features	Fainting attack	Anaphylaxis
Timing	Immediate, usually within minutes or during vaccine administration	Usually within 15 minutes, but can occur within hours of vaccine administration
Skin and mucous membranes	Generalised pallor, cold clammy skin	Itching (in children especially forehead, hands and ears), tingling around lips, generalised erythema, urticaria, swelling of lips and face
Respiratory system	Normal respiration; may be shallow, but not laboured	Cough, wheeze, hoarseness, stridor or signs of respiratory distress (E.g. tachypnoea, cyanosis, rib recession) upper airway swelling , (lip tongue, throat, uvula or larynx)
Cardiovascular	Bradycardia, weak/ absent peripheral, pulse strong carotid pulse Hypotension – usually transient and corrects in supine position Loss of consciousness – improves once supine or in head-down position	Tachycardia, weak/absent carotid pulse Rarely, bradycardia following tachycardia Hypotension – sustained and no improvement without specific treatment (Note: in infants and young children, limpness and pallor are signs of hypotension) Loss of consciousness – no improvement once supine or in head-down position

Gastrointestinal	Nausea, vomiting	Abdominal cramps, diarrhoea, nausea and/or vomiting
Central nervous system	Faintness, light headedness relieved by supine posture	Anxiety and distress, loss of consciousness not relieved by supine posture

In adults and older children, the most common immediate adverse event is a vasovagal episode (fainting), either immediately or soon after vaccination. As a precaution, anyone who complains of giddiness or light-headedness before or after vaccination should be advised to lie down until free of symptoms. Sudden loss of consciousness in young children should be presumed to be anaphylaxis, particularly if a strong central pulse is absent. A strong central pulse (E.g. carotid) persists during a faint or convulsion.

Diagnosis

The key to diagnosis involves pattern recognition: *Sudden onset of characteristic symptoms and signs within minutes to hours after exposure to a vaccine*. Clinical criteria for the diagnosis of anaphylaxis are detailed in Figure 1[11]. In infants, anaphylaxis could be difficult to recognise as they cannot describe their symptoms. Some of the signs of anaphylaxis are normal occurrences in babies; for example, flushing and dysphonia after crying, spitting out after feeding and incontinence. Healthy infants have a lower blood pressure and a higher resting heart rate than older children and adults. Therefore, age-appropriate criteria should be used for documenting hypotension and tachycardia[11].

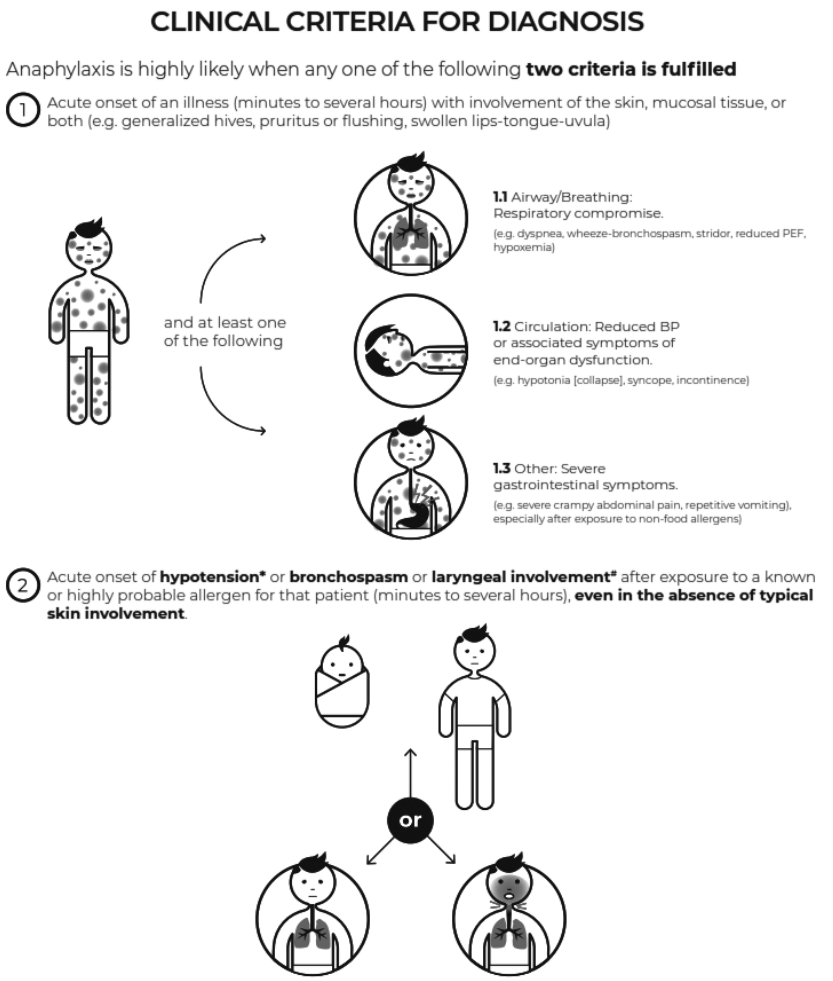

Figure 1[11]. Key criteria to diagnose anaphylaxis (courtesy – World Allergy Organization)

The World Allergy Organization (WAO) has amended diagnostic criteria for anaphylaxis[11].

Anaphylaxis is highly likely when any one of the following 2 criteria are fulfilled:

- Acute onset of an illness (minutes to several hours) with simultaneous involvement of the skin, mucosal tissue, or both (e.g. generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

AND AT LEAST ONE OF THE FOLLOWING:

  - Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
  - Reduced BP or associated symptoms of end-organ dysfunction (e.g. hypotonia [collapse], syncope, incontinence)
  - Severe gastrointestinal symptoms (e.g. severe crampy abdominal pain, repetitive vomiting), especially after exposure to non-food allergens

- Acute onset of hypotension anaphylaxis as a serious life-threatening reaction;
- Or bronchospasm or laryngeal involvement after exposure to a known or highly probable allergen for that patient (minutes to **several** hours), even in the absence of skin involvement.

Systematic approach to treatment of anaphylaxis

If precious minutes are lost early in the treatment of an acute anaphylactic episode subsequent management becomes difficult. The basic initial protocol in any given setting is outlined as steps in Figure 2[12]. After rapid assessment of the patient's circulation, airway, and breathing, treatment should commence promptly and simultaneously.

Positioning the patient

Patients with anaphylaxis should not suddenly sit, stand, walk or be placed in the upright position.

They should be placed in the supine position. Elevation of the feet is controversial. The rationale for the Trendelenberg position was that

elevation of the lower extremities would increase blood flow to central areas, including the heart. However, while in normotensive patients and in the elderly with poor vasomotor control this may not be deleterious and may even theoretically prevent hypotension, in the hypotensive patient there is no improvement in cardiac output, blood pressure or tissue oxygenation. In fact, it may reduce vital capacity and increase the work of breathing in these patients. In keeping with the conflicting evidence, placing the patient in the supine position without elevation of the lower extremities may be the safest option[13].

If the patient is having respiratory difficulty, the patient may be allowed to sit up[13]. Patients who are breathing and unconscious should be placed on their side (recovery position).

Pregnant patients should lie on their left side to prevent caval compression[14].

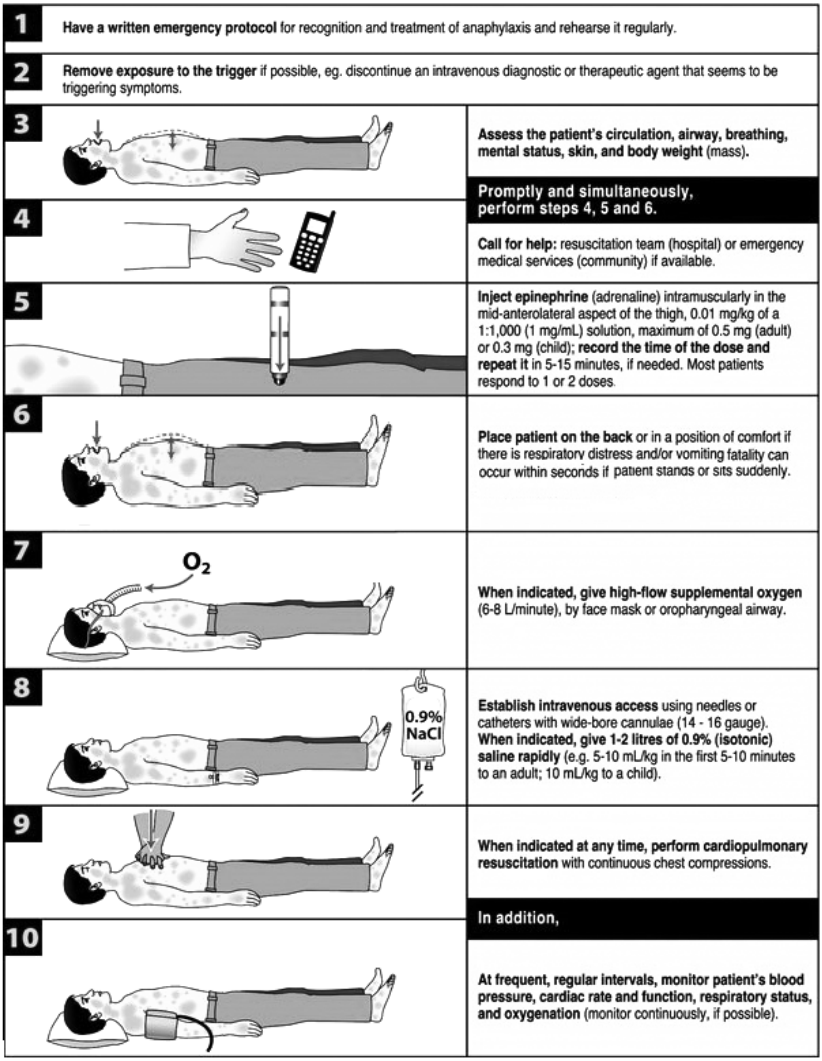

Figure 2[12]. **Immediate steps in managing anaphylaxis (courtesy – World Allergy Organization)**

Note: Cardiopulmonary resuscitation is initiated with continuous chest compressions only (hands-only) before giving rescue breaths. In adults, chest compression should be performed at a rate of 100-120/minute and at a depth of 5-6cm. In children, the rate should be at least 100-compressions/minute at a depth of 5cm (4 cm in infants).

Adrenaline (epinephrine)

INTRAMUSCULAR ADRENALINE is the most important life-saving therapeutic agent in the treatment of anaphylaxis and is the route of choice for most healthcare providers. As initial treatment, adrenaline should not be given via the intravenous (IV) route because of the risk of potentially lethal arrhythmias. In Sri Lanka, adrenaline is mostly under-used or inappropriately administered as bolus doses via the intravenous route which contributes to pulmonary oedema and death.

Table 2 provides details of adrenaline IM dosing according to age and weight[11-17]. There is large inter-individual variability in the response to adrenaline. In clinical practice, it is important to monitor the response and to titrate the dose according to effect. Repeat adrenaline at 5-minute intervals as needed (i.e. if breathing becomes more laboured or level of consciousness decreases). In a field setting, adrenaline may be administered to a maximum of three doses. Alternate right and left thigh or arm sites for repeat doses of adrenaline (to maximize absorption of adrenaline).

DO NOT inject adrenaline directly into an IM immunization site as it dilates blood vessels and speeds absorption of the vaccine (i.e. the offending allergen)[18].

In patients with spontaneous circulation, intravenous adrenaline could cause life-threatening hypertension, tachycardia, arrhythmias, and myocardial ischaemia[14].

Patients who develop anaphylaxis should be transported to the nearest hospital after one /multiple doses of adrenaline and other resuscitation measures, to receive expert help.

The section below on IV adrenaline only applies to those experienced in the use and titration of vasopressors in their normal clinical practice (e.g. anaesthetists, emergency physicians, intensive care doctors). Patients who are given IV adrenaline must be monitored - continuous ECG and pulse oximetry and frequent non-invasive blood pressure measurements as a minimum.

Table 2[11-17]. ADRENALINE in the INITIAL management of acute anaphylaxis

Site, and route of administration	Frequency of administration	Dose (ADULT)	Dose (CHILD)
Adrenaline (epinephrine) **1:1000, IM** to the midpoint of the anterolateral aspect of the middle third of the thigh **immediately** *Use a 25 mm needle and inject at 90° angle to skin. The skin should be stretched and not bunched (very small infants – 16 mm needle very obese adults – 38 mm needle)*	Repeat every 5-15 min as needed until there is resolution of the anaphylaxis or appearance of signs of hyperadrenalism *Note: Persisting or worsening cough associated with pink frothy sputum (sign of pulmonary oedema) is an important sign of hyperadrenalism*	**0.3-0.5 mL** 0.3 - 0.5 mg (300 - 500 µg) • 0.3 ml (0.3 mg) for small adults (30-50 kg) • 0.5 ml (0.5 mg) if weight >50 kg Maximum 0.5 mg (0.5 mL) / dose	**0.01 mL/kg** **0.01 mg/kg** (up to maximum of 0.3 mg (0.3 mL) / dose According to age • <1 year - 0.05 mg • 1-3 years (10-15 kg) – 0.10 - 0.15 mg • 3-5 years (15-20 kg) – 0.15-0.20 mg • 5-7 years (20-25 kg) – 0.20 - 0.25 mg • 7-12 years (25-30kg) – 0.25 - 0.30 mg
Repeat adrenaline at 5-minute intervals as needed (i.e. if breathing becomes more laboured or level of consciousness decreases). In a field setting to a maximum of three doses. Alternate right and left thigh or arm sites for repeat doses of adrenaline (to maximize absorption of adrenaline). **If the offending allergen is a vaccine**; DO NOT inject adrenaline directly into an IM immunization site as it dilates blood vessels and speeds absorption of the vaccine[18].			

IV adrenaline by bolus should be used only if cardiac arrest has occurred and not for any other reason.

FOR SPECIALIST USE ONLY

Table 3[11-17]. Intravenous infusion of adrenaline for life-threatening anaphylaxis-induced hypotension who have failed to respond to several IM doses of adrenaline and intravenous volume replacement

For specialist use only: Ensure patient is monitored
Adrenaline IV (1:10,000 contains 100 µg/mL). ***Never give the undiluted 1:1000 adrenaline concentration IV***.
With an infusion pump: Mix 1mL of 1:1000 adrenaline in 1000 mL of 0.9% saline (1 µg/mL) Start infusion at 0.5 to 1 mL/kg/minute (approximately 30 to 100 mL/hour in adults) then titrate according to reaction severity • **Moderate severity** Adrenaline 1 mg in 100 mL sodium chloride 0.9% at 0.5 mL/kg/hour (0.08 µg/kg/minute) • **Severe (hypotensive or hypoxic)** Adrenaline 1 mg in 100 mL sodium chloride 0.9% at 1 mL/kg/hour (0.17 µg /kg/minute) **Children** Since, children with life-threatening anaphylaxis usually have bronchospastic reactions, absorption of adrenaline from intramuscular site is very good and it is difficult to assess blood pressure in small children, it is probably safer to avoid IV adrenaline in small children unless the child is treated in an emergency critical care area under specialist supervision.
If you do not have an infusion pump, use a standard giving set. Adrenaline: 1: 1,000, 1 mg in 100 mL sodium chloride 0.9% IV, at approximately 100 mL/hour which is ~1 drop per 2 seconds for an adult for most standard drip sets. Titrate rate up and down according to response and side effects.
• Titrate up or down according to response, aiming for lowest effective infusion rate.

- Wait for 5 to 10 minutes after a change in the infusion rate to assess the response.
- Reduce the rate immediately if signs of adrenaline toxicity (tachycardia, tremor and pallor in association with a normal or raised blood pressure) develop. Persisting or worsening cough associated with pulmonary oedema is an important sign of adrenaline overdose and toxicity.
- As the reaction resolves, an infusion that was previously therapeutic can quickly start to have toxic effects. Therefore, when features of anaphylaxis improve, begin reducing the infusion, aiming for around half the starting rate if possible.
- One hour after the resolution of all symptoms and signs, wean the infusion over another 30 minutes and stop.

Table 4[12]. Potential side-effects and toxic effects of adrenaline

After the usual recommended therapeutic dose and route for anaphylaxis:	**Side effects**: Pallor, tremor, anxiety, palpitations, dizziness, headache; these symptoms indicate that a pharmacologic dose has been injected
With adrenaline in the following scenarios. 1. Overly rapid intravenous infusion 2. Repeated intravenous bolus doses 3. Dosing error (commonest error is using 1:1000 strength meant for IM injection for IV administration)	**Toxic effects**: Pulmonary oedema ventricular arrhythmias, hypertension, Prolonged use can result in severe metabolic acidosis (because of elevated blood concentrations of lactic acid), renal necrosis and tachyphylaxis. Acute coronary syndromes called "Kounis syndrome" (angina, myocardial infarction, arrhythmias) can also occur in untreated anaphylaxis in patients with known coronary

	artery disease, in those in whom subclinical coronary artery disease is unmasked, and even in patients (including children) without coronary artery disease in whom the symptoms are due to transient vasospasm

Note: Reasons for apparent lack of response to adrenaline:

Error in diagnosis, patient suddenly stands or sits (or is placed in the upright position) after adrenaline injection; rapid progression of anaphylaxis; patient taking a beta-adrenergic blocker, ACE inhibitor or other medication that interferes with adrenaline effect; adrenaline injected too late; dose too low on mg/kg basis; adrenaline is past expiry date; not enough injection force used; route or injection site not optimal.

Store adrenaline at less than 25°C and protect from light

Oxygen (give as soon as available)

Initially, give the highest concentration of oxygen possible using a mask with an oxygen reservoir. Ensure high flow oxygen (usually greater than 10 litres min-1) to prevent collapse of the reservoir during inspiration. If the patient's trachea is intubated, ventilate the lungs with high concentration oxygen using a self-inflating bag. Continuous monitoring of oxygenation by pulse oximetry is desirable.

Supplemental oxygen should be administered by face mask or by oropharyngeal airway at a flow rate of 6-8 L/min to (1) all patients with respiratory distress, (2) those receiving repeated doses of adrenaline or (3) presence of concomitant asthma, other chronic respiratory disease, or cardiovascular disease.

Fluids (give as soon as available)

During anaphylaxis, large volumes of fluids leave the patient's circulation and enter the interstitial tissue; therefore, rapid intravenous infusion of

0.9% isotonic saline (normal saline) should be commenced as soon as the need for it is recognized. Give 1-2 litres of 0.9% saline rapidly: 5-10mL / kg in the first 5-10 minutes to an adult, or 10mL/kg to a child. The rate of administration should be titrated according to the blood pressure, cardiac rate and function and urine output. All patients receiving such treatment should be monitored for volume overload.

Antihistamines

Antihistamines are no longer considered drugs of choice in the initial treatment of anaphylaxis because they do not relieve life threatening respiratory symptoms or shock. Concerns are about:

- Slow onset of action relative to adrenaline
- Potential harmful effects on the central nervous system such as somnolence and impairment of cognitive function mainly with first generation H_1-antihistamines and
- Lack of supporting evidence from randomized controlled trials[11-17]

  Although the evidence to support their use is weak, there are pharmacologically logical reasons for them. Antihistamines (H_1-antihistamine) may help counter histamine-mediated vasodilation and bronchoconstriction and have the virtue of safety. It should be used only after patient is stabilised with adrenaline and fluids. H_2-antihistamines are recommended in only a few anaphylaxis guidelines[13] as the evidence from randomized placebo-controlled trials is not strong. H_2-antihistamine, administered concurrently with an H_1-antihistamine, may potentially contribute to decrease in flushing, headache, and other symptoms, See Table 5 for dosing schedule.

Note:

- Sedating antihistamines IV or oral are best avoided as side effects (drowsiness or lethargy) may mimic some signs of anaphylaxis.
- Injectable promethazine should not be used in anaphylaxis as it can worsen hypotension and cause tissue necrosis[17].

Corticosteroids

The benefit of corticosteroids in anaphylaxis is unproven[11-17]. The latest guidelines suggest against administering glucocorticoids or antihistamines as an intervention to prevent biphasic anaphylaxis[19].While the use of steroids was believed to reduce protracted anaphylaxis or late phase reactions, a recent systematic review and meta-analysis concluded that steroid use did not affect the likelihood of a late phase reaction[20]. They may be helpful for asthmatics and could be used as adjuncts[17]. The onset of action takes several hours. It should not be used instead of adrenaline[11-17]. It is given only after the patient's condition is stabilized with adrenaline and fluids. For the dosing schedule see Table 5.

Beta-2 adrenergic agonists

Selective beta-2 adrenergic agonists such as salbutamol or terbutaline are sometimes given in anaphylaxis as additional treatment for wheezing, coughing, and shortness of breath not relieved by epinephrine. But never substitute these medications for adrenaline because they have minimal alpha-1 adrenergic agonist vasoconstrictor effects and do not prevent or relieve laryngeal oedema and upper airway obstruction, hypotension, or shock.

Table 5. Pharmacologic treatment once patient's condition is stabilized with adrenaline and fluids[14 - 17]

Drug	Route of administration	Dose (adult)	Dose (child)
Cetirizine	Single daily dose by mouth	10mg	• 6 m - 2 yrs: 2.5 mg • 2-5 yrs: 2.5-5 mg • >5 yrs: 5-10 mg
Chlorphenamine	IV infusion	10mg	• <6m: 250 µg/Kg • >6 m to 6 yrs: 2.5 mg • 6-12 yrs: 5 mg

Hydrocortisone	Administer IM or IV slowly Repeat every 6 h as needed	Above >12 years: 200 mg Follow up with prednisolone 50 mg orally daily for 4 days	2 mg/kg every 6 hours • <6 m: 25 mg • 6 m-6 yrs: 50 mg • 6-12 yrs: 100 mg Follow up with prednisolone 1 mg/kg up to a maximum of 50 mg orally daily for 4 days
Methyl-prednisolone	IV Every 6 h as required	50-100 mg	1 mg/kg IV (max 50 mg)
Ranitidine	IV or oral Every 8 h	50 mg	1 mg/kg (max 50 mg)
Salbutamol	Via nebulizer or metered dose inhaler (MDI) (for respiratory symptoms) Every 20 min or continuous	5 mg by nebuliser, driven by oxygen at least 8 L/minute), or continuous actuations of MDI 8-12 puffs of 100 mcg of salbutamol	5-10 puffs using MDI or 2.5-5 mg by nebulization
Adrenaline (1:1000) (for upper respiratory tract symptoms such as stridor)	Nebulization every 20 minutes to 1 hour	Up to 5 mL (5 mg)	Up to 5 mL (5 mg)

Observation and discharge from hospital

Patients who have had a suspected anaphylactic reaction (i.e. an airway, breathing or circulation (ABC) problem) should be treated and then

observed for at least 6-8 hours in a hospital with facilities for treating life-threatening ABC problems. They should be reviewed by a consultant and a decision made about the need for further treatment or a longer period of observation.

Patients with a good response to initial treatment should be kept under observation for up to 24 hours if they have

- severe reactions with slow onset.
- a history of severe asthma or a severe asthmatic component in the *current* episode.
- there is a possibility of continuing absorption of allergen such as vaccines.
- a previous history of biphasic reactions.
- the anaphylactic episode in the evening or at night.
- difficulty in accessing emergency care in case of deterioration.

Serum tryptase

The specific test to help confirm a diagnosis of an anaphylactic reaction is measurement of mast cell tryptase. Tryptase is the major protein component of mast cell secretory granules. In anaphylaxis, mast cell degranulation leads to markedly increased blood tryptase concentrations. Tryptase levels are useful in the follow-up of suspected anaphylactic reactions. Tryptase concentrations in the blood may not increase significantly until 30 minutes or more after the onset of symptoms, and peak 1-2 hours after onset. The half-life of tryptase is short (approximately 2 hours), and concentrations may be back to normal within 6-8 hours, so timing of any blood samples is very important. Blood samples for measurement of tryptase levels should be collected and sent to the Medical Research Institute, Borella (MRI).

Sample timing

The time of onset of the anaphylactic reaction is the time when symptoms were first noticed. It is important that this time is accurately recorded.

- Minimum: one sample at 1-2 hours after the start of symptoms.

- Ideally: Two timed samples:
    - First sample from 30 minutes to 3 hours (up to 6 hours acceptable) after the start of symptoms.
    - Second sample preferably at 24 hours or in convalescence (for example in a follow up allergy clinic). This provides baseline tryptase levels – some individuals have an elevated baseline level.

Serial samples have better specificity and sensitivity than a single measurement in the confirmation of anaphylaxis.

Sample requirements

- Use a serum or clotted blood sample.
- Record the timing of each sample accurately on the sample bottle and request form. State on the request form the time of onset of the reaction (symptoms). Record on the sample bottle the number of minutes or hours after the onset of symptoms the sample was taken
- As little as 0.5 mL of sample can be enough (children), but 5 mL (adults) is better.
- Optimally, store the serum from spun samples at 40-80°C for up to 48 hours. For longer delays, the serum sample should be stored at –20°C in the local laboratory before dispatch to a reference laboratory.
- For post mortem (PM) specimen, serum tryptase may be assessed if the patient had died within 30 minutes – 6 hours after the onset of anaphylaxis. The PM should have been carried out within 24 hours of death. The sample should be taken from the femoral artery, and processed as mentioned in 4.
- Haemolysed samples will not be accepted.

Notification

It is mandatory that all vaccine associated anaphylaxis be reported to the Epidemiological Unit in the format given as an annex in this book.

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CHAPTER 38

STORAGE AND TRANSPORT OF VACCINES

The control of vaccine-preventable diseases is attributable, in part, to proper storage and handling of vaccines. Vaccines exposed to temperatures outside the recommended ranges can have reduced potency and protection. In addition, there are certain vaccines, which are sensitive to light. Storage and handling errors can cost thousands of rupees in vaccine wastage and need for revaccination. Errors can also result in the loss of patient confidence when repeat doses are required. It is better not to vaccinate than to administer a dose of vaccine that has been stored improperly. Every facility that stores vaccines should have detailed written protocols for routine and emergency vaccine storage and handling. These protocols should be easily accessed by all staff members and should be updated annually.

Vaccines are sensitive to heat and freezing and, therefore, should be stored and transported at the correct temperature from the time they are manufactured until they are used. The system used for keeping and distributing vaccines in the recommended condition is called the **cold chain**.

Heat sensitivity of vaccines[1]

Most sensitive to heat ⟶ Least sensitive to heat

Group A	Group B	Group C	Group D	Group E	Group F
Oral poliovirus (OPV)	Influenza	Inactivated poliovirus (IPV) Japanese encephalitis (live) Measles-mumps-rubella (freeze-dried)	Cholera DTaP-hepatitis B-Hib-IPV (hexavalent) DTwP or DTwP-hepatitis B-Hib (pentavalent) Hib (liquid) Rotavirus (liquid and freeze-dried) Yellow fever (freeze-dried)	Bacillus Calmette-Guérin (BCG) Human papillo-mavirus (HPV) Japanese encepha-litis (Killed) Tetanus, DT, aTd, Tdap	Hepatitis B Hib (freeze-dried) Meningo-coccal A Pneumo-coccal

Freeze sensitive vaccines[1]

DO NOT FREEZE THESE VACCINES

- DTaP-hepatitis B-Hib-IPV (hexavalent)
- DTwP or DTwP-hepatitis B-Hib (pentavalent)
- Hepatitis B (Hep B)
- Hib (liquid)
- Human papillomavirus (HPV)
- Inactivated poliovirus (IPV)
- Influenza
- Pneumococcal
- Rotavirus (liquid and freeze-dried)
- Tetanus, DT, aTd, Tdap
- Cholera

Non-adherence to the recommended cold chain conditions results in reduction of vaccine efficacy leading to vaccine failure. It can also lead to an increased risk of adverse reactions following immunization, particularly after the use of unduly frozen vaccines. Depending on the nature of the product, vaccines can be damaged either by exposure to heat or freezing[1]. With the present distribution system in Sri Lanka, no vaccines should be stored frozen at the facility level. At the national level (long term storage >6 months) it is recommended to store OPV and MMR in -20°C freezer rooms.

Exposure to heat over time can be monitored using vaccine vial monitors (VVM) and the change in colour will guide decisions on the suitability of vaccines for use. During storage and transportation of freeze-sensitive vaccines (eg. DTP, TT, DT, aTd, hepatitis B and Hib) the risk of freezing is greater than the risk of heat exposure.

This chapter provides general guidelines on storage of vaccines. However, manufacturer's product information and package inserts should be referred to, for specific and detailed information about storage and handling of specific vaccines.

Sensitivity to light[1]

Some vaccines are very sensitive to light and lose potency when exposed to it. Such vaccines should always be protected against sunlight or any strong artificial light, and exposure should be minimized. Vaccines that are as sensitive to light as they are to heat include BCG, measles-mumps-rubella. These vaccines are often supplied in dark glass vials that give them some protection from damage due to exposure to light; but they should be kept in their secondary packaging for as long as possible to protect them during storage and transportation.

Storage temperature for vaccines[2]

Ice-lined refrigerators are specially designed for vaccine storage. Domestic refrigerators are not recommended as they do not have good temperature control and cannot keep vaccines cool during power failures of more than one to two hours[1].

A vaccine storage unit should be placed in a well-ventilated room with space around the sides and top and at least 4 inches between the unit and a wall.

All inactivated vaccines require refrigerator storage temperatures between 2-8°C, with a desired average temperature of 5°C. An open vial of oral polio vaccine could be kept at 2-8°C for a maximum period of four weeks (28 days). Storage of oral polio vaccine for a longer duration (>6 months) should be in a freezer compartment. Store frozen vaccines (varicella, MMR) in a freezer between -50°C and -15°C (-20°C is recommended).

Storage and transport of RNA vaccines

BioNTech/Pfizer COVID-19 vaccine requires storage at – 80°C with a shelf life up to 12 months, whereas the Moderna COVID-19 vaccine requires storage at -20°C with the same shelf life. Special packaging with dry ice (-78.5°C) is used for the BioNTech/Pfizer vaccine during transport. Both unopened Pfizer and Moderna COVID-19 vaccine vials can be stored for up to 1 month at 2-8°C.

Storage of vaccines in a refrigerator: (Fig. 1)

- The temperature of the refrigerator should be allowed to stabilize prior to storing vaccines. New refrigerators need 2 or more days of operation to establish a stable optimal operating temperature prior to storage of vaccines.
- The temperature of the main compartment of the refrigerator should range between 2-8°C.
- Every vaccine-containing refrigerator should have a calibrated thermometer and an electronic temperature monitoring device for monitoring temperature twice a day.
- If, at any time, it is discovered that stored vaccines have been exposed to temperatures outside the recommended ranges, these vaccines should remain properly stored – but segregated and marked “Do NOT Use” until guidance can be obtained.

- Do not keep vaccines with VVMs that have reached, or are beyond, their discard point. Do not keep reconstituted vaccines for more than six hours, or after the end of an immunization session. Discard all these items immediately.
- All vaccine storage refrigerators should have generator backup. Ideally, the generator should be automatic.
- In case of a power failure, do not open the refrigerator. Take immediate steps to restore power.
- Ice-lined refrigerators could maintain the required temperature for up to 24 hours if door is kept unopened. However, the domestic refrigerators cannot maintain the temperature for over eight hours. If these time periods are to be exceeded, take measures to transfer the vaccines to another storage facility.
- Multi-socket outlets should not be used for connecting the refrigerator to a power supply, because of the danger of being accidentally disconnected. Alternatively, plug guards or safety-lock plugs could be used to prevent the refrigerator from being inadvertently unplugged.
- Combination freezer/refrigerator units with one exterior door are not recommended for storage of vaccines as the risk of freezing of vaccines is high[3]. If this type of refrigerator is used, the vaccines that are sensitive to freezing should not be stored on the shelf immediately below the freezer compartment and should be kept away from the sides and bottom of the refrigerator where freezing could occur.
- The refrigerator door shelves should not be used for storing vaccines
- Do not store expired vaccines in the refrigerator.
- Food, drinks and other medications should not be stored in the refrigerator used for storing vaccines.
- Vaccines with names that sound alike or look alike should not be stored next to each other, e.g. DTaP and Tdap.

- Store frozen ice-packs in the freezer compartment to be used during transport of vaccines.
- Place water bottles where vaccines are not stored, such as the door, top shelf, and on the floor of the storage unit to stabilize the temperature of the unit.
- The door of the refrigerator should not be opened frequently.
- The refrigerator should not be packed solid and leave plenty of space so that air can circulate freely around vaccines and diluents.

Open vial policy[3]

Opened multi-dose vials of liquid vaccines from which one or more doses have been removed, using standard sterile procedures, may be used within **28 days**, *if all of the following conditions are met:*

- The expiry date has not passed; **and**
- The vaccine is approved for use for up to 28 days after opening the vial, **and**
- Vials have been stored under appropriate cold chain conditions; **and**
- The VVM on the vial, if attached, has not reached the discard point.

Keep opened multi-dose vials of OPV, DPT, TT, DT, aTd, IPV, hepatitis B and liquid formulations of Hib that meet the conditions above, in a special box in the main section of the refrigerator, so that you remember to use them first in the next session (Figure 1).

Discard opened vials of any vaccine (including single dose and multi dose, liquid and freeze dried) immediately, if any of the following conditions apply:

- Sterile procedures have not been followed when handling the vaccine vials
- If there is evidence of contamination, such as floating particles in the vaccine
- When you suspect that the vaccine has been contaminated.

Note:

- Liquid vaccines to which the statement above applies include bOPV, DPT, TT, DT, aTd, IPV, hepatitis B, and liquid formulations of Hib.
- Freeze-dried vaccines, which include BCG, MMR, yellow fever and freeze dried formulations of Hib, must be discarded six hours after reconstitution or at the end of the immunization session whichever comes earlier. Open vial policy is not applicable for freeze dried vaccines.

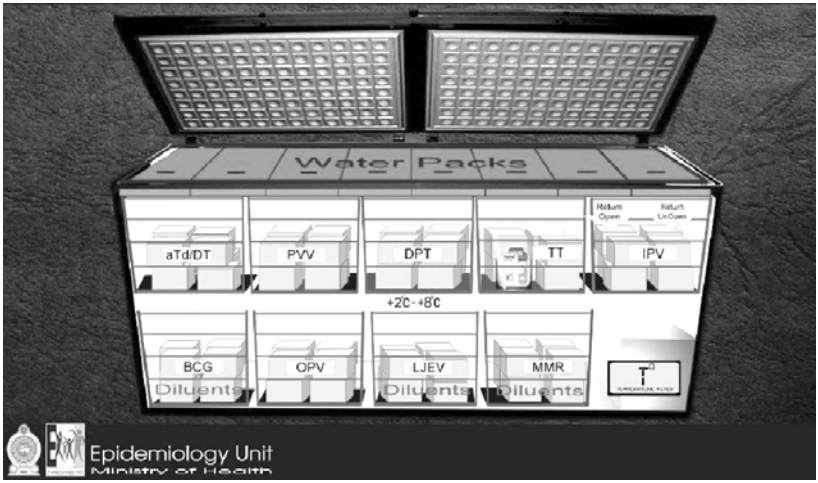

Figure 1. Storage of vaccines in a refrigerator[1]

Diluent

Diluent vials must **NEVER** be frozen. If the manufacturer supplies a freeze-dried vaccine packed with its diluent, ALWAYS store the product between 2-8°C. Only the diluent supplied by the manufacturer should be used for reconstitution of the index freeze-dried vaccines[1].

Temperature monitoring systems

Regular temperature monitoring is vital for proper cold chain management. A calibrated temperature monitoring device, preferably

with a buffered probe, should be placed as close as possible to vaccines. The temperature should be monitored twice daily in the morning and before leaving at the end of the day. Post a temperature log on each storage unit door or nearby in a readily accessible and visible location. Data of electronic temperature monitoring device need to be monitored regularly. If the temperature of the refrigerator is below 2°C or above 8°C, immediate corrective action should be taken.

Thermometers (Figure 2)

Use only calibrated thermometers with a Certificate of Traceability and Calibration. Calibration of thermometers is carried out at the Sri Lanka Standards Institute (SLSI) and the Industrial Technology Institute (ITI) in Colombo. Dial thermometers are no longer recommended by the WHO because they lose their calibration over time, especially if they are dropped.

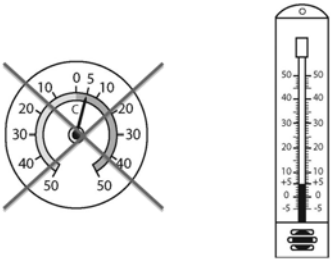

Figure 2. Dial thermometer and stem thermometer

Electronic temperature monitoring devices (Figure 3)

Digital electronic temperature monitoring device is the recommended method for temperature monitoring. It should have the following features. A digital display easily readable from outside the unit; a detachable probe in a buffered material, which more closely reflects vaccine temperatures rather than air temperature in the unit; an alarm for out-of-range temperatures; current and minimum and maximum temperature accuracy within +/- 0.5°C; a low battery indicator; memory that stores 30-60 day readings. The probe should be placed in the centre of the storage unit[2].

Electronic temperature monitoring devices are electronic, automatic, continuous, temperature monitoring devices which provide assurance of temperature maintenance during transport and in refrigerators. They are useful when there is no person to monitor temperature. One of the primary benefits of using electronic temperature monitoring devices is the ability to automatically collect data on changes in temperature on a 24-hour basis. They measure the temperature using sensors and are generally small, battery powered and portable. They are equipped with a microprocessor and an internal memory for data storage. Some electronic temperature monitoring devices utilize software to access and analyse the stored data using a computer, while others have a local interface device (keypad, LCD) where the data is displayed. In more advanced types, the data can be stored even up to 120 days. However, it is recommended that twice daily manual temperature recording be continued, irrespective of the use of electronic temperature monitoring devices, due to reported failures in electronic monitoring systems.

Figure 3. Electronic temperature monitoring device

These devices are placed with the vaccine load in a vaccine refrigerator. They record the refrigerator temperature at no more than 10-minute intervals and show the temperature history for any day in the last 30 days. As long as the temperature has remained within the recommended range, the device displays "OK" or a "✓"symbol. Several types of electronic temperature monitoring devices are prequalified by the WHO and Figure 3 shows an example.

Electronic temperature monitoring device should be placed in an appropriate position where they can be read easily and are unlikely to be damaged. If the refrigerator is used to store vaccines that are not freeze-sensitive, place the device on top of the load, in the warmest part of the refrigerator. If the refrigerator is used to store any freeze-sensitive vaccines, the device should preferably be placed in the coldest part of the refrigerator. This will be the bottom of a basket in chest refrigerators or nearest to the evaporator plate in front-opening models.

All temperature monitoring devices, drift over time, which affects their accuracy. Because of this, temperature monitoring devices should undergo periodic calibration every 1 to 2 years[4].

Cold chain monitoring systems

Vaccine vial monitors (VVM)

VVM is a label fixed to the outer surface of the vaccine vial which contains heat-sensitive material. VVM will measure increases of temperature, but not reductions of temperature. They register cumulative heat exposure over time. The combined effects of time and temperature cause the inner square of the VVM to darken, gradually and irreversibly. A direct relationship exists between the rate of colour change and temperature. The lower the temperature, the slower the colour change and the higher the temperature, the faster the colour change (Figures 4a and 4b).

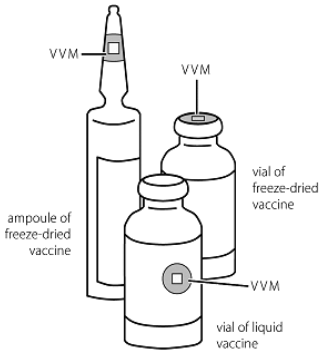

Figure 4a. Location of vaccine vial monitors

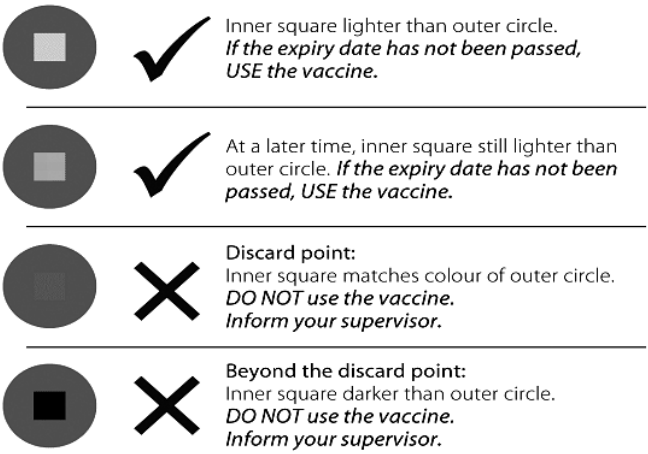

Figure 4b. Interpretation of the vaccine vial monitor[1]

The Freeze-tag™ and Freeze Watch™ which were used as indicators for detecting freezing are no longer used as the currently manufactured electronic temperature monitoring devices could detect both minus and plus temperature ranges.

Shake Test

The shake test is carried out when there is an indication or suspicion of exposure to freezing temperatures. However, in the following instances the vaccine vials should be discarded immediately without subjecting them to a shake test

- When a vaccine vial is found to be frozen
- When a suspect vial cannot produce a homogenous solution after shaking

The "Shake test" is carried out on adsorbed vaccines (eg. DTP, DT, aTd, TT) or liquid vaccines (eg. hepatitis B) suspected as having being exposed to freezing temperatures likely to have damaged them.

The Shake Test procedure*[1]: *(Figure 5)

- Obtain a vial of vaccine of the same batch from the same manufacturer and freeze it to a solid state for at least 10 hrs at -10°C and let it thaw. This is the control vial.
- Choose your test vial from the batch suspected as having been frozen.
- Shake vigorously the test and control vials together in one hand for 10-15 seconds.
- Allow to rest on a table.
- Compare the sedimentation rates of the deliberately frozen control vial with the suspect vial.
- If the test vial has a sedimentation rate similar to or faster than the control vial the batch of vaccines should not be used

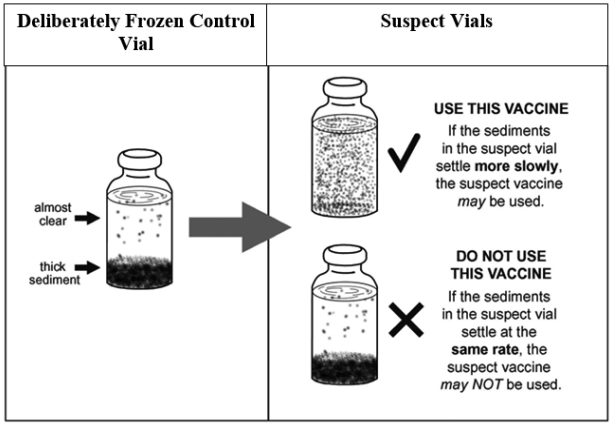

Figure 5. Interpretation of the shake test to determine damage due to freezing of vaccines[2]

Transport of vaccines to outreach health centres

Vaccine carriers (Figure 6) are used for this purpose. They are insulated containers that, when lined with frozen ice-packs (Figure 7), keep

vaccines and diluents cold during transportation. These are also used for temporary storage of vaccines when the refrigerator is being defrosted. Vaccine carriers may not be used for storage of vaccine beyond 12 hours.

Placing adsorbed vaccine vials, such as TT, DTP, and liquid vaccines, such as hepatitis B, in direct contact with ice cubes is not recommended as this could damage the potency of vaccines. The floatation of opened vials on melting ice may also lead to contamination of contents in vials.

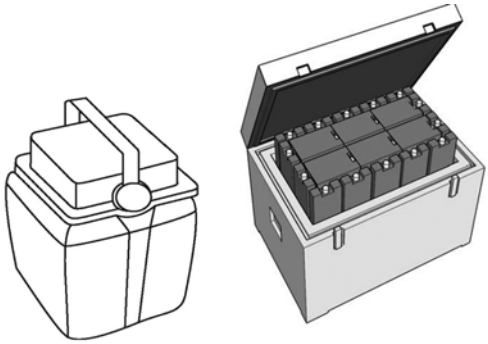

Figure 6. Vaccine carrier

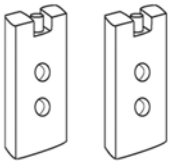

Figure 7. Ice-packs

Procedure for packing the vaccine carrier

- Remove the ice packs from the freezer.
- Wait for ice packs to be "conditioned" i.e. when the ice core of the pack starts moving (approximately 20-30 minutes in warm weather conditions).
- Place the frost-free ice packs around the inside walls of the carrier.
- Place the vaccines and diluents in a plastic container to prevent damage due to condensation.
- Take precautions to prevent vulnerable vaccines from being frozen (by keeping them in their packaging or wrapping a sheet of paper around or placing them in a plastic container).

- Secure the lid tightly.
- During immunization the foam pad supplied with the carrier should be used as a temporary lid to securely hold opened vials, while protecting unopened vials in the cool chamber below.

Freeze-preventive vaccine carriers

Standard vaccine carriers suffer from design limitations that contribute to freezing risks; they do not have built-in partitions or barriers to prevent direct contact between vials and the ice packs. Consequently, the responsibility for avoiding accidental freezing rests entirely with a healthcare worker's adherence to the Standard Operating Procedure (SOP) for *"conditioning frozen ice packs"*. This is risky, as there is always some margin for error. To address transportation-related freezing risks for standard vaccine carriers, WHO prequalified freeze-free carriers are available that would prevent freezing.

Figure 8. Freeze-preventive vaccine carrier

The new freeze-preventive vaccine carrier (FPVC) has an inner liner that contains foam and a thin layer of water as a phase-change material to separate the ice packs from the vaccines (Figure 8). This liner buffers the vaccines from direct exposure to ice packs.

Staff training and education

All personnel who handle or administer vaccines should be trained on storage and handling policies and procedures. Training and education of staff is mandatory when new vaccines are introduced and when there are any changes to the storage and handling guidelines for a particular vaccine.

Emergency plans

Each facility should have a detailed written emergency vaccine retrieval and storage plan in the event of refrigerator and/or freezer malfunctions, during power failures, natural disasters or other emergencies which might compromise appropriate vaccine storage conditions[4].

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CHAPTER 39
VACCINE HESITANCY

Introduction

Success made over the last four decades in improving global coverage of routine childhood immunization through the Expanded Programme of Immunization (EPI) is substantial. Between 1980 and 2018, the coverage of the third dose of diphtheria-tetanus-pertussis vaccine (DTP3) increased from around 25% to 85% globally[1]; similarly, the coverage of the first dose of measles-containing vaccine increased from 18% to 85%[2]. Despite these improvements, trends over the past decade point to a stagnation in global immunization coverage. Resistance to further improvement is largely attributed to a rise in vaccine hesitancy. Recent outbreaks of vaccine-preventable diseases (VPDs) around the globe, including in Europe, United States and Africa, highlights the role of vaccine hesitancy in parents' decision to delay or refuse vaccines for their children[3].

What is vaccine hesitancy?

The World Health Organization's (WHO) Strategic Advisory Group of Experts on Immunization (SAGE) Vaccine Hesitancy Working Group defines vaccine hesitancy as a "delay in acceptance or refusal of vaccines despite the availability of vaccination services"[4].

Vaccine hesitancy is not vaccine denial. It is very unlikely that one could convince the people who are determined not to vaccinate their children. But majority of the parents not seeking vaccination are only hesitant to give vaccines due to many issues related to safety, efficacy, social, religious or cultural reasons. It is this group which comprises a majority of parents that need to be addressed in order to change their minds for vaccination.

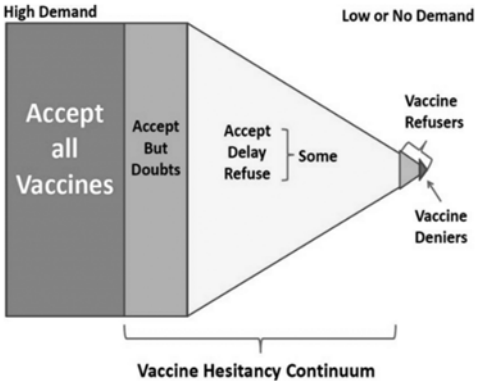

Figure 1. www.who.int/immunization/sage/meetings/2014/october/ SAGE working group revised report vaccine hesitancy

Recognizing the worldwide spread of vaccine hesitancy and its impact on the global immunization programme, in 2019, WHO named vaccine hesitancy as one of the top 10 threats to global health[5].

However, Sri Lanka is blessed with an excellent primary health care system. The national immunization programme, which comes under their purview, has maintained an exceptional track record of over 95% of vaccine coverage for the last three decades for all EPI vaccines. Superficially, vaccine hesitancy appears to be a very inconsequential concern in Sri Lanka with no attention necessary. However, when the hesitancy is powered by digital media platforms linking the global community to our doorsteps, it becomes inevitable that the Sri Lankan public would be infected with doubts about the safety and efficacy of vaccines. The beginning of such a confrontation was highlighted by the appalling response of the public to the appeal made by the government for the COVID-19 booster. This illustrates that vaccine hesitancy does exist in Sri Lanka.

Vaccine hesitancy is complex and context-specific, varying across time, place and type of vaccine. If a severe adverse reaction occurs following a vaccination, the news spreads rapidly across the country. Panic creates vaccine hesitancy among the public at least for a period of time (time

specific vaccine hesitancy). Similarly, vaccine hesitancy following an untoward reaction may be known to the public in and around the vicinity of the incidence (place specific vaccine hesitancy). Some vaccine hesitancy is tied to a specific vaccine, such as hesitancy based on the now-debunked yet persistent belief that the MMR vaccine could cause autism[6].

SAGE has identified important drivers or factors for global vaccine hesitancy. Most of the other causes of vaccine hesitancy could be parcelled in to these three major key drivers, namely Confidence, Complacency and Convenience (Three 'C's).

Confidence

Confidence in vaccine safety and efficacy is crucial. Any doubt about safety matters a lot for parents because vaccines are always given to normal healthy children. Parents do not want their child to suffer from even a trivial reaction. An extremely rare but severe adverse event could paralyse the entire vaccine programme. We have observed this during COVID vaccination. There were concerns about the possible association between the AstraZeneca and Johnson and Johnson vaccines and very rare cerebral venous sinus thrombosis[8]. For most people the benefits of vaccination for COVID vastly outweigh the risk. Yet the public perception was different. Perceptions of vaccine safety and efficacy are the strongest predictors of vaccine uptake and the majority of vaccine-hesitant people cite concerns about safety and side effects.

Vaccine hesitancy could also be triggered by anxiety about the administration of vaccines, including fear of needles[9], or by concern about possible side effects (E.g. concern of adolescent girls who are anxious about potential reactions to HPV vaccination). Other concerns are related to vaccine ingredients, such as thimerosal, which is used as a preservative, or adjuvants that boost the effectiveness of vaccines[10].

Complacency

Complacency is strongly associated with lower vaccine uptake. Low prevalence of certain diseases due to vaccination, may lead to

complacency. Perceptions among some people regarding personal risk and disease severity are low. Some are confident that even if the vaccine is not given, they would not get severe disease. Some believe that vaccination is not deemed a necessary preventative action. Other life and health responsibilities seem more important than vaccination. Some people believe that religious rituals would protect them from disease. Some faithfully believe in alternative medicine or folk remedies to prevent infection than vaccination. Sri Lanka has witnessed similar scenarios during the recent COVID pandemic. With the blessings of politicians and the media, a formula supposed to be given by a goddess became so popular at the peak of the pandemic that it hindered the vaccination drive significantly.

Convenience

Evidence points to the crucial role of well-planned and convenient vaccination delivery, emphasizing the role of an easy-to-reach location. The setup in Sri Lanka for the NIP has addressed this issue, prioritizing the convenience of the public. Other factors affecting convenience include willingness to pay and the financial costs incurred to reach the vaccination centre.

Vaccine hesitancy matrix (VHM)

A VHM was developed by the SAGE Working Group as a tool to assess different reasons for vaccine hesitancy in different countries and regions. VHM categorizes the reasons for hesitancy into "contextual influences," "individual and group influences," and "vaccine- or vaccination-specific issues" that provide a broad framework to understand vaccine hesitancy[4]. Each of these three influences further elaborates on the specific reasons for vaccine hesitancy.

Contextual influences

Contextual influences which include ethnicity, religion, occupation and socioeconomic status are often overlooked. It does not take account of the powerful structural factors such as race and access barriers which

may lead to low vaccine uptake in some groups. European data show lower intention to be vaccinated against COVID-19 among racial and ethnic minorities, those with lower education, younger people and people with previously poor compliance with recommended vaccinations[11]. A study done in Sri Lanka among young people between 18-35 years, has revealed that 55.5% were hesitant to receive the vaccine. The majority (66%) of vaccine hesitancy was in the <30 years' female population. This study also showed that with COVID-19 vaccine, hesitancy had a phasic pattern. The hesitancy for initial doses was only 37% but went up to 59% for booster doses and hesitancy future doses was 60%[12].

Individual and group influences

Individual and group influences are, by far, the most observed reason for vaccine hesitancy. Access to digital media, influence from peers, friends, family members and religious leaders could change an individual's decision to vaccinate.

Vaccine and vaccine related issues

Vaccine and vaccine related issues are also driven through digital media. Vaccine related issues are often specific to individual vaccines. Many observers point to the 1998 Lancet article by Wakefield et al (retracted in 2010) as the source of parental fears that MMR vaccination might cause autism. This was at a time when the search for the cause of increasing incidence of autism was already brewing. The autism vaccine saga is still lingering on, affecting the uptake of MMR vaccine even today. In the United States, however, anxieties were more focused on thimerosal in vaccines as a possible cause of autism[13]. The attention to thimerosal emerged in the context of a larger global movement that emphasized concerns about mercury in food and drugs and in the environment. In 1999, as part of a review of mercury-related ingredients in all food and drugs, the Food and Drug Administration found that the ethyl mercury content of thimerosal containing vaccines is essentially negligible[14] (ethyl mercury is less toxic than methyl mercury found in food such as marine fish). The U.S. Public Health Service and the American Academy of Paediatrics recommended the authorities to

remove thimerosal from childhood vaccines as a precautionary measure, even though there was no evidence of any harm[15]. This resulted in a backlash causing public suspicion resulting in a 38% decrease in thimerosal containing hepatitis B vaccination[16]. Another specific vaccine which has been affected by vaccine hesitancy is HPV vaccine. Among the many reasons for not vaccinating children with HPV, lack of knowledge regarding the disease and the vaccine itself was a major reason in many communities even in countries like US[17]. A descriptive cross-sectional study conducted among male and female adolescents aged 14-16 in selected schools in Sri Lanka showed that, only 30.89% participants had heard of HPV infection. Among them 81.3% had overall poor knowledge regarding HPV infection. Out of all participants, only 30.4% had heard of HPV vaccine[18].

Table. Working Group determinants of VHM

Contextual influences	
Influences arising due to historic, socio-cultural, environmental, health system/institutional, economic or political factors	• Communication and media environment • Influential leaders, immunization program gatekeepers and anti- or pro-vaccination lobbies • Historical influences • Religion/culture/ gender/socio-economic • Politics/policies • Geographic barriers • Perception of the pharmaceutical industry
Individual and group influences	
Influences arising from personal perception of the vaccine or influences of the social/peer environment	• Personal, family and/or community members' experience with vaccination, including pain • Beliefs, attitudes about health and prevention • Knowledge/awareness • Health system and providers – trust and personal experience • Risk/benefit (perceived, heuristic) • Immunization as a social norm vs. not needed/harmful

Vaccine/ vaccination-specific issues	
Directly related to vaccine or vaccination	• Risk/benefit (epidemiological and scientific evidence) • Introduction of a new vaccine or new formulation or a new recommendation for an existing vaccine • Mode of administration • Design of vaccination programme/mode of delivery (E.g. routine programme or mass vaccination campaign) • Reliability and/or source of supply of vaccine and/or vaccination equipment • Vaccination schedule • Costs • The strength of the recommendation and/ or knowledge base and/or attitude of healthcare professionals

Based on the above three primary influences, the SAGE Working Group developed indicators for vaccine hesitancy that were included as part of the global WHO/United Nations Children's Fund (UNICEF) Joint Reporting Form (JRF) to enable and improve monitoring of trends in global vaccine hesitancy in 2014; since then, vaccine hesitancy has been reported by the member countries, annually. From 2014 to 2017, 79-83% of the 194 member states completed the vaccine hesitancy section of JRF each year by reporting one or more vaccine hesitancy reason(s). Out of the hesitancy responses (N=343), 56% were "individual and group influences", 29% were "contextual influences", and 15% were "vaccine- or vaccination-specific issues"[19].

Emerging new drivers for vaccine hesitancy

Vaccine hesitancy is a very sensitive issue. Introduction of new vaccines to the NIP should be done very cautiously taking into consideration its impact on the public. Vaccine hesitancy could result from faulty vaccine implementation. Consequences from the Dengvaxia vaccination

campaign had a substantial negative impact on the NIP in the Philippines, which was considered as a "massive blow" to the nation's vaccination programme. Vaccine confidence plummeted in the Philippines. In 2015, about 82% of the population reported feeling that vaccines were generally safe; this dropped to 21% by 2018. Additionally, vaccination rates dropped in the NIP. For example, measles vaccine coverage was 88% in 2014, but this decreased to approximately 50% in 2019, and the incidence of measles increased 10-20 times higher than before the Dengvaxia controversy[20].

Vaccine hesitancy became a significant barrier in the latter part of the COVID-19 vaccination programme. Globally, there is a general reluctance to administer booster vaccines. The major reason for the global COVID-19 vaccine hesitancy is the confusion resulting from too many vaccines in the market within a short time span. This was due to too much information with varying opinions in an uncertain setting. Even health professionals were confused. General public was skeptical about the entire process of vaccines coming in to the market with the introduction of many brands and types of vaccines showing different efficacy rates against SARS CoV 2 infection. Some vaccines claimed 95% efficacy while others were showing only 50%. Vaccine manufacturing methods were different. Most vaccines were made fast-track to combat the pandemic. Most of the routine protocols were bypassed to make an accelerated process of vaccine manufacture rather than following a closely monitored, thoroughly scrutinized foolproof procedure. Emergence of adverse reactions not described during trials led to doubts among the public regarding vaccines. With the COVID-19 pandemic, myriad of new reasons emanated to fuel vaccine hesitancy.

Communication

Communication has two sides. Delivering information or spreading misinformation. Vaccine hesitancy arose globally as a result of the second overcoming the first.

Vaccine hesitancy has escalated in scope and scale. The high degree of vaccine questioning and reluctance to accept vaccination is amplified

by social media platforms. In addition, the introduction of new vaccines and combinations of vaccines mushrooming during the COVID-19 pandemic, prompts new questions. Consequent searching for freely available information in a landscape of misinformation and disinformation alongside accurate, scientifically based information confused the public.

At the 2020 Munich Security Conference, Director General of WHO, quoted "besides the COVID-19 pandemic, the world is also fighting an 'infodemic' of a few facts, mixed with fear, speculation and rumour which, within the context of ongoing uncertainties and knowledge gaps, has been amplified through technology and social media platforms"[21].

Anti-vaxxers are using modern communication methods more effectively than vaccine advocates. Cherry-picked scientific data, half-truth information and distorted scientific literature are being used by anti-vaccine lobbyists to change the minds of the public effectively and convincingly. A study in Italy investigated YouTube video content between 2007 and 2017 that focused on the suspected link between the MMR vaccine and autism[22]. The study showed that negative videos about the MMR vaccine outnumbered positive ones by a factor of 3, with the negative videos more widely viewed. A number of studies investigating HPV vaccine content on YouTube also showed that negative videos attracted more viewers than positive ones[23]. The major reason for anti-vaxxers to be powerful in social media, is that many of them, genuinely but mistakenly believe that their children are victims of vaccine misadventures and relate their stories in a heartfelt manner in the social media. It is difficult to convince such an emotionally disturbed audience to disbelieve those stories and vaccinate their children. They not only refrain from giving vaccines to their children, but also prevent others receiving vaccines.

Strategies to address vaccine hesitancy

Social media

The most positive and practical approach to address vaccine hesitancy would be to make use of the digital platform to reverse public opinion. A strong positive commitment is necessary from all stakeholders, vaccine champions and advocates. Using parents of children who succumbed

to vaccine preventable diseases through digital platforms to relay their emotional stories could be a promising approach. Social media platforms should exercise more accountability and remove harmful and misinformed content. Instead, social media and other digital platforms could be utilized to provide the opportunity to collect data on vaccine hesitancy in real time and to investigate the effect of vaccine sentiment on actual vaccine uptake and vaccine-preventable diseases. Social media could be used to identify all the key drivers of vaccine hesitancy in a given community.

A web based vaccine drive organized in Malaysia appears to work extremely well. Dedicated vaccine experts in the country gathered together to form this website, Immunise4life, which has now expanded as a network to answer all the questions related to vaccines. Public has easy access with a lot of community support. This is one of the most successful media driven programmes in South East Asia, to combat vaccine hesitancy.

One of the drawbacks in taking such an approach to use digital media and platforms in a significant scale and applying it globally, is the inequity in access to and reach of digital media. However, as the digital revolution unfolds globally reaching every corner, the global health community must keep pace. The consequences of not doing so are loud and clear, as we have seen in the context of the COVID-19 pandemic with regard to the rapid spread of misinformation and consequent vaccine hesitancy.

Role of medical professionals

Physicians and other health care providers are still among the most trusted persons when it comes to health care advice. The Wellcome Global Monitor, surveyed people in 140 countries and found that 73% of the respondents said that they would trust a doctor or a nurse more than others; the percentage was 90% in the higher-income countries[18]. Vaccine acceptance could increase if health care providers offer support and encouragement and listen to what matters from the patient's perspective. It is extremely important to equip physicians with information on the nature and scope of circulating concerns in their communities, to help them address such concerns in the clinic while also enabling appropriate interventions at the community level. The dialogue has to

be genuine and the physician should listen patiently and attentively to their stories before discussing the problem with them. Often parents come with new information and misinformation gathered from social media and hence the physician has to be up to date when counselling such parents.

Imposing laws

Imposing laws, tailoring health benefits or restricting access to schools based on vaccination status has been tried in many countries, especially in Australia, which worsened the situation.

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CHAPTER 40
FREQUENTLY ASKED QUESTIONS

- **In the National Immunization Programme (NIP) of Sri Lanka, numerous vaccines are given routinely and most diseases are well controlled. There are other vaccines available outside the NIP such as rotavirus, chickenpox, hepatitis A, influenza and pneumococcal vaccines. Are they recommended for use?**

  There are many effective vaccines outside the NIP which are recommended for prevention of infections. The decision to vaccinate should be taken in consultation with the health care professional based on the individual's needs.

- **If a child has received only one dose of a course of vaccine, is it necessary to restart the vaccine course?**

  No. The vaccine schedule could be safely continued as if there has been no delay. The recommended intervals between further doses should be maintained. The exception is rabies vaccine where expert advice should be sought.

- **Does natural immunity produce better protection than vaccine induced immunity?**

  Yes. However, although certain viral diseases such as chickenpox produce natural immunity, the disease may cause severe complications, and/or be fatal. In addition, many other diseases do not produce the protective level of immunity even after the natural disease, E.g. tetanus. Vaccination is safer than contracting the disease and re-vaccination could be carried out, if necessary.

- **Is an interval of 4 weeks mandatory between immunization with two different vaccines?**

  This is true regarding injectable live vaccines because the desired antibody response may not be achieved if a second live vaccine is given before four weeks. The above interval between vaccinations is not applicable if both are inactivated or one live and one inactivated type of vaccine is given.

- **There are additional components combined into vaccines, such as tetanus or diphtheria toxoids with meningococcal vaccine (conjugate vaccines) and yellow fever virus with dengue/JE vaccine (chimeric vaccines). Do these vaccines confer immunity to these additional components?**

  No.

- **Why are the DPT, IPV and pentavalent vaccines given in the anterolateral mid-thigh and not the gluteal region?**

  This is done to prevent damage to the sciatic nerve. Moreover, vaccines deposited in the fat of the gluteal region do not invoke the appropriate immune response due to irregular absorption of the vaccine.

- **We encounter situations where some of the vaccines have been administered abroad under different schedules. What would be the more appropriate schedule to continue?**

  Vaccination schedules are based on the disease prevalence in each country. It would be more appropriate to continue with the schedule of the country where the person is going to live. If a person is on holiday, it is not rational to commence on the local schedule or to reschedule his future vaccination. On the other hand, for people who have returned from abroad and are going to live in this country, it would be advisable to have their subsequent vaccinations re-scheduled according to the local schedule. In addition, other vaccines included in the local schedule should be offered such as Japanese encephalitis (JE) vaccine.

- **Students going for overseas studies are recommended a number of vaccines within a short period. Is it safe to give all of them?**

  It is advisable to plan an overseas stay well in advance, enabling adequate time intervals for vaccinations. Please refer to the accelerated schedules under each chapter.

Most vaccines could be given as accelerated schedules. Two or more live vaccines could be administered concurrently at different sites, if the person has to travel within a short period of time.

- **Should vaccination be delayed in low-birth-weight babies?**

  Low birth weight babies should receive BCG vaccine when they are fit to be discharged from the hospital. They should receive their routine vaccinations at the recommended age.

- **What precautions should be taken when vaccinating preterm babies?**

  It is important that preterm infants have their immunizations according to the NIP. Their age should be calculated from the date of birth. Extremely premature babies (≤28 weeks of gestation) should be monitored for 48-72 hours following vaccination, due to the risk of developing apnoea, particularly for those with a history of respiratory immaturity. In such situations, the 2nd month vaccination is recommended to be administered in a hospital where a paediatrician could be consulted for further advice.

- **Which live vaccines are recommended for household and close contacts of an immunocompromised person?**

  MMR, varicella and rotavirus vaccines. The immunocompromised should be protected from these infections but these vaccines cannot be given to them. There is no risk of transmission of the vaccine virus to the immunocompromised if a family member is vaccinated with these vaccines.

  However, OPV is contraindicated as the vaccine virus could be transmitted and could cause vaccine associated paralytic polio (VAPP) in the immunocompromised.

- **What is your advice for a child who has not developed a scar after BCG vaccination?**

  In general, it takes about 10-12 weeks to produce a scar. Absence of a BCG scar is not indicative of a lack of protection. In 10-12 % of vaccinees, scar formation may not take place at all. Therefore,

revaccination is not recommended by WHO[1]. However, the NIP of Sri Lanka recommends that a child between 6 months to 5 years of age should be revaccinated without a TST[2].

- **Is it safe to recommend the COVID-19 vaccine to a person planning a pregnancy?**

  Yes, COVID-19 vaccination is recommended for people who are pregnant, breastfeeding, or planning a pregnancy[3].

- **Why should a pregnant mother be vaccinated against COVID-19?**

  Vaccination prevents severe illness and death in pregnancy. In addition, vaccination of pregnant women has shown that it may not only protect their babies but also minimize hospitalization due to COVID-19 up to the age of 6 months[3].

- **If someone has already developed COVID-19, is it necessary to go ahead with vaccination?**

  Yes. It is important to get the vaccine even if you have already had COVID-19, as the vaccine will provide added protection to the individual. However, it is recommended to delay the COVID-19 vaccination by 3 months from the onset of symptoms or, if someone remained asymptomatic, from the day of the positive test

- **When there is a reaction to DTwP vaccine in the routine NIP schedule, is it better for the patient to go for DTaP vaccine for the next dose or use DT?**

  As the reactogenicity is less with DTaP vaccine, it can be used when there is a reaction to DTwP vaccine. The DT can also be given, as the DTaP is only available in the private sector.

- **Could one interchange different brands of vaccines regarding children who had begun the vaccination with DTwP or DTaP?**

  There is no clinical data to support switching from one type of DTwP to another type of DTwP vaccine and DTaP vaccine within the primary vaccination programme, but there is no contraindication to do so.

However, it is preferable to continue with the same brand unless it is not available or the person develops adverse effects for one brand.

- **Is it possible for an adult to get whooping cough if the full course of DTP vaccination was completed during childhood?**

  Yes. The immunity acquired from immunization is not life-long. Epidemiological evidence suggests that routine immunization of adolescents and adults could significantly result in lowering of the incidence and severity of the disease. Pertussis vaccination for adults (Tdap) may be given at intervals of ten years.

- **What follow up action should be taken if a 12-year-old child was given a tetanus toxoid instead of aTd?**

  A dose of aTd is recommended after 6 months.

- **Is it useful to include a booster dose of Hib vaccine during the 2nd year of life?**

  Several studies have strongly supported the beneficial effects of a Hib booster dose in the second year of life[4,5,6].

- **What is the duration of protection of the Hepatitis A vaccine? Does it provide life-long immunity?**

  One dose of Hepatitis A vaccine will protect the recipient for at least 1 year. A second dose given after 6 to 12 months will usually confer lifelong protection.

- **Is there any reason why hepatitis B vaccine is recommended to diabetic patients?**

  People with diabetes are at increased risk for contracting hepatitis B if they share glucometers, finger prick devices or other diabetes-care equipment such as syringes or insulin pens.

  The best way to prevent hepatitis B is by getting those patients vaccinated. CDC recommends hepatitis B vaccination for all unvaccinated adults with diabetes who are younger than 60 years of age[7].

- **If I do not belong into any risk group, would it be necessary for me to take the hepatitis B vaccine?**

  Studies have demonstrated that nearly 15% of people who get infected with hepatitis B are unable to identify a risk factor for the disease. Therefore, when there is an effective vaccine available it is advisable to use it rather than being unprotected. It also prevents primary hepatocellular carcinoma.

- **If the paediatric hepatitis B vaccine is unavailable in the country, what would be the next available option?**

  A half a dose of adult hepatitis B vaccine could be given.

- **How would you advise a healthcare worker who had had only 2 doses of Hepatitis B vaccine 10 years ago and is requesting to complete the 3rd dose as per overseas employment requirement?**

  The 3rd dose should be given and the antibody titer measured after 1 month. If the antibody titer is <10 mIU/mL a second full series should be given[8].

- **Is it beneficial to give the HPV vaccine to women who are already sexually active?**

  Ideally, HPV immunization should be completed before the onset of sexual activity. However, women who have begun sexual activity will benefit from vaccination if they have not yet become infected with the vaccine preventable HPV serotypes. Vaccination will also prevent re-infection with vaccine specific serotypes. The vaccines are recommended up to the age of 46 years by the manufacturer.

- **Does the HPV vaccine protect against all types of cervical cancers?**

  No. There are two types of vaccines commercially available in Sri Lanka: quadrivalent (oncogenic serotypes 16 and 18 and non-oncogenic 6 and 11) and bivalent (oncogenic serotypes 16 and 18). Serotypes 16 and 18 account for nearly 70% of all cervical cancers. In addition, there is evidence to suggest that the vaccines provide

some cross protection against certain other oncogenic serotypes. In addition, there is a nine-valent HPV vaccine (oncogenic serotypes 6, 11, 16, 18, 31, 33, 45, 52, 58) providing high and consistent protection against infections related to above types, with ~90% of cervical and other HPV-related cancers and pre-cancers[9]. The nine valent HPV vaccine is currently unavailable in Sri Lanka.

- **How long does the HPV vaccine protection last after three doses?**

  Current studies have shown that the HPV vaccine results in a high antibody level not requiring booster doses for at least 10 years. Studies will continue and more data regarding the effectiveness of the vaccine will be available in the future[10,11].

- **Does the HPV vaccine interfere with the efficacy of the contraceptive pill?**

  There is no evidence to suggest that the vaccine affects the efficacy of the contraceptive pill.

- **Does the HPV vaccine cause premature menopause (primary ovarian insufficiency or POI)?**

  So far, retrospectively conducted population-based studies have not revealed any statistically significant risk of developing POI after HPV[12].

- **If HPV vaccination is administered unintentionally during pregnancy, would that be harmful to the fetus?**

  HPV vaccines are not currently recommended for pregnant women due to the fact that vaccines have not been tested in pregnancy during clinical trials. CDC and vaccine manufacturers have monitored and studied safety of the HPV vaccine in pregnant women. Close monitoring has not revealed any harmful effects. If a woman receives HPV vaccine and later learns that she is pregnant, there is no reason to be alarmed.

- **Do I have to take flu vaccine every year to remain protected from influenza?**

  Yes. Unlike other vaccines, the flu vaccine is only effective for a year. The composition of the influenza vaccine is reviewed annually by WHO, based on recent virus surveillance studies, epidemiological trends and post-vaccination studies, in order to decide which type of influenza virus strains should be included in the flu vaccine. Therefore, a new vaccine is needed each year due to changes occurring in the antigenic structure of the virus, making the pre-existing antibodies ineffective in binding and neutralizing the virus.

- **Does a child need to be vaccinated with MMR vaccine, if she or he has a history of any fever-rash illness including measles or rubella?**

  Yes, every child must be vaccinated with two doses, as per the NIP schedule at the recommended ages, irrespective of any past fever-rash illness or suspected measles/rubella.

- **Why is it important to give two doses of MMR vaccine?**

  Two doses will provide the recipient and the community with better protection.

  With the first dose of MMR vaccine, 5-10% children will remain vulnerable to these diseases. However, after the 2nd dose, only 1% will remain susceptible[13].

- **What is the minimum interval between two doses of MMR vaccinations?**

  A minimum of 4 weeks

- **If a person has developed mumps after the first dose of MMR, is it necessary to administer the second dose?**

  Yes. As MMR is a combined vaccine, even if the person has contracted natural infection to one disease in the past or before the second dose, it is important to complete the schedule. There is no evidence to suggest that an additional dose of vaccine causes any harm.

- **Can the MMR vaccine be given on the same day as the Mantoux test?**

  If a person is infected with *Mycobacterium tuberculosis*, live vaccines may temporarily suppress the response to tuberculin testing. Thus, the test can be done before or at the same time as vaccination. If the person has already been vaccinated, testing should be postponed for 4 to 6 weeks after vaccination[14].

- **Who are at increased risk of developing pneumococcal disease?**

  Young children and elderly people are mostly at risk. Children below the age of 5 years, especially those under 2 years, immuno-compromised children, those who are prone to develop recurrent respiratory infections, asthma and children living in overcrowded environments and with poor access to healthcare facilities are at risk.

- **Could pneumococcal vaccination cause pneumonia as a side effect?**

  No. Both the pneumococcal polysaccharide and pneumococcal conjugate vaccines are inactivated, do not contain live organisms, and cannot cause the diseases against which they protect.

- **Should I recommend the pneumococcal conjugate vaccine (PCV) to children below 5 years as there is insufficient local data to show the importance of recommending it?**

  There is sufficient global and regional data justifying the use of PCV vaccination in this age group, although there is a lack of local data on the disease burden. Therefore, having insufficient local data should not be a barrier for recommending PCV regarding decision-making. Reasonable estimates of invasive pneumococcal disease (IPD) based on the incidence of clinical syndromes may help to make informed decisions on the introduction of PCV conjugate vaccine for vulnerable groups. WHO has recommended PCV to children under 5 years in all countries in the position paper[15, 16, 17].

Preventing pneumococcal disease is a priority for many countries at present and some of them have already reached their targets. Furthermore, introduction of pneumococcal vaccine to children has decreased the incidence of pneumonia among the older adult population.

- **What is the role of pneumococcal vaccination during an influenza epidemic?**

  Individuals who are at high risk would be predisposed to secondary bacterial infections such as pneumonia following influenza. It has been identified that nearly 50% of bacterial pneumonia in those individuals was due to *S. pneumoniae* and is responsible for up to 20% of deaths.

  Therefore, pneumococcal vaccination becomes lifesaving in some individuals during flu epidemics.

- **In the recent past it has been observed that some practitioners recommend a 4-dose schedule of the 10 valent PCV while the others recommend only 3 doses for infants under 6 months of age. Which is better?**

  Countries have their own schedules for pneumococcal vaccination. The US offers a 4-dose schedule at 2-, 4- and 6- months primary schedule followed by a 4th dose at 12-15 month. The UK has a 2-dose schedule at the age of 3 months and one year. Some European countries have a 3-dose schedule at 2 and 4 months followed by a dose at 12 months of age.

- **Why is it recommended to give inactivated polio vaccine (IPV) together with bOPV in the NIP?**

  The currently available bOPV contains only two types of polioviruses whereas IPV contains all three types. Studies show that when IPV is used along with OPV, it builds better mucosal (intestinal) immunity than when OPV is used alone and thus increases both the protection to the individual and the community[18].

- **Is the rotavirus vaccine cost effective in Asian countries?**

  Studies conducted in Bangladesh, India and Afghanistan have clearly shown that hospital admissions and deaths from RV diarrhoea have been significantly reduced by the rotavirus vaccine[19,20].

- **When one member of a family has developed chickenpox is it justifiable to vaccinate the rest of the family members who may be susceptible?**

  Yes. The varicella vaccine, if administered within 3-5 days of exposure is 75-90% effective in preventing the disease and complications or modifying the severity of illness. In addition, it is important to protect susceptible immunocompromised persons, neonates and pregnant mothers with varicella zoster immunoglobulin (VZIG) as soon as possible, if available.

- **"Chickenpox in children is usually not serious". Why not allow children to get the disease?**

  It is not possible to predict who will have a mild or serious disease. When there is an effective vaccine, it is not worth taking this risk. Even a child with a mild disease could transmit the disease to susceptible persons in the household and the community.

- **Is there 100% assurance that a person is protected from chickenpox if 2 doses of vaccine have been administered?**

  No vaccine is 100% effective in preventing any disease. For chickenpox vaccine, about 90% of people with two doses are completely protected from chickenpox infection and almost 100% from severe disease. On the other hand, if a vaccinated person does get chickenpox, it is usually a mild form with <50 skin lesions.

- **What do you give to a child younger than 1 year of age if they were exposed to the chickenpox or zoster virus?**

  The minimum age for varicella vaccine is 12 months. Vaccination is not recommended for infants younger than 12 months of age even as post-exposure prophylaxis. CDC recommends a healthy infant should receive no specific treatment or vaccination after exposure to VZV.

The child can be treated with acyclovir if chickenpox occurs. Immunosuppressed children and neonates should receive VZIG.

- **If a child gets breakthrough varicella infection, (less than 50 lesions) could the child go to school?**

  No. Breakthrough varicella represents replication of wild varicella virus in a vaccinated person. Although most breakthrough diseases are mild, the child is infectious and activities should be restricted to the same extent as an unvaccinated person with varicella.

- **When a mother has chickenpox at the time of delivery, can the neonate be protected by chickenpox vaccination?**

  No. The vaccine is only recommended after infancy. To reduce the risk of severe disease in infants, it is recommended that neonates born to mothers who developed varicella within 5 days before to 2 days after delivery should receive VZIG, regardless of whether the mother received VZIG.

- **If a person is immunocompromised, is it advisable to vaccinate family members who may be susceptible to chickenpox?**

  Yes. Because it is important to protect the immunocompromised who cannot be vaccinated. Transmission of vaccine virus from a healthy individual is rare, but if the vaccinee develops varicella, immunocompromised individual should not be exposed to the vaccinee.

- **Could the chickenpox vaccination prevent herpes zoster in that individual at a later stage?**

  Yes. Chickenpox by natural infection has a much higher chance of causing herpes zoster infection later in life than the chickenpox vaccine[21].

- **Can the chickenpox vaccine cause herpes zoster as it contains live virus?**

  Yes. But chickenpox by natural infection has a much higher chance of causing herpes zoster infection later in life than the chickenpox vaccine[21].

- **What is the place of chickenpox vaccination in the post exposure clinical management of a family?**

  Important factors to consider for family protection include the type of exposure, evidence of acquired or natural immunity and host-immune status of family members and finally the ability to receive chickenpox vaccination safely. Varicella vaccination may prevent infection or modify the disease severity among the rest of the unaffected members of the family or close contacts. Furthermore, varicella vaccination would be effective in prevention of chickenpox if administered within 3-5 days of exposure[22].

- **Is it safe to recommend varicella vaccine to an expecting mother who has been already exposed?**

  No. It is not recommended during pregnancy. If she has no natural immunity of varicella or has not been vaccinated, post-exposure prophylaxis with varicella zoster immune globulin is indicated[22].

- **How long does varicella vaccine induced protection last?**

  The currently available evidence suggests that varicella vaccination would be protective for at least 10 years after immunization. However, the proportion of protected people may decline gradually after the first few years. A Japanese survey has revealed that protective level among the vaccinated children have persisted for more than 20 years[23,24].

- **How long should a female avoid pregnancy, after receiving rubella and chickenpox containing vaccines?**

  The minimum interval should be one month for chickenpox vaccine and rubella containing vaccines, because of the theoretical risk to the developing foetus.

  However, pregnancy within this period is not an indication for termination as no teratogenic effects have been identified[25].

- **Are there any specially recommended vaccinations for diabetic patients?**

  American Diabetic Association (ADA), WHO and The Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices, recommend influenza, hepatitis B and pneumococcal vaccines for all patients with diabetes[26,27].

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Annex I
NATIONAL IMMUNIZATION PROGRAMME OF SRI LANKA 2023

VACCINE	AGE											COMMENTS
	Birth	Month 2	Month 4	Month 6	Month 9	Month 12	Month 18	3 years	School entry	10 – 15 years	Pregnancy	
BCG	●											· Within 24 hours of birth, before leaving hospital. · Children between 6 months - 5 years of age, with no evident BCG scar.
bPolio (bivalent polio) fIPV (fractional IPV)		● ●	● ●	●			●		●			
DTP-Hep B-Hib		●	●	●								
DTP							●					
MMR					●			●		● *		*Females only (one dose at 15-44 years for all females who have not been fully immunized earlier)
JE (live)						●						
DT									●			
aTd (adult tetanus & diphtheria)										●		
HPV										● ●		Females only (grade six at school, 2 doses at least 6 months apart)
Tetanus											●	· First pregnancy – 1st dose after the 12th week of pregnancy. 2nd dose: 6 – 8 weeks after the first dose. · Subsequent pregnancies - one dose of tetanus toxoid during every subsequent pregnancy, up to a maximum of 5 doses.

Annex II
VACCINES OUTSIDE THE NATIONAL IMMUNIZATION PROGRAMME OF SRI LANKA 2023

VACCINE		AGE									COMMENTS
		Birth	Month 2	Month 4	Month 6	Month 12	Month 18	2nd year of	School entry	Over 10 years	
DTaP-Hep B- IPV-Hib			■	■	■		■				
DTP-Hib							■				
Hib			■	■	■		■				
Pneumococcal conjugate			■	■	■						
Rotavirus	Monovalent		■	■							Should be completed by 24 weeks of age
	Pentavalent		■	■	■						
Tdap (reduced antigen diphtheria, reduced antigen acellular pertussis)									■	■	Adolescents and adults
Hepatitis A											Over 2 years of age, 2 doses at 0 & 6-12 months later
Hepatitis B											3 doses at 0, 1 & 6 months
Hepatitis A + B											Over 2 years of age, 3 doses at 0, 1 & 6 months
HPV											· Bivalent o 9-14 years – 2 doses at 0 & 6 months o 15-45 years – 3 doses at 0, 1 & 6 months · Quadrivalent o 9-14 years – 2 doses at 0 & 6 months o 15-45 years – 3 doses at 0, 2 & 6 months
Influenza											Have to be given annually after 6 months of age · 6 months-3 years – half the adult dose · Previously unvaccinated child <9 years of age – 2 doses 1 month apart · Children >9 years and adults – single dose
Typhoid (injectable)											Over 2 years of age Single dose effective for 3 years
Varicella											After 1 year of age • 1st dose 12 months-12 years of age, 2nd dose in 4-6 years(minimum gap – 3 months) • 1st dose >13 years of age, 2nd dose 4-8 weeks later

SPECIAL CIRCUMSTANCES

Cholera	Refer chapter 5
COVID-19	Refer chapter 6
Meningococcal	Refer chapter 16
Pneumococcal	Refer chapter 17
Rabies	Refer chapter 19
Yellow fever	Refer chapter 24

Annex III
RECOMMENDATIONS FOR ROUTE AND SITE OF IMMUNIZATION

VACCINE	TYPE	ROUTE	SITE
BCG	Live attenuated bacteria	ID	Deltoid of left arm
Cholera	Live attenuated bacteria	Oral	-
Diphtheria toxoid – tetanus toxoid - pertussis (DTP)	Toxoid & inactivated bacteria	IM	Anterolateral aspect of thigh
Diphtheria toxoid – tetanus toxoid – pertussis - hepatitis B - *H. influenzae* type b (DTP-HepB-Hib) (pentavalent)	Toxoid & inactivated bacteria, recombinant viral antigen & polysaccharide protein conjugate	IM	Anterolateral aspect of thigh
Diphtheria toxoid – tetanus toxoid – acellular pertussis - hepatitis B – *H. influenzae* type b - inactivated polio virus (DTP-Hep B–Hib-IPV) (Hexavalent)	Toxoid & inactivated bacteria, recombinant viral antigen, polysaccharide protein conjugate & inactivated virus	IM	Anterolateral aspect of thigh
Diphtheria - tetanus toxoid (DT)	Toxoid	IM	Deltoid
Hepatitis A - hepatitis B (combined vaccine)	Inactivated virus and recombinant viral antigen	IM	Deltoid
Hepatitis A	Inactivated virus	IM	Deltoid
Hepatitis B	Recombinant viral antigen	IM	<2 years – anterolateral aspect of thigh >2 years – deltoid
Influenza	Inactivated virus	IM	Deltoid
Human papillomavirus	Recombinant viral antigen	IM	Deltoid
Japanese encephalitis	Live attenuated virus	SC	Deltoid
Measles – mumps - rubella (MMR)	Live attenuated virus	SC	Deltoid
Meningococcal	Polysaccharide conjugate	IM	Deltoid
Pneumococcal conjugate	Polysaccharide compound conjugate	IM	<2 years – anterolateral aspect of thigh >2 years – deltoid
Pneumococcal polysaccharide	Polysaccharide	IM / SC	>2 years - deltoid
Oral polio (OPV)	Live attenuated virus	Oral	
Inactivated polio (IPV)	Inactivated virus Fractional dose	IM ID	Deltoid
Rotavirus	Live attenuated virus	Oral	
Rabies	Inactivated virus	IM / SC / ID	Deltoid
Tetanus	Toxoid	IM	Deltoid
Tetanus toxoid - diphtheria toxoid reduced antigen (aTd)	Toxoid	IM	Deltoid
Tetanus toxoid - diphtheria toxoid reduced antigen — aceluar pertussis reduced antigen (Tdap)	Toxoid & inactivated bacterial antigen	IM	Deltoid
Typhoid	Capsular polysaccharide	IM	Deltoid
Varicella	Live attenuated virus	SC	Deltoid
Yellow Fever	Live attenuated virus	SC	Deltoid

ID - Intradermal **IM – Intramuscular** **SC - Subcutaneous**

Annex IV

List of AEFI to be reported and investigated

1. Serious AEFI: Any AEFI causing
a) Death b) Hospitalization c) Disability d) Congenital anomaly
2. Local adverse events
a) Injection site abscess b) BCG lymphadenitis c) Severe local reactions
3. Central nervous system adverse events
a) Vaccine derived paralytic poliomyelitis (within 4-30 days of OPV) b) Guillain-Barre syndrome (within 30 days after immunization) c) Encephalopathy (within 72 hours after vaccination) d) Encephalitis (within 1-30 days after vaccination) e) Meningitis (within 1-30 days after vaccination) f) Seizures
4. Other adverse events requiring investigation
a) Anaphylaxis b) Persistent screaming c) Hypotonic hyporesponsive episode d) Osteitis/osteomyelitis (within 8-16 months of vaccination) e) Toxic shock syndrome (within few hours of immunization)
5. Other adverse events not requiring investigation
a) Allergic reactions (other than anaphylaxis) b) Arthralgia c) High fever (>39°C) d) Nodule at the injection site
6. Other severe and unusual events

(Source: Epidemiology Unit, Ministry of Health)

Annex V

AEFI Form 1

Notification Form for Adverse Events Following Immunization (AEFI)

Patient Information

Name: MOH Division:

Age: ☐☐ months/years Sex: Male ☐ Female ☐ Telephone:

Name & address of the Parent/Guardian:

Information on the vaccine (primary suspected and other)

Vaccine (Generic Name)	Vaccine (Trade name)*	Route	Dose (1st, 2nd, 3rd, 4th)	Batch/Lot Number	Expiry date	VVM Status (I, II, III, IV)

Diluent used: Yes ☐ No ☐ If "yes", Diluent batch/lot number Expiry date of Diluent

**Trade name is necessary only in private sector immunization*

Place vaccine administered: Date:

Person vaccine administered: Doctor ☐ PHNS/Nurse ☐ PHM ☐ PHI ☐ Time: am/pm

Adverse Events

Local Adverse Events Requiring investigation	Injection site abscess ☐ BCG Lymphadenitis ☐ Severe local reaction ☐
CNS Adverse Events Requiring Investigation	Vaccine associated paralytic poliomyelitis ☐ GBS ☐ Encephalopathy ☐ Encephalitis ☐ Meningitis ☐ Seizures Febrile ☐ Seizures Afebrile ☐
Other Adverse Events Requiring Investigation	Anaphylaxis ☐ Persistent screaming ☐ Osteitis / Osteomyelitis ☐ Hypotonic Hyporesponsive Episode ☐ Toxic Shock Syndrome ☐
Adverse Events Not Requiring Investigation	Allergic reaction ☐ Arthralgia ☐ High fever (>39^{0}C / 102^{0}F) ☐ Nodule at the injection site ☐
Other Adverse Events	a) b)

Instruction: Before reporting an AEFI, please refer to the definition for the relevant AEFI given in overleaf and make sure that reporting event agrees with the criteria stipulated in the definition

Date & Time onset of adverse event:

Date & Time referring to medical care :

Medical History/Other	**Outcome**
	Hospitalized: Yes No If "Yes": Hospital: BHT: Still in the hospital ☐ Discharged ☐ Outcome: Recovered completely ☐ Partially recovered ☐ Death ☐

Reporting source

Date of the notification: Institution & Designation: Telephone:

Name & Signature of the notifying officer/General Practitioner:

(Medical Officers who attend any patient suffering from Adverse Effects Following Immunization shall notify in this form to the Medical Officer of Health the area of the patients residence)

Annex VI

Anaphylaxis Event Record

(To be completed by a Medical Officer)

Patient details											
Name:				MOH Area:			RDHS Area:				
Age	Date of birth		Sex	Ethnicity		Hospital:			BHT number:		
Past allergic history: Has patient had previous allergic reactions? ☐ Yes ☐ No If 'Yes', Allergen (Drug/Vaccine/Food/Other) - *specify*?											
Part I: Clinical features											
Date & time of clinical examination: Date(dd/mm/yy)								Time : am/pm			
Skin & Mucosa	☐ Urticaria ☐ Erythema ☐ Pruritus ☐ Prickle sensation						*Specify* the site of reaction:				
	Eye	☐ Red bilateral		☐ Red unilateral		☐ Itchy					
	Angioedema	☐ Tongue ☐ Throat ☐ Uvula ☐ Larynx ☐ Lip ☐ Face ☐ Limbs ☐ Other									
Respiratory system	☐ Sneezing ☐ Rhinorrhoea ☐ Sore throat	☐ Hoarse voice ☐ Stridor	☐ Sensation of throat closure ☐ Cough	☐ Tachypnoea ☐ Difficulty in swallowing ☐ Rhonchi	☐ Wheezing ☐ Indrawing / retractions ☐ Chest tightness	☐ Grunting ☐ Cyanosis ☐ Difficulty in breathing					
Circulatory system	BP (mmHg)	☐ Measured hypotension	☐ Decreased central venous pulse	☐ Capillary refill time >3secs	Heart rate (m)	☐ Tachycardia					
CNS	☐ Loss of consciousness		☐ Distress	☐ Other(*specify*):							
GIT	☐ Diarrhoea	☐ Nausea	☐ Abdominal pain/cramp	☐ Vomiting							
Diagnostic Criteria	☐ Rapid onset of occurrence of above sign & symptoms			☐ Two or more systems are affected							
Part 2: Suspected Product and exposure Information											
Date & Time of drug/vaccine administration: Date(dd/mm/yy)							Time : am/pm				
Drug ☐ Oral ☐ Parenteral			☐ Vaccine	☐ Serum	☐ Other (*specify*).						
Generic name :				Trade name :							
Batch number :	Expiry date :		*For vaccine*: VVM status ☐ I ☐ II ☐ III ☐ IV ☐ 1st dose ☐ 2nd dose ☐ 3rd dose ☐ 4th dose								
If diluent used, specify batch number & expiry date:											
If parenteral medicine/vaccine: ☐ Single dose ☐ Multi dose				☐ Liquid ☐ Lyophilised							
Route of administration: ☐ Oral ☐ IV ☐ IM ☐ SC ☐ ID ☐ Other(*specify*)											
Site of Administration: ☐ Deltoid ☐ Thigh ☐ Buttock ☐ Other (*specify*)											
Person who administered: ☐ Doctor ☐ Nurse ☐ PHI ☐ PHM ☐ Other (*specify*)											
Place of administration/reaction: ☐ Hospital ☐ MOH ☐ Clinic ☐ Private Hospital ☐ GP ☐ Other(specify)											

Annnex v

Part 3: Management	
Was Adrenaline administered? ☐ Yes ☐ No If 'Yes', Route : ☐ IM ☐ SC ☐ IV ☐ Other (*specify*) Dose:……ml Place: ☐ Clinic ☐ MOH ☐ Hospital ☐ Other (*specify*) Time (*of 1st dose*):……am/pm Person who administered adrenaline: ☐ Doctor ☐ Sister/Nurse ☐ PHI/PHM ☐ Other	
Was a repeat dose of adrenaline given? ☐ Yes ☐ No	If 'Yes', describe (*including the time*)
What other medicines were administered? ☐ Yes ☐ No	If 'Yes', describe (*including the time*)
Any other details concerning medicines/management (*including CPR*)?	
Investigation	Blood taken for mast cell Tryptase: ☐Yes ☐ No If 'Yes' specify the time interval after event: *(Note: Serum Tryptase levels peak 60-90 min after the onset of anaphylaxis and persist to 6 h. Therefore It is recommended that blood should be taken between 1 and 2 h after the initiation of symptoms.)*
Part 4: Outcome	
Onset of first symptom: Date (dd/mm/yy) Time: …….. am/pm	
Outcome: ☐ Full recovery ☐ Not fully recovered ☐ Recovered with sequelae ☐ Death Specify details:	
Time at outcome (recovery/death) Date (dd/mm/yy) Time: am/pm ☐ Unknown	
Highest impact of Adverse drug event/Adverse Event Following Immunization: ☐ Did not interfere with daily activities ☐ Interfered, but did not prevent daily activities ☐ Prevented daily activities	
Part 4: Any other comment	
Details of Reporting Source	
Name: Designation: Institute: Signature Date: Telephone:	

Definition: Anaphylaxis is defined as a severe, life-threatening, generalized or systemic hypersensitivity reaction, characterised by rapidly developing life-threatening airway and/or breathing and/or circulation and or gastrointestinal problems usually (not always) associated with skin and mucosal changes.

Annex VII

GENERIC AND BRAND NAMES OF VACCINES AVAILABLE IN SRI LANKA

Name of vaccine	Product/ brand name	Manufacturer
BCG	BCG vaccine	Serum Institute of India
COVID-19	Comirnaty	Pfizer BioNTech
	Covishield	Serum Institute of India/ AstraZeneca
	Moderna	Moderna/ NIAID
	Sinopharm	Beijing Institute of Biological Products
	Sputnik V	Gamaleya Research Institute
Diphtheria, pertussis (whole cell), tetanus, hepatitis B, *Haemophilus influenzae* type b (pentavalent)		Biological E. Limited, India
		Serum Institute of India
Diphtheria, pertussis (acellular), tetanus, hepatitis B, *Haemophilus influenzae* type b, IPV (hexavalent)	Infanrix Hexa	GSK, Belgium
	Hexaxim	Sanofi Pasteur, France
Dipththeria, tetanus, acellular pertussis vaccine (adolescents and adults)	Boostrix	GSK, Belgium
Diphtheria, tetanus for adults and adolescents	aTd	Serum Institute of India
Haemophilus influenzae type b (Hib)		Serum Institute of India
	ACT HIB	Sanofi Pasteur, France
Hepatitis A	Havrix (junior & adult)	GSK, Belgium
	Avaxim	Sanofi Pasteur, France
Hepatitis B	Engerix-B	GSK, Belgium
	Euvax B (paediatric & adult)	LE Life Sciences, Korea
Hepatitis A+B combined	Twinrix adult	GSK, Belgium
Human papillomavirus (HPV)	Cervarix (bivalent)	GSK, Belgium
	Gardasil (quadrivalent)	MSD, USA
Influenza	Vaxigrip (pediatric & adult)	Sanofi Pasteur, France
	Influvac and InfluvacN	Abbott Biologicals B.V. Netherlands
Japanese encephalitis	JE (live)	Chengdu Institute of Biological Products, China
	IMOJEV	Sanofi Pasteur, France
MMR	Priorix	GSK, Belgium
		Serum Institute of India

Name of vaccine	Product/ brand name	Manufacturer
Meningococcal conjugate ACWY	Menactra	Sanofi Pasteur, France
	Nimenrix	Pfizer, USA
Pneumococcal polysaccharide	Pneumovax 23	MSD Pharma, USA
Pneumococcal conjugate	Synflorix	GSK, Belgium
Polio (oral)	OPV (bivalent)	Sanofi Pasteur, France
Polio (injectable)	Inactivated poliomyelitis (trivalent)	Bilthoven Biologicals B.V. Netherlands
Rabies	Verorab	Sanofi Pasteur, France
	Abhayrab	Human Biological Institute, India
	Speeda	Liaoning Cheng Da Biotechnology, China
Rotavirus	Rotarix (monovalent)	GSK, Belgium
	Rotateq (pentavalent)	MSD, USA
Tetanus	Tetanus vaccine	Biological E. limited, India
		Serum Institute of India
Typhoid	Typhim Vi	Sanofi Pasteur, France
	Typbar	Bharat Biotech, India
	Typherix	GSK, Belgium
Varicella	Varilrix	GSK, Belgium
Yellow fever	Stamaril	Sanofi Pasteur, France

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Book Review by Professor Guwani Liyanage, Professor in Paediatrics, University of Sri Jayawardenapura

SLMA Guidelines and Information on Vaccines Seventh Edition 2020

ISBN 978-955-9386-50-6, 400 pages

SLMA Guidelines and Information on Vaccines provides concise clinical guidance for healthcare professionals, about the safest and most effective use of vaccines in their practice. It was first launched in 2001, co-edited by Dr. Lucian Jayasuriya and Prof. Anura Weerasinghe. The latest 7th edition, co-edited and authored by a group of experts, is dedicated to late Prof. Anura Weerasinghe for his contribution as an editor for over 16 years. Notably, from the first edition to the latest 7th edition, Dr Jayasuriya had been a co-editor; his commitment to publish the revised and updated editions during the last two decades must be truly appreciated.

The guideline contains information for all EPI and non-EPI vaccines available in Sri Lanka. It is user-friendly, easy to navigate, yet replete with up-to-date information. Also, it gives additional information on vaccination in special circumstances. The 7th edition contains five new chapters: the impact of immunisation, immunisation in pregnancy, immunisation of competitive sports person, immunisation in disasters, epidemics and outbreaks and immunisation of the immunocompromised.

The chapter on immunisation of competitive sports persons is remarkable. Although a minor illness such as diarrhoea or an upper respiratory infection is not a major illness for a healthy young adult, it could be very critical for an athlete to miss or fail the most important competition in his life. Apar t from the usual vaccines, when travelling to endemic areas, the athletes should be immune against specific diseases. Therefore, it is obvious that the general guidelines on vaccination cannot be directly transferred to sportspersons, and the vaccinations should be scheduled so that possible side effects are least likely to occur in periods of competition.

Immunisation during pregnancy is detailed in Chapter 24. Immunisation has become part and parcel of antenatal care. However, some confusion among healthcare professionals and patients exists about the safety and timing of immunisation. The healthcare provider's recommendation is the most important factor that influences the pregnant women to get the required vaccination done. Thus, it is important that we should be aware of the current best evidence and communicate those to pregnant women.

Natural disasters and outbreaks have become more frequent worldwide, and they may adversely affect the short and long-term wellbeing of children and adults. Evidence had revealed that exposure to a natural disaster increases the likelihood of acute illnesses such as diarrhoea, fever, and acute respiratory illness, particularly in children under 5 years. The 7th edition of SLMA Guidelines and Information on Vaccines provides current recommendations for managing such emergencies to lessen the harm.

Dengue is a significant and increasing threat to public health in Southeast Asia. Specific antiviral medications are not available for dengue, and prevention using vector control has limited success. Thus, all medical professionals, particularly in these high-risk regions, should be aware of the vaccine status, which may be the most important element to control dengue disease in the future.

All in all, this book provides valuable guidance based on the best scientific evidence available. It targets paediatricians, family practitioners, internists, obstetricians, adult physicians, residents, medical students, nurses, and many others. It is a one-stop source for everything one needs to know about vaccines. Untiring efforts of the editors, reviewers, and contributors to put the scientifically rigorous information on vaccine together are a great accomplishment.

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