

SLMA GUIDELINES AND INFORMATION ON VACCINES

NINTH EDITION

SRI LANKA MEDICAL ASSOCIATION
COLOMBO
2026



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First Edition 2001

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Eighth Edition. 2023

ISBN 978-624-5972-15-9

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Dedication

This Ninth Edition is dedicated with deep respect and gratitude to Dr. Lucian Jayasuriya, in recognition of his visionary leadership and unwavering commitment to the SLMA Guidelines and Information on Vaccines over the past eight editions. His guidance, scholarly excellence, and steadfast dedication have been instrumental in shaping this publication into a trusted and authoritative resource. His enduring contributions continue to inspire all those involved in advancing immunisation practice and public health



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Third Edition 2008

SLMA Guidelines on Vaccines and Information on Vaccines

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Fourth Edition 2011

SLMA Guidelines and Information on Vaccines

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INTRODUCTION

We are pleased to present the ninth edition of the SLMA Guidelines and Information on Vaccines, a continued effort to provide an up-to-date, practical, and authoritative resource for healthcare professionals. This edition comprises 41 chapters, which have been thoroughly revised to reflect current evidence, evolving immunisation practices, and emerging public health priorities. Notably, we have included a new chapter on the respiratory syncytial virus (RSV) vaccine, recognizing its growing importance in preventive medicine and recent advances in vaccine development.

We are delighted to welcome new contributors to this edition: Dr. Rohitha Muthugala, Consultant Virologist at the Medical Research Institute, Colombo, Dr. Neesha Rockwood, Dr Mario Alles, Dr Chathuri Gunasekera, Dr Anusha Fernando, senior lecturers from the Department of Microbiology and Immunology, Faculty of Medicine, Colombo, Dr Sashimali Wickramasinghe, Consultant Community Physician, Epidemiology Unit and Dr Umedha Jayasinghe, Consultant Venereologist from the National STD Control Programme of the Ministry of Health. Their expertise has enriched the content and strengthened the multidisciplinary perspective of the book.

The process of developing this edition began on 5th March 2025, with a series of structured meetings held fortnightly on Wednesdays at the Sri Lanka Medical Association (SLMA), Wijerama House, Colombo 7. These sessions provided a vibrant platform for discussion, peer review, and collaborative refinement of each chapter. We extend our sincere gratitude to all authors for their dedication and scholarly contributions. We are especially thankful to the volunteers who formed the Core Review Group, whose enthusiasm and critical engagement greatly enhanced the quality of the work. Their commitment made the editorial process both productive and intellectually rewarding.

We acknowledge with appreciation the unwavering support extended by the President, Council, and staff of the SLMA. We are particularly grateful to the Chair and members of the SLMA Expert Committee on

Communicable Diseases for entrusting us with the freedom to shape the content of this book.

We gratefully acknowledge the visionary leadership and unwavering dedication of Dr Lucian Jayasuriya as the Founding Editor, whose pioneering efforts laid the strong foundation that has enabled this book to flourish through to its 9th Edition.

Finally, we wish to express our gratitude to Serum Institute-Citihealth for sponsoring the printing of this volume for the ninth edition. We note with regret the conclusion of GSK's marketing activities in Sri Lanka and acknowledge their longstanding support in facilitating the dissemination of this resource.

We hope that this edition will continue to serve as a valuable guide for clinicians, public health practitioners, and all those involved in immunisation practices.

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Joint Editors

PREFACE

A new chapter in the history of medicine began in 1796, when Edward Jenner inoculated an eight-year-old boy with material obtained from cowpox lesions, thereby demonstrating protection against smallpox. This pioneering work laid the foundation for vaccination and ultimately contributed to the global eradication of smallpox nearly two centuries later.

Since the latter part of the twentieth century, remarkable advances have transformed the field of vaccine development. Innovations in both scientific discovery and production technologies have led to the introduction of new and highly effective vaccines. The COVID-19 pandemic underscored the immense value of these advances, highlighting the critical role of vaccines in safeguarding global health.

The World Health Organization (WHO) launched the Expanded Programme on Immunisation (EPI) in 1974. During the 1980s, WHO and UNICEF collaborated to achieve universal childhood immunisation against six diseases: tuberculosis (BCG), poliomyelitis (OPV), diphtheria, tetanus, pertussis, and measles.

Sri Lanka has a long and distinguished history in immunisation. Smallpox vaccination was introduced in Ceylon as early as 1896, followed by BCG in 1949, DPT in 1961, and OPV in 1962. The national EPI was established in 1978, with measles vaccination added in 1984. Since then, the programme has expanded to include many additional vaccines, both within and beyond the EPI. Today, Sri Lanka's immunisation programme is recognised among the best globally, having achieved sustained high coverage and effective control of several vaccine-preventable diseases.

In 2001, the Communicable Diseases Committee of the Sri Lanka Medical Association (SLMA) initiated the development of guidelines for the use of non-EPI vaccines. Subsequent editions expanded the scope to encompass all vaccines available in Sri Lanka. I wish to acknowledge with deep appreciation the invaluable contributions of the

late Professor Anura Weerasinghe, who initiated this effort and served as Joint Editor for the first five editions.

These guidelines, regularly revised and updated, are intended to assist practitioners by providing evidence-based, consensus recommendations from authors and reviewers. As new knowledge emerges, future editions will continue to reflect these developments.

I extend my sincere gratitude to the Joint Editors, led by Professor Jennifer Perera, as well as to the chapter authors and reviewers, for their dedication in producing this ninth edition in a timely manner. I am also deeply indebted to Dr. Lucian Jayasuriya for his leadership in advancing this work through the Expert Committee on Communicable Diseases of the SLMA. Finally, I acknowledge with thanks the support of Serum Institute-Citihealth for sponsoring the printing of this publication.

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

FOREWORD

It is my great pleasure, as the President of the Sri Lanka Medical Association, to introduce the ninth edition of the *SLMA Guidelines and Information on Vaccines 2026*.

In an era where medical science evolves at a rapid pace, the SLMA remains steadfast in its commitment to providing healthcare professionals with authoritative, evidence-based, and practical resources. This latest volume, featuring 41 meticulously revised chapters, stands as a testament to that noble mission. It reflects the most current immunization practices in line with emerging public health priorities.

Recent global outbreaks underscore the critical importance of keeping our clinical knowledge updated. In an interconnected world, re-emerging pathogens and shifting viral dynamics present a constant threat to national health security. Staying abreast of the latest vaccine developments is no longer optional; it is our primary line of defense against cross-border transmissions and local outbreaks. By equipping our healthcare workforce with contemporary, evidence-based immunisation protocols, we build the resilient clinical infrastructure necessary to intercept and neutralize these evolving infectious threats before they breach our communities.

I would also like to acknowledge the tireless contributions of all the authors and the dedicated Core Review Group, whose rigorous peer review and scholarly refinement were essential to maintaining the high standards of this publication. I extend my sincere gratitude to everyone involved for their intellectual rigour and unwavering dedication.

We owe a lasting debt of gratitude to Dr Lucian Jayasuriya, our Founding Editor. His visionary leadership laid the foundation that has allowed this resource to flourish across nine editions. My thanks also go to the SLMA Expert Committee on Communicable Diseases and the SLMA Council for their steadfast support throughout this journey.

Finally, I express my deep appreciation to all our sponsors, whose generous contributions allow us to sustain this vital work.

It is our hope that this ninth edition will serve as an indispensable guide for clinicians and public health practitioners alike, ultimately strengthening the immunisation framework of our nation and safeguarding the health of all Sri Lankans.

Dr. Manilka Sumanatileke
President,
Sri Lanka Medical Association

ABBREVIATIONS

AAP	American Academy of Paediatrics
ABC	airway, breathing, circulation
ACIP	Advisory Committee on Immunization Practices
ACWYX	pentavalent meningococcal vaccine
ACE	angiotensin converting enzyme
ACS	acute coronary syndrome
AE	accident & emergency
AEFI	adverse events following immunization
AFP	acute flaccid paralysis
AIDS	acquired immunodeficiency syndrome
AIIRD	autoimmune inflammatory rheumatic diseases
aIIV3	adjuvanted inactivated influenza vaccine
ALL	acute lymphocytic leukaemia
ALT	alanine aminotransferase
AMR	antimicrobial resistance
aP	acellular pertussis
APC	antigen presenting cell
ARDS	acute respiratory disease syndrome
ARSN	Asian Rotavirus Surveillance Network
ART	antiretroviral therapy
ARTI	acute respiratory tract infection
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
BNT16262	boosting with an mRNA vaccine
bOPV	bivalent oral polio vaccine
BP	blood pressure
BSA	bovine serum albumin
CAP	community acquired pneumonia
CARPA	complement activity related pseudo allergy

CAR-T	chimeric antigen receptor T cells
$CCID_{50}$	cell culture infective $dose_{50}$
CCIIV3	cell culture based inactivated influenza vaccine
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
CHIKV	chikungunya virus
CIN	cervical intraepithelial neoplasia
CIOMS	Council for International Organizations of Medical Sciences
CKD	chronic kidney disease
CLD	chronic liver disease
CLL	chronic lymphocytic leukaemia
CMVIG	cytomegalovirus immunoglobulin
CNS	central nervous system
COPD	chronic obstructive pulmonary diseases
COVID - 19	coronavirus disease 2019
CRS	congenital rubella syndrome
CSF	cerebrospinal fluid
CVD	coronary vascular disease
cVDPV	circulating vaccine derived poliovirus
CVID	common variable immunodeficiency
CYD-TDV	chimeric yellow fever tetravalent dengue vaccine
DAMPs	damage associated molecular patterns
DC	dendritic cells
DENV	dengue virus
DF	dengue fever
DMARDS	disease modifying anti rheumatic drugs
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
DTP3	third dose of DTP 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 whole cell pertussis and *H influenzae* type b vaccine
dTpa	reduced antigen, diphtheria, tetanus and acellular pertussis vaccine
DTwP	diphtheria, tetanus and whole cell pertussis vaccine
ELISA	enzyme linked immunosorbent assay
EMA	European Medicines Agency
EPI	Expanded Programme of Immunisation
ERIG	equine rabies immunoglobulin
ETEC	enterotoxigenic *Escherichia coli*
ETU	Emergency Treatment Unit
EUA	Emergency use Authorisation
EYE	Eliminate yellow fever epidemics
FA	fluorescent antigen
FDA	Food and Drugs Administration
FLW	first line workers
fIPV	fractionated injectable polio vaccine
FDC	follicular dendritic cells
FVS	fetal varicella syndrome
fYFV	fractional yellow fever vaccine
GACVS	Global Advisory Committee on Vaccine Safety
GAVI	Global Alliance on Vaccination and Immunisation

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
HCP	healthcare professional
HCW	health care worker
HDC	human diploid cell
HD-IIV3	high dose inactivated influenza vaccine
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
HR	high risk
HSCT	haematopoetic stem cell transplantation
HTIG	human tetanus immunoglobulin
HTLV	human T cell lymphotropic virus
HZ	herpes zoster
IA2030	Immunisation Agenda 2030

ICU	intensive care unit
ICVP	International Certificate of Vaccination and Prophylaxis
ID	intradermal
IDSA	Infectious Diseases Society of America
IEI	inborn errors of immunity
IFN	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
ILI	influenza like illness
ILR	ice-lined refrigerators
IM	intramuscular
IMD	invasive meningococcal disease
IMIG	intramuscular immunoglobulin
IP	incubation period
IPD	invasive pneumococcal disease
IPV	inactivated polio vaccine
ISSR	immunisation stress related response
IST	immunosuppressive therapy
ITI	Industrial Technology Institute
ITP	immune mediated thrombocytopenic purpura
IU	international units
IV	intravenous
iVDPV	immunodeficiency associated vaccine derived polio virus
IVIG	intravenous immunoglobulin
JE	Japanese encephalitis
JE-CV `	Japanese encephalitis chimeric vaccine

JEV	Japanese encephalitis virus
KDIGO	kidney disease improving global outcomes
LAIV	live attenuated influenza vaccine
LCD	liquid crystal display
LJEV	live attenuated Japanese encephalitis vaccine
LMIC	low- and middle-income countries
LRTI	lower respiratory tract infections
LR	low risk
LP	lipid nanoparticles
LV	left ventricle
mAB	monoclonal antibodies
MCV1	first dose of measles containing vaccine
MCV4	tetravalent meningococcal conjugate vaccine
MDR	multi drug resistant
Men A	serogroup A meningococcal vaccine
Men B	serogroup B meningococcal vaccine
MenACWY	tetravalent meningococcal vaccine
MenACWY-D	tetravalent meningococcal vaccine conjugated with diphtheria toxoid
MenACWY-CRM	tetravalent meningococcal vaccine conjugated with CRM
MHC	major histocompatibility complex
mIU	milli international units
mL	millilitre
MMR	measles, mumps and rubella vaccine
MMRV	measles, mumps, rubella and varicella vaccine
MOH	medical officer of health
MPL	monophosphoryl lipid
MPSV4	tetravalent meningococcal polysaccharide vaccine
MRI	Medical Research Institute
mRNA	messenger ribonucleic acid
MSM	men who have sex with men
MSMD	Mendelian susceptibility to mycobacterial disease
Mtb	*Mycobacterium tuberculosis*

MVA	modified vaccinia Ankara
NA	not applicable
N saline	0.9 % sodium chloride
NAT	nucleic acid amplification testing
NCD	non-communicable diseases
NCP	North Central Province
NGO	non-governmental organisation
NHIG	normal human immunoglobulin
NK	natural killer
NIP	National Immunisation Programme
NMRA	National Medicinal Drugs Regulatory Authority
NPI	National Policy on Immunisation
NS	nephrotic syndrome
NTHi	non-typeable *H influenzae*
OCV	oral cholera vaccine
OD	orally daily
OMV	outer membrane vesicle
OPV	oral polio vaccine
PATH(CVIA)	Centre for Vaccine Innovation & Access
PCEC	purified chick embryo cell vaccine (for rabies)
PCR	polymerase chain reaction
PCU	primary care unit
PCV / PCVs	pneumococcal conjugate vaccine(s)
PCV10	10 valent pneumococcal conjugate vaccine
PCV13	13 valent pneumococcal conjugate vaccine
PCV7	7 valent pneumococcal conjugate vaccine
PCV 15	15 valent pneumococcal conjugate vaccine
PCV 20	20 valent pneumococcal conjugate vaccine
PEP	post exposure prophylaxis
PrEP	pre exposure prophylaxis
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	polyribosylribitol
PRP-CRM 197	with CRM protein
PRP-D	with diphtheria toxoid
PRP-OMP	with meningococcal outer membrane protein
PRP-T	with tetanus toxoid
PRR	pattern recognition receptors
PT	pertussis toxin
PTB	pulmonary tuberculosis
PVRV	purified vero cell rabies vaccine
QIV	quadrivalent influenza vaccine
RABV	rabies virus
RIG	rabies immunoglobulin
RNA	ribonucleic acid
RRP	recurrent respiratory papillomatosis
RSV	respiratory syncytial virus
RTS, S/ASO1	malaria vaccine formulation (RTS, S antigen with AS01 adjuvant system)
rVSV-ZEBOV	recombinant vesicular stomatitis virus - Zaire Ebola Virus
RZV	recombinant subunit herpes zoster vaccine
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SAGE	Strategic 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
SOP	standard operation procedures

SOT	solid organ transplant
ST	sensitivity
STI	sexually transmitted infection
TB	tuberculosis
Td	tetanus toxoid and diphtheria toxoid
TCV	tissue culture vaccine
Tdap	reduced antigen tetanus, 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-	tumour necrosis factor
tOPV	trivalent oral polio vaccine
TST	tuberculin skin test
TT	tetanus toxoid
TTCV	tetanus toxoid containing vaccine
TViCV	typhoid Vi conjugate vaccine
TWG	technical working group
Ty21a	oral typhoid vaccine
UNICEF	United Nations Children's Fund
VAERS	vaccine adverse event reporting system
VAPP	vaccine associated paralytic poliomyelitis
VBM	variants being monitored
VCD	virologically confirmed dengue
VDPV	vaccine derived polio virus
VE	vaccine efficacy
ViPS	unconjugated Vi polysaccharide vaccine
Vi-rEPA	Vi polysaccharide conjugated pseudomonas aeruginosa exotoxin A vaccine
VLPs	virus-like particles
VOC	variants of concern
VOI	variants of interest
VOHC	variants of high consequence

VPDs	vaccine preventable diseases
VVM	vaccine vial monitor
VZIG	varicella zoster immunoglobulin
VZV	varicella zoster virus
WaSH	wash sanitation and hygienic practices
WC	whole cell
WHO	World Health Organization
wP	whole cell pertussis vaccine
WPV	wild polio virus
XDR	extremely drug resistant
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
ZVL	live attenuated herpes zoster vaccine

CHAPTER 1

THE IMPACT OF IMMUNISATION

The Global impact of immunisation

Vaccination is among the most transformative public health interventions, reshaping global patterns of morbidity and mortality. Its long-term goal is to interrupt pathogen transmission and ultimately eliminate or eradicate disease, while its immediate purpose is to prevent illness and reduce morbidity. Since Edward Jenner's 1796 demonstration that cowpox inoculation protected against smallpox, vaccines have been developed for over 30 infectious diseases. Advances in vaccine technologies-from inactivated and live attenuated vaccines to subunit, recombinant, viral vector, and messenger RNA platforms-have further accelerated progress[1].

Globally, immunisation has significantly improved child survival and life expectancy. Smallpox was eradicated in 1980, the first human disease to be eliminated worldwide, while poliomyelitis has been reduced to a few endemic regions. Conjugate and polysaccharide vaccines have also dramatically reduced severe bacterial infections. For example, pneumococcal conjugate vaccines resulted in a 69% decline in invasive disease among young children within a year, alongside indirect protection in older adults[2]. Similarly, the United Kingdom observed sustained reductions in *Haemophilus influenzae* type b infections after vaccine introduction[3].

Despite these successes, vaccine-preventable diseases still account for an estimated 300 million illnesses and five million deaths annually. Immunisation remains highly cost-effective: vaccines prevented at least 20 million deaths between 2011 and 2020, with returns of USD 51 for every dollar invested in low- and middle-income countries[4-5]. Routine childhood vaccination alone averts 4–5 million deaths each year, with projections of 51 million more deaths prevented by 2030[4].

The WHO Immunisation Agenda 2030 (IA2030) aims to ensure equitable vaccine access and reduce vaccine-preventable deaths by 50%[6]. Since the launch of the Expanded Programme on Immunisation in 1974, global coverage has exceeded 80% for key vaccines[7]. However, challenges persist: 67 million children missed routine immunisations between 2019 and 2021, including 48 million "zero-dose" children[8]. Consequently, 2.5 million children under five still die annually from preventable diseases[9]. Declines in MMR coverage have also led to measles outbreaks, underscoring the need for sustained investment and vigilance[10].

Table 1. Milestones in global immunisation

Disease (type of vaccine)	**Year of first vaccine use / first licensure**
Smallpox/variola (live related virus)	1796
Anthrax (inactivated/ cell free antigen)	1881 inactivated 1970 cell free antigen
Cholera (killed whole-cell; modern oral killed + recombinant B-subunit)	1885 1991 oral killed + recombinant B-subunit
Rabies (inactivated/ cell culture)	1885 inactivated 1970 cell culture-derived
Tetanus (toxoid)	1890s antitoxin 1924 toxoid
Typhoid (inactivated whole-cell parenteral), modern Typhoid (conjugate / Vi-polysaccharide)	1896 inactivated whole cell 2018-2020 modern Vi conjugate
Plague (killed whole cell)	1897
Diphtheria (toxoid)	1923
Pertussis (whole-cell, modern acellular)	1910s–1920s whole-cell 1991 acellular
Tuberculosis/BCG (live attenuated)	1921
Yellow fever (live attenuated)	1931

Influenza (inactivated, later live attenuated/ modern recombinant)	1945 inactivated 2003 live attenuated 2013 recombinant
Typhus epidemic (inactivated)	1937
Polio IPV (inactivated), OPV (live attenuated)	1955 Salk IPV 1961 Sabin OPV
Japanese encephalitis (Inactivated mouse-brain; modern live attenuated & inactivated Vero-derived)	1954 inactivated 1988 live attenuated 2009 inactivated Vero cell culture-derived
Measles (live attenuated)	1963
Mumps (live attenuated)	1967
Rubella (live attenuated)	1969–1970
Pneumococcal polysaccharide (PPSV23) Pneumococcal conjugate (PCV)	1977–1983 23-valent pneumococcal polysaccharide vaccine (PPSV23) 2000 pneumococcal conjugate 7- valent
Meningococcal (polysaccharide monovalent) Meningococcal (polysaccharide quadrivalent Meningococcal (recombinant subunit)	1970s polysaccharide monovalent serogroup C 1974 polysaccharide quadrivalent serogroup A, C, W, Y 2013-2015 recombinant subunit serogroup B
Haemophilus influenzae type b (conjugate)	1985
Hepatitis B (recombinant subunit)	1981
Varicella/chickenpox (live attenuated)	1995
Hepatitis A (inactivated)	1992–1995
Rotavirus (live attenuated)	1999 RotaShield - withdrawn 2006 modern licensed
Human papillomavirus/HPV (virus-like particle recombinant)	2006 4-valent 2014 9-valent

Varicella zoster/shingles (live attenuated, later recombinant adjuvanted subunit)	2006 live attenuated 2017 recombinant adjuvanted subunit
Dengue (live attenuated chimeric)	2015 first licensed; Dengvaxia - withdrawn 2022 TAK-003/Qdenga
Ebola (rVSV-ZEBOV) (live recombinant viral vector – rVSV)	2019 first regulatory approvals
Malaria (RTS, S/AS01) (recombinant VLP with adjuvant)	2015 licensure/pilot 2021 WHO recommendation for use in children in high burden areas
COVID-19 (mRNA; adenoviral-vectored; inactivated; protein subunit)	2020–2021 EUA licensure
Mpox specific vaccines (Non-replicating viral vector – Modified Vaccinia Ankara (MVA)	Historically, smallpox vaccines would have been efficacious 2019–2022 specific mpox vaccine (MVA)

The impact of immunisation in Sri Lanka

Sri Lanka has achieved and sustained exceptionally high immunisation coverage consistently above 95% for key vaccines and represents a model of effective primary healthcare delivery and community engagement. The Sri Lankan National Immunisation Programme (NIP) is one of the strongest in South Asia, built upon universal access to free healthcare, a robust primary healthcare infrastructure, and high literacy rates. In recent years, Sri Lanka's experience has also demonstrated resilience in vaccine delivery during humanitarian crises, pandemics, and political transitions.

Sri Lanka's immunisation journey began in 1803 with smallpox vaccination, marking one of the earliest organised immunisation efforts in Asia. The establishment of the EPI in 1978 standardised national coverage, with progressive integration of vaccines targeting major childhood infections[11]. Sri Lanka's continuous expansion of its NIP has been guided by WHO recommendations and local disease burden

assessments. A strong network of Medical Officers of Health and field public health staff ensures systematic follow-up and documentation, resulting in high national consistency.

Table 2. Key milestones in immunisation in Sri Lanka

Year	Vaccine / Event	Year	Vaccine / Event
1803	Smallpox vaccine introduced	1995	Launch of national immunisation days (polio elimination)
1949	BCG vaccine introduced	1996	Rubella vaccine for women of childbearing age
1961	DTP vaccine introduced	2001	Measles–rubella vaccine introduced
1962	Oral polio vaccine	2003	Hepatitis B vaccine
1978	Expanded Programme of Immunisation launched	2008	Pentavalent vaccine (DTP-Hep B-Hib)
1989	Universal childhood immunisation achieved	2011	Measles-measles–rubella (MMR) vaccine
1991	Tetanus toxoid schedule for pregnant women	2017	HPV vaccine introduced
2009	Live-attenuated JE vaccine introduced	2020	COVID-19 vaccine introduced

Recent immunisation coverage and global comparison

Sri Lanka consistently achieves some of the highest immunisation coverage rates globally, outperforming both regional and world averages. The country's DTP3, measles, hepatitis B, polio and Hib vaccine coverage are 98% or greater[12] while newer vaccines such as HPV and JE also show above global average uptake through school-based and community outreach programs.

Table 3. Immunisation coverage comparison, 2024

Vaccine	Sri Lanka	South Asia Average	Global Average
DTP3	99%	92%	85%
Measles (1st dose)	99%	89-90%	80%
Polio (3rd dose)	99%	90%	84%
Hepatitis B (3rd dose)	97%	90%	85%
Hib (3rd dose)	98%	85-90%	70-80%
HPV (2-dose completion)	48%	Very heterogenous	31%

Sources: WHO/UNICEF Estimates of National Immunisation Coverage (WUENIC), 2024 [12,13,14].

Disease burden reduction and cost savings.

Vaccination has transformed infectious disease control in Sri Lanka, reducing polio, diphtheria, pertussis, and neonatal tetanus to near-zero. Each US$1 invested yields over US$16 in savings[15]. Rubella and CRS were eliminated in 2020, measles in 2019, though a brief resurgence in 2023–2024 prompted rapid catch-up immunisation responses.

Table 4. Impact of immunisation on disease burden of selected vaccine-preventable diseases in Sri Lanka

Disease	Pre-vaccine	Post vaccine (2024)	WHO Status
Poliomyelitis acute flaccid paralysis	~1800 cases (1962)	0 (last case 1993) 76	Eliminated
Neonatal tetanus	~10,800 cases (1975-80)	0 since 2009	Eliminated
Diphtheria	Hundreds annually (1970s)	0	Eliminated
Measles	~12–49 cases per 100,000 per year (1971-1980)	298	Controlled
Mumps	≈ 20,000 to 200,000 cases per year	302	Controlled

Rubella CRS	Notable rubella epidemics 1994–1995 producing ~275 and ~169 CRS cases respectively	20	Eliminated
Pertussis	>1000 (1970s)	72	Controlled
Japanese encephalitis	1–10 cases per 100,000 in peak seasons/years (varies by district and year)	14	Controlled

CRS Congenital rubella syndrome

Sources: Epidemiology Unit, Ministry of Health, Sri Lanka; WHO Immunisation Data Portal, 2024 [16]

Impact of COVID-19 vaccines on the global pandemic

The rapid development of COVID-19 vaccines marked a milestone in immunisation, with mRNA and viral vector platforms authorised within a year of SARS-CoV-2 identification. By end-2023, over 13 billion doses were administered globally, saving an estimated 20 million lives[17,18]. High-coverage countries saw significant declines in mortality and hospitalisation despite emerging variants[19].

Sri Lanka began vaccination in January 2021, achieving over 90% adult coverage by 2022[20]. Leveraging existing immunisation infrastructure, the rollout demonstrated strong public trust, logistical capacity, and the value of sustained investment in national immunisation programmes.

References

1. Ghattas M, et al. Vaccine Technologies and Platforms for Infectious Diseases: Current Progress, Challenges, and Opportunities. Vaccines (Basel). 2021; 9(12):1490.
2. Whitney CG, et al. Decline in invasive pneumococcal disease after the introduction of protein- polysaccharide conjugate vaccine. *The New England Journal of Medicine*. 2003; 348:1737-46.

3. Vaccines: WHO position paper. *Weekly Epidemiological Record*. 2016; 91:145-168.
4. Carter A, et al Modeling the impact of vaccination for the immunisation agenda 2030: Deaths averted due to vaccination against 14 pathogens in 194 countries from 2021 to 2030. *Vaccine*. 2024; 42 Suppl 1:S28-S37.
5. Sim SY, et al. Return on investment from immunisation against 10 pathogens in 94 low- and middle-income countries, 2011–30. *Health Affairs*. 2020; 39 (8):1343-1353.
6. World Health Organization. *Immunisation Agenda 2030: A Global Strategy to Leave No One Behind*. Geneva: WHO; 2020. World Health Organization. Immunisation Agenda 2030: A Global Strategy to Leave No One Behind. Geneva: WHO; 2020. https://www.who.int/publications /m/item/immunisation-agenda-2030-a-global-strategy-to-leave-no-one-behind
7. UNICEF. *The State of the World's Children 2023: For Every Child, Vaccination*. New York: https://www.unicef.org/reports/state-worlds-children-2023
8. UNICEF. (2023). The State of the World's Children 2023: https://www.unicef. org/media/108161/file/SOWC-2023-full-report-English.pdf
9. World Health Organization. (2015). *Proposed programme budget 2016–2017: Report by the Secretariat.* 68th World Health Assembly, document A68/7. Geneva: https://apps.who.int/gb/ebwha/pdf_ files/wha68/a68_7-en.pdf
10. Thompson KM. The Health and Economic Benefits of United States Investments in Measles and Rubella Control and Elimination. *Vaccines* (Basel). 2024; 12(11):1210.
11. Gunasekara D, et al. Historical evolution of immunisation in Sri Lanka. *Sri Lanka Journal of Child Health*. 2018; 47(3):220–6.
12. World Health Organization & UNICEF. (2025, July 15). *WHO/UNICEF Estimates of National Immunisation Coverage (WUENIC) – 2024 revision.* https://worldhealthorg.shinyapps.io/wuenic-trends/
13. WHO Immunisation Data Portal. *Sri Lanka Country Profile*. Geneva: https://immunisationdata.who.int/dashboard/regions/south-east-asia-region/LKA
14. *WUENIC 2024.* https://data.unicef.org/wp-content/uploads/2025/07/WUENIC-progress-and-challenges.pdf

15. Ozawa S, et al. Return on investment from childhood immunisation In Low- And Middle-Income Countries, 2011-20. *Health Affairs* (Millwood). 2016; 35(2):199-207.
16. Epidemiology Unit, Ministry of Health. *National Immunisation Programme Annual Report 2024*. Colombo: https://www.epid.gov.lk/storage/post/pdfs/ en_67c181e537afa_Vol_52_no_01-english.pdf
17. Watson OJ, et al. Global impact of the first year of COVID-19 vaccination: A mathematical modelling study. *Lancet Infectious Diseases*. 2022; 22(9):1293–302.
18. Mathieu E, et al. A global database of COVID-19 vaccinations. *Nature Human Behaviour*. 2021; 5:947–953.
19. Tartof SY, et al. Effectiveness of mRNA COVID-19 vaccines against hospitalisation and death. *New England Journal of Medicine*. 2021; 385(19):1825–33.
20. Epidemiology Unit, Ministry of Health. *Sri Lanka COVID-19 Vaccination Campaign Report 2022*. Colombo: MoH; 2023. https://www.epid.gov.lk/ storage/post/pdfs/en_640feff0076ea _Vol_50_no_01-english.pdf

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CHAPTER 2

IMMUNOLOGICAL BASIS OF VACCINATION

Introduction

Immunisation 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

(a) 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]

(b) 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 (DC). Blood borne pathogens are directly taken up by DCs 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 recognise conserved foreign molecules found only on pathogens (pathogen associated molecular patterns or PAMPs). Recognition is followed by activation of these cells and molecules. DCs found in the skin and other sites are crucial in the subsequent activation of the specific immune system[1]. The DC senses potential 'danger' when recognising PAMPs. Recognition is followed by uptake of the pathogen and activation of the DCs and other APC.

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 as well as free antigen to the draining lymph node
- blood borne antigen localising to the spleen

During this process, the DC 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 DCs produce virus coded peptides in the cytoplasm. These peptides are presented in conjunction with MHC Class I molecules.

(c) Trained immunity

The innate immune system can develop memory to past infection, termed **trained immunity[4].** Microbial insults can, non-antigenically, stimulate, via PRR, haematopoietic stem cells or myeloid cells (central

trained memory) and peripheral macrophages (peripheral trained memory). During this process, pro-inflammatory genes are transcribed, and metabolic rewiring and epigenetic changes take place. These epigenetic changes persist, and a faster and more efficient innate immune response can take place following exposure to a dissimilar microorganism (a **heterologous** challenge) subsequently.

(d) Activation of the specific immune system

(i) Cell mediated immunity: 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 DCs 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 DCs. These co-stimulators are up-regulated only if PAMPs are recognised by DCs. As these patterns are only found on pathogens, the DC 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, Th2 and Th17 cells; Tfh cells or memory cells[2]. In addition, DC, by presenting peptides from intracytoplasmic microbes (e.g. viruses) activates CD8 T cells, which become cytotoxic T cells.

DCs which are activated by microorganisms such as *M. tuberculosis* produce cytokines that switch a naïve CD4+ T cell to an activated Th1 cell, while helminths and some bacterial pathogens induce a Th2 response. Bacteria and fungi induce Th17 cells. Th1 cells produce cytokines (IL 2, IFN γ) that activate CD8+ cytotoxic T lymphocytes and macrophages, while Th2 cells produce cytokines (IL4, 5 and 13) that have anti-helminthic activity. The Th17 subset is primarily involved in recruiting neutrophils and monocytes to sites of infection and inflammation. In the germinal centers, Tfh cells activate B lymphocytes to produce T dependent antibodies.

(ii) Humoral immunity: B cells that recognise protein antigens need help from CD4+ T cells to produce antibody. The same antigen that

activated T cells will activate B cells in the follicle; the activated T and B cells then migrate towards each other and meet at the edge of the follicle. The initial B cell response occurs at an extra-follicular focus, with help from Th1 and Th2 cells, resulting in the production of short-lived plasma cells secreting low affinity antibody[2]. This happens within a few days of the infection/immunisation and is short lived. This is followed by a response in the germinal centre. Some of the activated T and B cells move to the germinal centre, with the T cells becoming Tfh cells. The activated B cells 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 proliferates, 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, which move to the bone marrow, some surviving for decades. Almost half of the antibody present in a healthy adult is produced by these long-lived plasma cells[2]. 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 Tfh cell help and are hallmarks of antibody responses to protein antigens. This response takes 10–14 days to appear and terminates in 3–6 weeks. Peak antibody concentrations occur 4–6 weeks after primary immunisation.

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, as well as B 1 cells in mucosal tissue and peritoneum, produce short lived plasma cells secreting mainly IgM (T independent antibodies) in

response to polysaccharides. 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 immunisation, a phenomenon referred to as hyporesponsiveness[5].

(e) Function of the immune system

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.

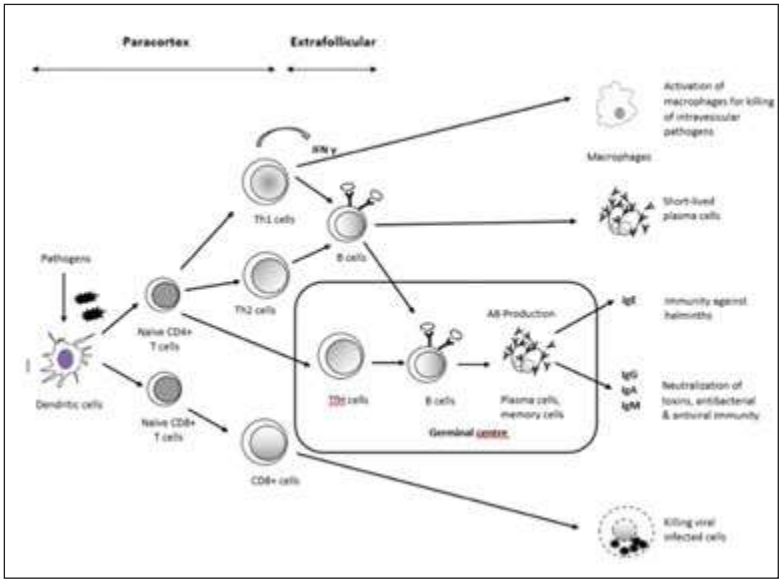


Figure: Normal immune response
(Courtesy: Dr. Dhanushka Dasanayake)

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.

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"[6]. There are two main types of vaccines, live and non-live.

The different types of vaccines are[6]

- live (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 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 immunocompromised individuals[6].

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[6].

mRNA vaccines have been used against SARS-CoV-2[7]. It comprises 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[7]. A DNA vaccine against SARS-CoV–2 is also available[8]. 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[6]. All vaccines (except the BCG vaccine) mainly confer protection by inducing antibodies[6]. 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[6].

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[5] 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[7]. The effector mechanisms of vaccine immunity are given in the table.

Table. Effector mechanisms of vaccines[9]

Antibody response	Prevents infection by extra-cellular pathogens by • Neutralisation (prevent entry into cells) • Opsonophagocytosis (clearance of pathogens by neutrophils and macrophages) • Complement activation • Binding to toxins and prevent its 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, neutralising 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[9]. Memory cells are important in vaccine responses[6]. 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[9].

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 neutralising antibody is present in the serum. Polysaccharide vaccines and most inactivated vaccines do not provide mucosal protection and therefore do not provide sterilising immunity[9]. 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[10]. IFN γ producing CD4 cells may be useful in infants who have been immunised 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[9]. 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[9].

Antibody alone may prevent infection, but disease attenuation and clearance of infection are mediated by T cells, even in the absence of antibody[9].

A number of epidemiological studies have shown the benefit of live vaccines against heterologous pathogens due to trained immunity, leading to an overall reduction in mortality. Beneficial nonspecific effects have been noted for the BCG, and measles containing vaccines. Fewer cases of fatal respiratory infections and sepsis seem to be responsible for the lower mortality with BCG. However, this effect is short lasting[11]. Evidence suggests that mononuclear cells strongly increase pro-inflammatory responses against heterologous infections after BCG.

Correlates of protection[9]

The mere presence of antibody does not indicate that the patient is protected. A correlate of protection, which is a measurable parameter, that indicates that a person is protected, is required. Such correlates of protection (i.e. antibody titers) have been identified for a number of diseases.

Determinants of primary vaccine response[9]

- Intrinsic immunogenicity of the vaccine
- Type of vaccine –

  Live viral vaccines

  - They elicit better responses than non-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[9]. 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 immunisation 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 immunisation 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[9,12].

- 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)[6]. 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[13].
- 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[14]. 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 generated in the para-follicular area produce antibodies that 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[9]. This occurs most efficiently with live vaccines, less efficiently with non-live vaccines, but not with polysaccharide vaccines[9]. 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.)[15]. In addition, virus like particles used in the HPV vaccine evoke antibody responses which can persist decades[6].

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[9].

Vaccination at extremes of age or patients with chronic disease may evoke short lived responses. For example, infants have few niches in the bone marrow to accommodate B cells[6].

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)[9]. A secondary antigen exposure (boost) will give better affinity antibodies.

With pathogens with a short incubation period, memory cells are not adequate; the persistence of protective antibody levels are necessary[6]. For this reason, multiple boosters are given against diphtheria and tetanus.

Adjuvants

Adjuvants enhance the magnitude and duration of the immune response[16], including seroconversion rates, dose sparing and reduction of doses[17]. 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[18].

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)[19]. MPL is a natural agonist recognised 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[19]. 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[15]. ASO1 contains two immunostimulatory molecules, MPL and the saponin QS-21, formulated together in liposomes[18]. This is used in malaria and zoster vaccines[19].

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[16]. An inactivated SARS–CoV-2 vaccine, "Covaxin", incorporates a new adjuvant, idazoquinoline (Algel-IMDG), which also activates TLR, in this instance TLR 7/8[20].

The mRNA vaccines used during the Covid epidemic contained lipid nanoparticles (LNP) enclosing the mRNA. The LNP act as an adjuvant by enhancing uptake and recruiting cells[21].

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.

References

1. Turvey SE, et al. Innate immunity. *Journal of Allergy and Clinical Immunology*. 2010; 125(2 Suppl 2): S24-32.
2. Abbas AK, et al. Cellular and Molecular Immunology. 11th Ed. Philadelphia. Elsevier.2025
3. Iwasaki A, et al. Control of adaptive immunity by the innate immune system. *Nature Immunology.* 2015**;** 16:343-53.
4. Netea MG, et al. Trained innate immunity: Concept, nomenclature, and future perspectives. *Journal of Allergy and Clinical Immunology*. 2024; 154(5):1079-1084.
5. Pace D. Glycoconjugate vaccines. *Expert Opinion on Biological Therapy*. 2013; 13(1):11–33.
6. Pollard AJ, et al. A guide to vaccinology: from basic principles to new developments. *Nature Reviews Immunology*. 2021; 21:83–100.
7. Chaudhary N, et al. mRNA vaccines for infectious diseases: principles, delivery and clinical translation. *Nature Reviews: Drug Discovery*. 2021; 20:817–838.
8. Sheridan C. First COVID-19 DNA vaccine approved, others in hot pursuit. *Nature Biotechnology* 2021. https://www.nature.com/articles/d41587-021-00023-5. Accessed 12th Feb 2022
9. Siegrist CA, et al. Vaccine Immunology. In: Orenstein W, et al, Editors. Plotkin's Vaccines. 8th edition. Philadelphia, PA: Elsevier. 2022; 17-36.
10. Ritz N, et al. Influence of BCG vaccine strain on the immune response and protection against tuberculosis. *FEMS Microbiology Reviews*. 2008; 32:821–841.

11. Baydemir I, et al. Trained immunity-inducing vaccines: Harnessing innate memory for vaccine design and delivery. *Clinical Immunology*. 2024 ; 261:109930.
12. de Lalla F, et al. Immune response to hepatitis B vaccine given at different injection sites and by different routes: a controlled randomised study. *European Journal of Epidemiology*. 1988 ; 4(2):256-258.
13. Payne RP, et al. Immunogenicity of standard and extended dosing intervals of BNT162b2 mRNA vaccine, *Cell*. 2021; 184 (23):5699-5714.
14. Chiu N C, et al. To mix or not to mix? A rapid systemic review of heterologous prime – boost Covid-19 vaccination. *Expert Review of Vaccines*. 2021;20 (10):1211–1220.
15. Slifka MK, et al. How advances in immunology provide insight into improving vaccine efficacy. *Vaccine*. 2014; 32(25):2948–2957.
16. Pulendran B, et al. Emerging concepts in the science of vaccine adjuvants. *Nature Reviews Drug Discovery*. 2021; 20:454–475.
17. Coffman RI, et al. Vaccine adjuvants: putting innate immunity to work. *Immunity*. 2010; 33(4):492-503
18. Alving CR, et al. Adjuvants for human vaccines. *Current Opinion in Immunology*. 2012; 24(3): 310–315.
19. O'Hagan DT, et al. The continued advance of vaccine adjuvants – 'we can work it out'. *Seminars in Immunology*. 2020; 50:101426.
20. Ella R, et al. A Phase 1: Safety and Immunogenicity Trial of an Inactivated SARS-CoV-2 Vaccine-BBV152. *Lancet Infectious Diseases*. 2021; 21:637–646.
21. Lavelle EC, et al. Vaccine adjuvants: Tailoring innate recognition to send the right message. *Immunity*. 2024; 57(4):772-789.

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CHAPTER 3

GENERAL INFORMATION ON VACCINES

Vaccines contain weakened or inactivated organisms, or their antigens, that stimulate an immune response without causing disease. Some newer vaccines use genetic blueprints to produce antigens in the body. Despite inherent batch variability, safety and efficacy are ensured through good manufacturing practices, quality control, and cold-chain maintenance.

As a non-producing country, Sri Lanka ensures vaccine quality through stringent registration, lot release, AEFI surveillance, and access to laboratory testing when required.

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

- Nucleic acid based
- Viral vectored

Live attenuated vaccine

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

Inactivated Vaccines

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

e.g. Inactivated polio, inactivated influenza, 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 (primary course) 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. recombinant vaccines, toxoids, polysaccharide vaccines

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

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, pneumococcal conjugate vaccine (PCV), 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 information 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.

a. 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 amount of 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. However, the key advantages of mRNA vaccines include having fewer side effects and being more immunogenic even in the elderly and immunocompromised. The ability to develop vaccines rapidly against different strains of pathogens is an added advantage.

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

b. 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 transcribed to mRNA within the cell nucleus before it could be translated to protein antigens which stimulate an immune response. Presently there is one DNA vaccine that is registered and several others 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

a. 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

b. 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)
- Intranasal route: administered into the nose (live influenza vaccine)
- 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)

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 Immunisation 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 immunisations

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

Unknown or uncertain immunisation status

A physician may encounter some children with uncertain immunisation status. Many young adults and some children do not have adequate documentation of immunisations and recollection by the parent or guardian may be of questionable validity. In general, these persons should be considered disease susceptible and appropriate immunisations 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[4].
- When vaccines are administered simultaneously, separate syringes and different 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[4].
- Several live vaccines could be administered on the same day at different sites. If parenteral live vaccines are not administered concurrently, a minimum gap of 4 weeks should be kept between immunisations[4].
- 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 are not recommended to be given within three months of receiving immunoglobulin, blood or blood products. The interval depends on the blood product, and vaccine (refer Chapter 35).

Antimicrobial therapy and vaccination

Antimicrobial therapy is not a contraindication to vaccination, with the following exceptions[4];

- Vaccination with the 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 virus-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 immunisation has successfully reduced the incidence of vaccine-preventable diseases, vaccination could cause both minor and rarely, serious adverse effects. Public awareness and controversy about vaccine safety have 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 for 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 is 1.3 episodes per million vaccine doses administered for all vaccines[5].

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[6].

Allergy to vaccine components

Vaccine components could cause allergic reactions in some recipients. These reactions could be local or systemic and could be mild, moderate or severe, which rarely include anaphylaxis. The vaccine components responsible could include the vaccine antigen or more frequently the excipients such as animal proteins, antibiotics or stabilizers, such as gelatin[6].

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[7]. 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[8].

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 immunisation with these vaccines. While gelatin is the culprit allergen in the West and Japan, BSA is implicated in Sri Lanka[9]. Patients who develop anaphylaxis to cows' milk or red meat should consult a specialist before immunisation 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 33).
- 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.

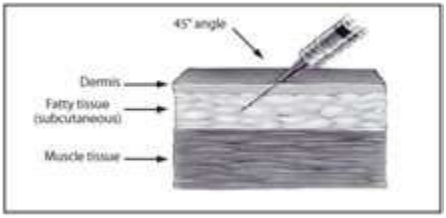
- Because of the theoretical risk to the fetus, women known to be pregnant should not receive live attenuated vaccines[3].

Injection techniques

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

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

1. Subcutaneous (SC) injections



Subcutaneous injections are recommended to be administered at a 45^0 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[10].

Sites recommended for subcutaneous injections:

Upper Arm: Deltoid region

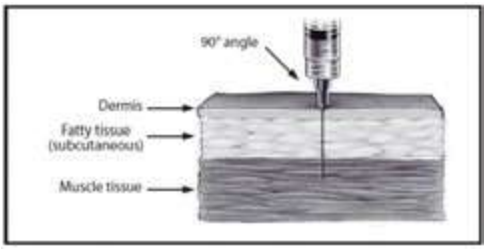
Abdomen: On either side of the umbilicus

Thigh**:** Antero-lateral region



Sites on the body where a subcutaneous injection can be given

2. Intramuscular (IM) injections



Intramuscular injections are recommended to be administered at a 90^0 angle.

All adjuvanted vaccines should be given IM.

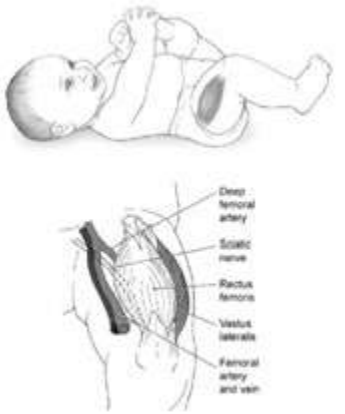
Sites recommended for intramuscular injections:

Infants - antero-lateral thigh

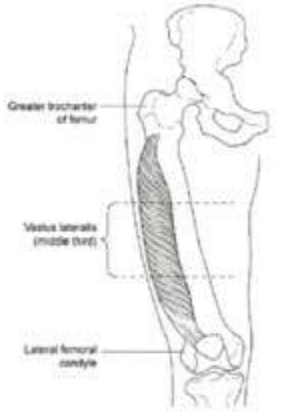
Children over 1 year and adults - deltoid region

Needle size:

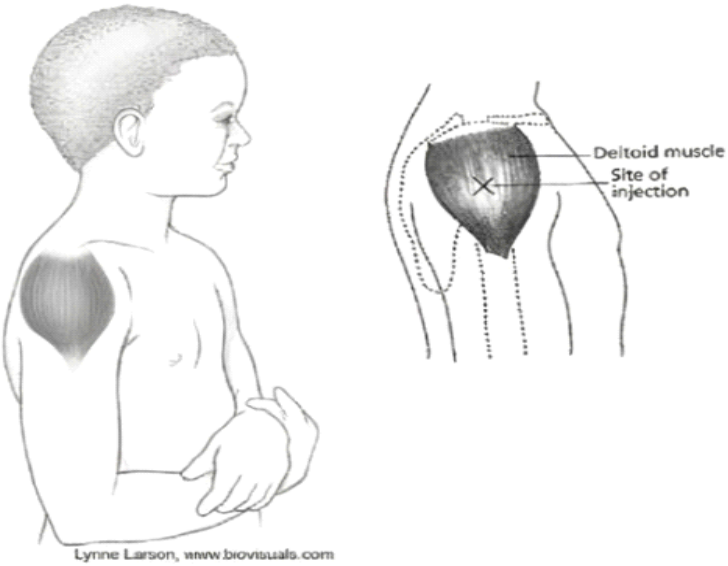
Intramuscular injections should go into the muscle below the subcutaneous layer. Therefore, the needle must be thicker and longer to ensure that the vaccine is injected into the muscle. Pull back the plunger to make sure that you are not in a blood vessel before injecting the vaccine. Needles that are 23-25G and 1 to 1.5 inches long are usually appropriate[10].



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



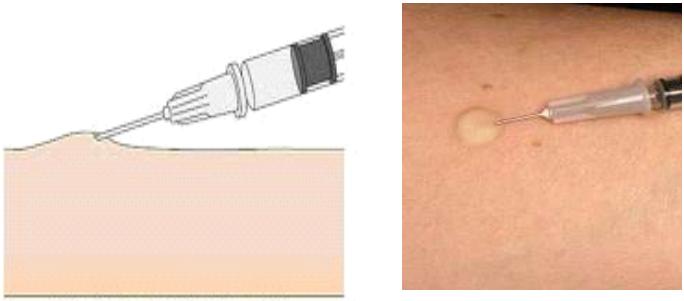
The vastus lateralis site of the right thigh, used for an intramuscular injection



Intradermal (ID) injections

For intradermal injection, a needle of 27G and $^{3}/_{8}$ to $^{3}/_{4}$ 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

Documentation of vaccination (Immunisation record)

The immunisation record provides a history of all the vaccines administered. It is crucial for tracking a person's immunisation status.

A person receiving any vaccine/s, should be given a clearly written immunisation card/record. This record should include the following information:

- name and the date of birth/age of the vaccinee
- date of vaccination
- name/s of vaccine/s administered (attach vaccine vial label/sticker or clearly written batch number and date of expiry)
- vaccine dose and route of administration
- name, designation and signature of health care provider and place of vaccination
- if a series of vaccination is required, dates for the next vaccination/s
- comments on any significant observation/adverse events following immunisation

The vaccinee or the parent/guardian should be educated regarding the importance of retaining this record and producing it during subsequent visits to health care settings/providers.

References

1. Pollard A J, et al. A guide to vaccinology: from basic principles to new developments. *Nature Reviews Immunology*. 2021; 21(2):83-100.
2. Kimberlin DW, et al, editors. Interchangeability of vaccine products. In: Red Book: 2021–2024 Report of the Committee on Infectious Diseases. 32nd ed. Itasca (IL): American Academy of Pediatrics; 2021. p. 34–35.
3. CDC. General recommendations on immunisation. *Morbidity and Mortality Weekly Report*. 2011 Jan 28;60(RR-2):1–60.
4. CDC. General best practice guidelines for immunisation. *Morbidity and Mortality Weekly Report*. 2022 Mar 15;71(1):1–XX.
5. Kroger A, et al, editors. General best practice guidelines for immunisation: best practices guidance of the Advisory Committee on Immunisation Practices (ACIP) [Internet]. Atlanta (GA): Centers for Disease Control and Prevention; [cited 2025 Mar 3]. Available from:

https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/downloads/general-recs.pdf

6. McNeil MM. Vaccine-Associated Anaphylaxis. *Current Treatment Options in Allergy*. 2019;6 (3):297-308. doi: 10.1007/s40521-019-00215-0.
7. Update: Vaccine side effects, adverse reactions, contraindications, and precautions - recommendations of the Advisory Committee on Immunisation Practices (ACIP) *Morbidity and Mortality Weekly Report* 1996; (RR-12):1-35.
8. UK Health Security Agency. Yellow fever: the Green Book, chapter 35–yellow fever immunisation information for public health professionals [Internet]. London: GOV.UK; 2013 Mar 20 [updated 2024 Feb 6; cited 2025 Mar 17]. Available from: https://www.gov.uk/government/publications/yellow-fever-the-green-book-chapter-35
9. Kelso JM, et al. Task Force Report - Adverse reactions to vaccines, practice parameter: update on egg allergy and influenza vaccine. *Journal of Allergy and Clinical Immunology* 2012; 130 **(1)**: 35-39.
10. De Silva NR, et al. Sensitisation to bovine serum albumin as a possible cause of allergic reactions to vaccines. *Vaccine* 2017;35(11): 1494–1500.
11. Royal College of Nursing. Safe injection technique [Internet]. London: Royal College of Nursing; [cited 24 March 2026]. Available from: http://www.evidence.nhs.uk

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CHAPTER 4

BACILLUS CALMETTE - GUÉRIN (BCG)

Introduction

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, remains one of the most significant infectious diseases worldwide. Despite being a preventable and curable disease, TB remains a significant global health burden, ranking among the top 10 causes of death worldwide[1]. The burden of TB is disproportionately high in low- and middle-income countries, where factors such as poverty, overcrowding, malnutrition, and limited access to healthcare services contribute to its persistence[2].

According to the WHO Global Tuberculosis Report 2025, an estimated 10.7 million people developed TB globally and 1.23 million deaths were reported globally. The TB incidence rate (new cases per 100 000 population per year) was 131 and the case fatality rate was 11.5%[3].

The emergence of drug-resistant TB further complicates control efforts, with multidrug-resistant TB and extensively drug-resistant TB posing serious threats to global TB elimination strategies[3,4]. TB is also closely linked with HIV infection, as co-infection accelerates disease progression and increases mortality risk[3].

TB is one of the top 10 causes of death worldwide and the leading cause of death from a single infectious agent. Most of the people who develop TB disease each year, are in 30 high TB burden countries: they accounted for 87% of the global total in 2024. The top eight (67% of the worldwide total) were India (25%), Indonesia (10%), the Philippines (6.8%), China (6.5%), Pakistan (6.3%), Nigeria (4.8%), the Democratic Republic of the Congo (3.9%) and Bangladesh (3.6%)[3,4]. In 2024, 54% of people who developed TB were men, 35% were women and 11% were children. Children account for an estimated 1.3 million TB cases annually, reflecting their vulnerability to rapid disease progression following infection[3].

Sri Lanka is considered a low-incidence country within the South-East Asian region, but TB remains an important public health concern. The estimated incidence in Sri Lanka is approximately 62 cases per 100,000 population, with several thousand cases reported annually. Gaps between estimated incidence and notified cases indicate that undiagnosed or unreported cases persist[5]. According to the National Programme for Tuberculosis Control and Chest Diseases (NPTCCD), approximately 8,000 new TB cases are reported annually, underscoring the critical need for early and effective diagnostic and treatment strategies to control the disease spread[6,7].

The UN Sustainable Development Goals include ending TB epidemics by 2030 and to reach this goal, in 2015 the WHO Member States endorsed the End TB Strategy which aims to reduce the number of TB deaths by 95% by 2035. This goal focuses on early detection and treatment of TB in all patients, prevention for populations at risk by vaccination and supportive system to strengthen the health and social sectors[8].

The Bacillus Calmette–Guérin (BCG) vaccine, first introduced in 1921, remains the only licensed vaccine against TB. BCG provides the greatest protection against severe forms of childhood TB, particularly tuberculous meningitis and disseminated (miliary) TB. BCG vaccination has also been shown to confer partial protection against leprosy and may provide protection against certain non-tuberculous mycobacterial infections. Additionally, attenuated *M bovis* BCG is used therapeutically in non-muscle-invasive bladder cancer as an intravesical immunotherapy[8].

Protection against pulmonary TB and TB infection is more variable and depends on factors such as geographic location, exposure to environmental mycobacteria, host immune responses, and vaccine strain. It has been shown that high global coverage (90%) and widespread use of BCG in routine infant vaccination programmes could prevent over 115 000 TB deaths per birth cohort in the first 15 years of life[8].

BCG vaccination was introduced in Sri Lanka in 1949 and has remained an integral component of the National Immunisation Programme (NIP), achieving high coverage levels and contributing to protection against severe childhood TB.

Types of Vaccine

BCG is a live attenuated bacterial vaccine derived from *M bovis*. The BCG vaccine, was first produced serial subculturing of *M bovis* by Albert Calmette and Camille Guérin at the Pasteur Institute in Lille, France, between 1908 and 1921 which eventually led to its attenuation. Once the vaccine's efficacy was established, Calmette and Guerin distributed their strain globally in 1924 to regions that requested their newfound vaccine[9,10].

Since 2004, the following strains have accounted for 90% of BCG vaccinations worldwide[9,10].

These include

- Pasteur 1,173 P2 (France)
- Danish 1,331 (Denmark)
- Glaxo 1,077 (Danish derivative)
- Tokyo 172-1 (Japan)
- BCG-1 (Russia)

According to the most recent update of the BCG World Atlas (2020), the most widely used BCG vaccine strains globally are Danish 1,331 (16.6%), Pasteur 1173P2 (9.2%), and Tokyo 172 (7.3%)[10].

Today, BCG vaccine strains vary in their ability to induce immune responses. Multiple studies have demonstrated significant differences in both the magnitude and quality of neonatal immune responses elicited by various strains[11].

Efficacy

The BCG vaccine confers strong protection against severe forms of tuberculosis in children such as miliary TB and tuberculous meningitis. It gives 70–85% protection against tuberculous meningitis and miliary

TB in children. The efficacy of BCG vaccine in preventing adult pulmonary TB, particularly in high-burden settings, remains limited[12,13].

Factors influencing the BCG vaccine efficacy include[14]

- Geographical variation
- Exposure to environmental mycobacteria
- Genetic background
- Nutritional status
- Age at vaccination
- Co-infections (e.g. HIV)
- Immunocompromised state

Protection after BCG vaccination could last for up to 10 to 15 years and the protection will decline with time[8].

Indications

According to the WHO recommendations, countries or settings with a high incidence of TB and/or high leprosy burden, a single dose of BCG vaccine should be administered at birth as soon as possible to all healthy neonates, for prevention of TB and leprosy[8].

If BCG vaccine cannot be given at birth, it should be given at the earliest opportunity thereafter and should not be delayed, in order to protect the child before exposure to infection occurs. BCG can be administered simultaneously with other routine childhood vaccines at different injection sites[8].

BCG Scar

A characteristic local reaction occurs following BCG vaccination:

- A small papule develops at the injection site within 2–3 weeks
- The lesion may ulcerate slightly
- Healing occurs over 6–12 weeks, leaving a superficial scar

The presence of a scar is commonly used as evidence of vaccination. However, the absence of a visible scar does not necessarily indicate vaccine failure, and the lack of scar formation alone is not an indication for revaccination[8].

Vaccination in older age groups

BCG vaccination of unvaccinated, TST-negative school children may provide long term protection up to 20 years or longer[8].

BCG vaccination of older age groups is recommended for the following[8].

- Unvaccinated TST negative older children, adolescents and adults from settings with high incidence of TB and/or high leprosy burden
- Unvaccinated TST negative older children, adolescents and adults moving from low to high TB incidence/ leprosy burden settings
- Unvaccinated TST negative persons at risk of occupational exposure in low and high TB incidence areas (e.g. health-care workers, laboratory workers, medical students, prison workers, other individuals with occupational exposure)

Vaccination of preterm infants and low birth weight infants

Based on limited available evidence from small observational studies conducted in different high TB endemic settings, BCG vaccination at birth in healthy preterm infants born after 32–36 weeks of gestation was found to be safe and effective[8].

Storage

Store between 2-8 °C. It should be protected from light and not frozen.

After reconstitution:

- The vaccine should be used within six hours
- The remaining vaccine should be discarded as infectious waste
- If not used immediately after reconstitution, the vaccine should be kept cool (2-8°C) and protected from light

- As reconstituted BCG vaccine does not contain a preservative, all opened multi-dose vials must be discarded at the end of the immunisation session, or within 6 hours, whichever comes first

BCG is a live attenuated vaccine, so maintaining the cold chain **(2–8 °C)** from manufacture to administration is essential to preserve potency[15].

Dosage

Vaccine should be reconstituted according to the manufacturers instructions in the leaflet supplied with the vaccine ampoule/vial. The reconstituted vaccine contains a homogenous suspension of BCG vaccine in a concentration of 0.5 mg per mL[16].

The reconstituted vaccine is given intradermally at a dosage of

- 0.05 mL for children below one year
- 0.1 mL for aged one year or above

Administration

The site of inoculation should be in the deltoid region (i.e., halfway down the deltoid muscle) in the left upper arm. It is more likely lead to keloid formation if given at higher sites and the tip of the shoulder should be avoided[16].

Correct intradermal BCG vaccination results in minor local reactions (erythema, induration,tenderness) followed by a small ulceration at the site of injection which usually heals within 4-6 weeks leaving behind a scar. Presence of a scar is used as a marker of previous BCG vaccination[16].

The age and immune status of the vaccinee, the skills of the vaccinator, as well as the strain and dose of the BCG vaccine, may influence the extent of these responses[16].

Antiseptics should not be applied over the site prior to injection and the WHO states that **no skin disinfection is needed** for BCG unless the skin is visibly soiled. If the skin is visibly soiled, normal saline or distilled water could be used to clean the area[17].

The national policy of Sri Lanka is that a single dose of BCG vaccine should be given to all the infants as soon as possible after birth[16].

Revaccination

The **World Health Organization (WHO) does NOT recommend BCG revaccination.** Evidence suggests that revaccination does not provide significant additional protection against tuberculosis or leprosy[18].

Therefore:

- a negative TST or IGRA is not an indication for repeat vaccination
- absence of a BCG scar alone is not an indication for revaccination

If children are brought without a scar (after 6 months of the initial dose) despite BCG vaccination they could be revaccinated with a 2nd dose of BCG vaccine after 6 months up to 5 years of age even without doing a Mantoux test. Even in the absence of BCG scar following the second dose a further dose is not recommended[16].

Contraindications

BCG vaccine is contraindicated for the following individuals[10].

- Individuals known to be allergic to any component of the vaccine
- Pregnancy
- Congenital or severe combined immunodeficiency syndromes
- Immunodeficiency syndromes (e.g. HIV/AIDS, known or suspected congenital Immunodeficiency, leukaemia, lymphoma or other malignant diseases)
- Patients undergoing immunosuppressive treatment (e.g. corticosteroids, alkylating agents, biological response modifiers, antimetabolites, radiation)
- Infants exposed to immunosuppressive treatment in utero or via breastfeeding

Precautions

Special considerations apply in certain situations[10].

- Infants born to mothers with active TB,
    - Neonates should be evaluated for congenital TB
    - If asymptomatic, TB preventive therapy may be initiated
    - BCG vaccination can be given after completion of preventive therapy if the infant remains healthy
- Neonates receiving intravenous antibiotics - after the antibiotic course is complete with a minimum interval of 6 hours from the last dose
- Premature babies – at the time of discharge from the hospital
- BCG vaccination should be deferred in newborns listed below until further investigations are completed
    - Neonates with siblings who have a confirmed inborn error of immunity
    - Neonates with a family history suggestive of an immune disorder (severe or recurrent infections, BCGosis) or unexplained sibling death in infancy

      Such neonates should be referred to a consultant paediatrician / immunologist for advice.

Adverse Effects

Adverse events/complications of BCG vaccination are local and may be a result of improper vaccination technique such as subcutaneous / intramuscular injection or inadequate sterile measures taken during vaccination[16].

Most adverse effects following vaccination are mild and self-limiting.

- Non healing ulcer - ulcer which develops at BCG site usually heals by 6 weeks. Rarely, it

  fails to heal.
- Abscess formation at the site.

- Enlargement of regional lymph nodes with or without abscess formation (BCG adenitis).

  A minor degree of adenitis (1-2 cm) in left axilla may occur in the weeks following vaccination and should not be regarded as a complication. In fact, such nodal enlargement is a sign of successful vaccination. However, rarely, enlarged regional nodes become larger and may suppurate.

- Disseminated infection with *M bovis* – BCG is a live vaccine of attenuated *M bovis*.

  Therefore, systemic or disseminated infection can occur only if there is an impairment of immunity.

- Anaphylactic reactions may occur rarely

Management of adverse events

Since faulty immunisation technique can cause local complications, measures should be taken to teach proper immunisation technique to nurses. Local complications are usually self-limiting. However, isoniazid may be given for 3- 6 months for non-healing ulcers or sinuses if they do not respond to an initial course of antibiotics such as erythromycin[16].

Enlarged nodes without suppuration usually resolve spontaneously and are not an indication for treatment with isoniazid. However, a large non-suppurative node may need surgical excision.

In the case of suppurative lymphadenitis, incision and drainage (not aspiration) should be done before commencing a course of isoniazid. Where there is a discharge or suppuration, it is always better to collect a sample for both AFB and pyogenic culture[16].

Co-administration of vaccines

The BCG vaccine is supplied as a freeze-dried preparation that must be reconstituted with the provided diluent[8,16].

There is evidence that BCG vaccine can be safely co-administered with other routine childhood vaccines such as diphtheria-pertussis-tetanus

(DTP), polio, hepatitis B, Haemophilus influenzae type b (Hib) and measles and rubella vaccines[8].

New Tuberculosis Vaccines in Development

Although the only vaccine used against TB is BCG, it is not protective against adult TB or endemic areas. Therefore, the development of new vaccines remains a strategically important and urgent task in the global fight against tuberculosis. There appear to be three different approaches to vaccine development: development of an entirely new TB vaccine, creation of a novel recombinant vaccine derived from the existing BCG vaccine, and development of a booster vaccination to reinforce an existing BCG[19].

The first approach involving a novel vaccine were based on the use of different mycobacterial species, construction of fusion proteins and insertion of an antigenic protein into a viral vector[19].

- *Mycobacterium incidus pranii* (MIP) - Development status is under Phase III trials
- *Mycobacterium vaccae (M. vaccae)* - Development status is under Phase III trials
- M72/AS01E - Development status is under Phase II trials
- RUTI - Development status is under Phase II trials

Development of a novel recombinant vaccine derived from an existing BCG strain was used subsequently and current evidence supports the efficacy of these vaccines. Currently, there are four recombinant BCG vaccines under investigation to replace the parental BCG strain[19].

- VPM1002 - Development status is under Phase II Trails

Development of a BCG vaccine augmenting booster vaccine –

The concept of BCG revaccination as a booster in BCG-primed populations has been investigated over the past decades with conflicting results[19].

- BCG revaccination – they are under Phase II trials

Yet, the BCG vaccine remains the only licensed TB vaccine worldwide, and neonatal BCG vaccination remains a cornerstone of TB prevention in many countries.

References

1. Glaziou P, et al. Global epidemiology of tuberculosis. *Seminars in Respiratory and Critical Care Medicine*. 2018; 39(3):271–85. de/DOI/DOI?10.1055/s-0038-1651492
2. Ratnawati EB, et al. Comparison of tuberculin skin test and interferon-gamma release assay in the diagnosis of latent tuberculosis infection among Indonesian healthcare workers. *Journal of Natural Science, Biology and Medicine*. 2019; 10:53–59.
3. World Health Organization. Global tuberculosis report 2025. Geneva: WHO; 2025. 1–58.
4. OECD, World Health Organization. Health at a glance: Asia/Pacific 2024 [Internet]. OECD; 2024 [cited 2025 Jan 12]. Available from: https://www. oecd.org/en/publications/health-at-a-glance-asia-pacific-2024_51fed7e9-en.html.
5. Epidemiology Unit, Ministry of Health Sri Lanka. TB annual report 2023. Colombo: Ministry of Health; 2023.
6. Hewage S, et al. Active screening of patients with diabetes mellitus for pulmonary tuberculosis in a tertiary care hospital in Sri Lanka. *PLoS One*. 2021; 16(4):e0249787.
7. Mohotti BK, et al. Extra pulmonary tuberculosis: a retrospective study in Matara District, Sri Lanka. *Journal of Ruhunu Clinical Society*. 2020; 25(1):30–4. Available from: https://account.jrcs.sljol.info/index.php /sljo-j-jrcs/article /view/93.
8. World Health Organization. The End TB Strategy [Internet]. 2015 [cited 2017 Oct]. http://www.who.int/tb/strategy/endtb/en/.
9. World Health Organization. BCG vaccines: WHO position paper. *Weekly Epidemiological Record.* February 2018. Geneva: WHO; 2018.
10. Brosch R, et al. Genome plasticity of BCG and its impact on vaccine efficacy. *Proceedings of the National Academy of Sciences USA*. 2007; 104(13):5596–601.
11. Oettinger T, et al. Development of the *Mycobacterium bovis* BCG vaccine: review of historical and biochemical evidence for a genealogical

tree. *Tubercle and Lung Disease*. 1999; 79(4):243–50.

12. Asadian M, et al. Genomic characteristics of two widely used BCG vaccine strains: Danish 1331 and Pasteur 1173P2. *BMC Genomics*. 2022; 23(1):609.
13. Colditz GA, et al. The efficacy of bacillus Calmette-Guérin vaccination of newborns and infants in the prevention of tuberculosis: a meta-analysis. *Pediatrics*. 1995; 96(1):29–35.
14. Ali SH, et al. Efficacy, immunogenicity, and safety of BCG revaccination against Mycobacterium tuberculosis: a systematic review and meta-analysis. *Human Vaccines & Immunotherapeutics*. 2026; 22(1): 2630512.
15. World Health Organization. Temperature sensitivity of vaccines. Geneva: WHO; 2006. (WHO/IVB/06.10).
16. National Programme for Tuberculosis and Chest Diseases. National manual for tuberculosis control – update 2021. Sri Lanka: Ministry of Health; 2021.
17. World Health Organization. WHO best practices for injections and related procedures toolkit. Geneva: WHO; 2010.
18. World Health Organization. SAGE Working Group report [Internet]. 2017 [cited 2017 Sep]. Available from: http://www.who.int/immunisation/sage/ meetings/2017/october/en/
19. Cho T, et al. A review of the BCG vaccine and other approaches toward tuberculosis eradication. *Human Vaccines & Immunotherapeutics*. 2021; 17(8):2454–70.

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CHAPTER 05

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. Reported cholera cases rose by 5% and deaths by 50% in 2024 compared to 2023, with more than 6000 people dying from a disease that is both preventable and treatable[1]. While these numbers are themselves alarming, they are underestimates of the true burden of cholera. The case fatality rate can exceed 50% among untreated severe cases, but with adequate and timely rehydration, the case-fatality ratio is <1%[2].

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 the 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[3]. *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 is named as

subtype Hikojima[3]. There is no known cross-protection between the O1 and O139 serogroups.

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[4]. 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. This variant which appears to be the predominant strain globally at present, is more virulent and causes more severe illness than the original El Tor strains[5].

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 faecal contaminated water, shellfish or other foods. Person-to-person spread may occur through the faeco-oral route.

Risk of cholera is very rare in travellers from non-endemic countries to endemic countries, with a risk of 0.01-0.001% per month of stay[4].

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 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. In 2023, the 7th cholera pandemic continued to surge, with 535,321 cases reported to WHO, up from 472,697 in 2022. Cholera cases were reported from 45 countries, territories and areas, an increase from 44 in 2022 and 35 in 2021[1]. 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 mobilisation. 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 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)[6]
    - WC, killed modified whole cell bivalent (O1 and O139) vaccines without the B subunit[4,6]. There are 2 formulations of this, where one (simplified formulation) could be administered as a single dose especially in outbreak situations.
- Live attenuated oral vaccine
    - Live attenuated oral single-dose vaccine (lyophilised CVD 103-HgR)[6]. It protects against toxigenic strains of *V cholerae* O1 but not against serogroup O139. It is approved in the USA for adult travellers[1,7,8.]

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% against El Tor and classical cholera combined, and slightly lower against El Tor than classical cholera3,4. The OCV are reported to be effective against the El Tor variants as well[9].

Live attenuated oral 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[9,10,11].

Because of the limited availability of OCV, the International Coordinating Group (ICG), which manages the OCV emergency stockpile, took the unprecedented decision in October 2022 to temporarily suspend the standard 2-dose vaccination regimen in cholera outbreak response campaigns and instead used a single-dose approach, which was accepted by the Strategic Advisory Group of Experts on Immunisation (SAGE)[1].

The change in strategy, which continued throughout 2023 and into 2024, enabled the available vaccines to protect more people and responses to cholera outbreaks amidst the ongoing supply shortfall. Evidence on the duration of protection is limited.

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)[4].
- 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[7].

Since immunisation 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. OCV is safe during pregnancy.

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]. Immunisation 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. (Refer Table 1 for vaccine schedule).

Table 1: Vaccination schedule

Product	Age group	Primary immunisation	Booster for individuals with continuing risk of infection or before re-exposure[3]
WC-rBS	Adults and 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 immunisation should be restarted	Duration after previous vaccination • < 2 years - a single dose • ≥2 years – full vaccination (2 doses)
	Children 2-5 years of age	3 doses, at least 1-6 weeks-apart. If the subsequent dose is delayed for more than 6 weeks, the primary course should be restarted	Duration after previous vaccination • ≤6 months - a single dose • >6 months – full vaccination
Modified killed WC	Adults and children ≥1 year of age	2 doses, 14 days apart For outbreaks - recommendation is a single dose of vaccine (Protection last for about 1year)	Manufacturer has not given recommendations on re-vaccination
Oral live attenua -ted [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]	

*A single-dose vaccination regimen was introduced in 2022 as a cholera outbreak response.

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[4].
- 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[4]. 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[12]. No data exist on use of CVD 103-HgR in pregnant or breastfeeding women[8.12].

Adverse events

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

Contraindications

Vaccine should not be administered to persons with either known hypersensitivity to any component of the vaccine or having shown signs of severe reactions due to previously taken doses.

Storage

2-8 °C. Do not freeze.

References:

1. World Health Organization. Weekly epidemiological record. *Weekly Epidemiological Record*. 2024 Sep 6;(36).
2. Centers for Disease Control and Prevention (CDC). Cholera. In: CDC Yellow Book. 2025 Apr 23. https://www.cdc.gov/yellow-book/hcp/travel-associated-infections-diseases/cholera.html
3. Baber MR. *Vibrio, Mobilincus, Gardnerella and Spirillum*. In: Guide to microbial infections: pathogenesis, immunity, laboratory investigation and control. 19th ed. 2018. p. 221–226.

4. World Health Organization. Cholera vaccines: WHO position paper. *Weekly Epidemiological Record*. 2017; 92(34):477–500.
5. Sambe-Ba B, et al. Identification of atypical El Tor *Vibrio cholerae* O1 Ogawa hosting SXT element in Senegal, Africa. *Frontiers in Microbiology*. 2017; 8:748.
6. Centers for Disease Control and Prevention (CDC). Vaccines for cholera. https://www.cdc.gov/cholera/vaccines.html
7. World Health Organization, Centers for Disease Control and Prevention (CDC). Background paper on whole-cell, killed, oral cholera vaccines. 2017 Mar 31.
8. Wong KK, et al. Recommendations of the Advisory Committee on Immunisation Practices for use of cholera vaccine. *Morbidity and Mortality Weekly Report*. 2017; 66(18):482–485.
9. Medscape. Vaxchora (cholera vaccine). 2021 Feb 3 [cited 2022 Jun 27]. https://reference.medscape.com/drug/vaxchora-cholera-vaccine-1000082
10. Shaik H, et al. Current and future cholera vaccines. *Vaccine*. 2020; 38:A118–A126. doi:10.1016/j.vaccine.2019.12.011
11. Centers for Disease Control and Prevention (CDC). Cholera vaccine for travellers. 2022 Jun 8 https://wwwnc.cdc.gov/travel/news-announcements/cholera-vaccine-for-travellers
12. Khan AI, et al. Safety of oral cholera vaccines during pregnancy in developing countries. Human Vaccine Immunotherapy. 2017; 13(10):2245–6. doi:10.1080/21645515.2017.1356525

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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 6th February, 2026, there have been 779,088,505 confirmed cases and 7,109,667 deaths[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 protein S. The spike protein, including the receptor binding domain (RBD), are the chief antigenic targets for the immune response.

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. Viral RNA has been detected up to 7-12 days of symptom onset[4]. The incubation period is 1-14 days (typically 4-5 days).

The infectivity rates differ, depending on the variant. The estimated reproductive number (R_0) for the original wild-type strain was 2.8, with subsequent strains becoming more infectious. The Delta strain had an estimated R_0 of 5.1 and the Omicron strain an estimated R_0 of 9.5[4].

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[1,3,5]) had a worse prognosis. However, with widespread immunisation, the severity has decreased, even in those with co-morbidities[6].

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 (thrombocytopaenia, thrombosis)[1].

Some patients may develop persistent neurological, respiratory or cardiovascular symptoms. These are termed "long COVID-19" or Post-Acute Sequelae of SARS-CoV-2 (PASC) infection, defined as symptoms that last for more than 3 months after onset[7].

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[8]. 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); sub lineages of Omicron include BA.1, BA.2, BA.3, BA.4, BA.5, XBB and BA.2.86[4,9]. The

current variant of interest is JN 1[9]. Recent strains are associated with less severe outcomes[4].

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). All vaccines produced neutralising antibody against S protein, blocking uptake of the virus, via the ACE receptor. The vaccines used elsewhere include, an adenovirus vector-based COVID-19 vaccine (Janssen Ad26.COV2-S [recombinant]) and a recombinant S protein (grown in baculovirus infected insect cells) as the antigen with the Matrix-MTM adjuvant (Novavax Nuvaxovid)[4]. A recently approved booster vaccine (Sanofi Pasteur, VidPrevtyn Beta®) also uses a recombinant S protein but is targeted against the Beta variant[4]. The AstraZeneca/Oxford and Gam-COVID-Vac "Sputnik V" vaccines are no longer available.

The mRNA vaccines use the pathogen's genetic code for the S protein, encoded in RNA, contained in lipid nanoparticles. These are taken up by host cells and the mRNA is translated; the protein then acts as an intracellular antigen to stimulate the immune response. mRNA is normally degraded within a few days[4].

Vaccine efficacy

The mRNA vaccines showed the highest efficacy in preventing symptomatic disease with a 2-dose regime in clinical trials (mRNA-1273 and BNT162b2, 94% and 95% respectively) compared to AZD1222/Chadox1 ncov-19 of 70%[4]. However, neutralising antibody (nAb) titres decline by 6 months, with the resultant need for boosters.

Studies also showed that a mix and match strategy (for example immunisation with a viral vector vaccine followed by an mRNA vaccine) lead to stronger and longer lasting immune response.

Reinforcing immunisation

A third adult dose of AstraZeneca, Novavax, Moderna and Pfizer BioNTech vaccines successfully boosted individuals who had been primed with two doses of Pfizer BioNTech or AstraZeneca vaccine around 3 months earlier[4]. Heterologous boosting showed higher antibody responses. However, mutations in the spike protein reduced nAb titres, and repeated booster doses were needed to increase nAb.

T cell responses were conserved, as the T cell epitopes were in more conserved regions of the virus (nucleocapsid, for example). SARS CoV 2 specific T cells showed durability and cross protection, even against variant strains. The continued emergence of new variants and subvariants, however, resulted in reduced general efficacy of the first-generation COVID-19 vaccines, requiring the development of second-generation vaccines aiming for longer-lasting protective effects. The Food and Drugs Administration (FDA) of the US instructed that bivalent vaccines incorporating antigens from both the ancestral strain and prevalent variants be used, to broaden immune response and circumvent immune evasion from variants. The initial bivalent mRNA vaccines from Pfizer and Moderna, incorporating ancestral Spike WA1/2020 and BA.1 were given emergency user license. Persons who had previously received 1 or 2 doses of monovalent vaccines showed an increased nAb to the Wuhan strain, but less so to the Omicron strain, even though statistically significant, compared to the monovalent vaccines. Subsequently, bivalent vaccines containing BA.4/5 were used in 2023. Monovalent vaccines by Pfizer and Moderna mRNA vaccines targeting the XBB 1.5 variant were approved for use in 2024, as well as mRNA vaccines against the JN.1 variant, approved in the UK, Europe and USA. USA has additionally approved the use of KP.2 variant vaccines[4].None of these vaccines are available in Sri Lanka.

Dosage[10]:

Table 1: Summary of the updated SAGE recommendations for COVID-19 vaccines[2]

Vaccination status	Population	Recommendation
Never received a COVID-19 vaccine	All adults	1 dose*
	Children and adolescents with comorbidities	
	Health workers with direct patient contact	
	Pregnant persons	1 dose
	Any individual who is immunocompromised	2-3 doses
Previously received at least 1 dose of a COVID-19 vaccine	Adults over 75 or 80 years old**	Revaccination 6-12 months after the most recent dose
	Adults over 50 or 60 years old[3] with comorbidities	
	Any individual who is immunocompromised	
	Adults over 50 or 60 years old**	Revaccination 12 months after the most recent dose
	Adults with comorbidities	
	Health workers with direct patient contact	
	Pregnant persons	Single dose in each pregnancy
	Healthy adults	Revaccination not routinely recommended
	Children and adolescents	

Legend

High-priority use groups	Subpopulations with special considerations

*2 doses recommended for inactivated vaccines

**Age cut-off depending on countries

Pfizer BioNTech COVID-19 vaccine (Comirnaty® JN.1)

Dose[4]

For those aged 12 years and above, the dose of the monovalent Pfizer BioNTech variant vaccines is 30 µg. The vaccine is supplied in a ready to use multi-dose vial containing 6 doses of 0.3mL.

A single dose of 0.3 mL should be administered, regardless of prior COVID-19 vaccination status, and at least three months from the previous dose.

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% [12]. Severe systemic effects, defined as those that interfere with daily activity, included fatigue in 4% and headache in 2%[12].

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 favorable. A few cases of erythema multiforme were also reported.

Paediatric Pfizer BioNTech COVID-19 vaccine (Comirnaty® 10 JN.1)

For children aged 5-11 years, the dose of Pfizer BioNTech COVID-19 vaccine is 10 µg. The paediatric monovalent variant vaccine is supplied in a ready to use single dose vial containing 1 dose of 0.3mL.

Moderna COVID-19 vaccine (Spikevax® JN.1)

Dose:

For those aged 18 years and above, the dose of the monovalent Moderna variant vaccines is 50 μg. A single dose of 0.5 mL should be administered, regardless of prior COVID-19 vaccination status, and at least three months from the previous dose.

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.

Paediatric Moderna COVID-19 vaccine (Spikevax® JN.1) f

From 6 months of age, 0.25 ml per dose.

See package insert for dosages.

Table 2: WHO recommendations for vaccination[11]

High priority-use groups		
Target population	***Vaccination of persons who have never received a COVID-19 vaccine***	***Revaccination of persons who have received at least 1 dose of a COVID-19 vaccine***
Oldest adults Older adults with multiple comorbidities that put them at a higher risk of severe COVID-19	Single dose	6-12 months after previous dose

Older adults Older adults with obesity or a comorbidity that put them at a higher risk of severe COVID-19	Single dose	Approximately 12 months after previous dos

Medium priority-use groups		
Target population	***Vaccination of persons who have never received a COVID-19 vaccine***	***Revaccination of persons who have received at least 1 dose of a COVID-19 vaccine***
Healthy adults Children and adolescents aged 6 months to 17 years with severe obesity or a comorbidity that put them at a higher risk of severe COVID-19	Single dose	Not routinely recommended

Low priority- use groups		
Target population	***Vaccination of persons who have never received a COVID-19 vaccine***	***Revaccination of persons who have received at least 1 dose of a COVID-19 vaccine***
Healthy children and adolescents aged 6 months to 17 years	If countries opt to vaccinate low priority-use groups, they should consider single dose for ages 5 years and above; two doses for age 6 months to 4 years	Not routinely recommended

Sub-populations with special considerations		
Target population	***Vaccination of persons who have never received a COVID-19 vaccine***	***Revaccination of persons who have received at least 1 dose of a COVID-19 vaccine***
Persons with moderate and severe immunocompromising conditions (adults, adolescents and children >6 months of age)	Two or three doses in consultation with the health care provider	6-12 months after previous dose; optimal interval should be determined in consultation with health care provider

References

1. Long B, et al. Clinical update on COVID-19 for the emergency clinician: Presentation and evaluation. *The American Journal of Emergency Medicine* 2022; 54:46-57.
2. WHO. https://www.who.int/emergencies/diseases/novel-coronavirus-2019 Accessed 6th February, 2026.
3. Chavez S, et al. Coronavirus disease (COVID-19): A primer for emergency physicians. The *American Journal of Emergency Medicine* 2021; 44:220-9.
4. Covid 19 - SARS-CoV-2. Immunisation against infectious disease. UK Health Security Agency. [Accessed 10th November, 2025].
5. Zhou F, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; 395(10229):1054-62.
6. Ong SWX, et al. Clinical and virological features of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants of concern: A retrospective cohort study comparing B.1.1.7 (Alpha), B.1.351 (Beta), and B.1.617.2 (Delta). *Clinical Infectious Diseases* 2022; 75(1): e1128-e36.
7. Bai Z, et al. Extracting post-acute sequelae of SARS-CoV-2 infection symptoms from clinical notes via hybrid natural language processing. *npj Health Systems*. 2025; 2: https://doi.org/10.1038/s44401-025-00033-410.1038/s44401-025-00033-4.

8. Dhama K, et al. Global emerging Omicron variant of SARS-CoV-2: Impacts, challenges and strategies. *Journal of Infection and Public Health* 2023; 16(1): 4-14.
9. WHO. https://www.who.int/activities/tracking-SARS-CoV-2-variants. [Accessed 10th November, 2025].
10. WHO. COVID-19 advice for the public: Getting vaccinated. https://www. who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines/advice. [Accessed 12th Jan 2026].
11. WHO roadmap on uses of COVID-19 vaccines in the context of Omicron and high population immunity. Updated 10th November 2023.
12. Polack FP et al. Safety and efficacy of the BNT162b2 mRNA covid-19 vaccine. *New England Journal of Medicine. 2020. DOI:10.1056/NEJMoa*2034577.

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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 life-long immunity to that virus (homologous protection) and 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 duration 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 that 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 characterised by the sudden onset of fever lasting between 2-7 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. Adults with co-morbidities having DF may experience incapacitating disease and complications such as unusual haemorrhage, including gastrointestinal bleeding, hypermenorrhoea and massive epistaxis.

The more severe form of dengue infection is dengue haemorrhagic fever (DHF), and it represents a small proportion of all dengue illnesses. DHF is characterised in its early stages by the signs and symptoms of DF described above, followed by increased vascular permeability and bleeding, typically in its latter stages. 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. It is more common in children less than 15 years of age in geographical areas with the

detection of all four serotypes (hyperendemic), in association with repeated dengue infections. However, the incidence of DHF in adults is increasing[3].

Sri Lanka has experienced regular dengue outbreaks for over three decades, with a gradual increase in their intensity, severity, and geographic spread. Although dengue is reported throughout the country, nearly 50% of the cases are reported from the Western province, particularly in the Colombo and Gampaha districts, with a mean age of reported cases of approximately 29 years during outbreaks[4]. Age-stratified seroprevalence studies carried out in the Colombo district have demonstrated a progressive rise in seroprevalence over time, indicating increasing transmission intensity, with seroprevalence reaching 60% by nine years of age[5]. In contrast, a recent dengue seroprevalence study among school-going children aged 10-20 years across nine districts has reported an overall seroprevalence of 24.8%, highlighting substantial geographic variation in population-level dengue virus immunity[6].

Types of vaccine

Two live-attenuated dengue vaccines are licensed for selective use: CYD-TDV (Dengvaxia) and TAK-003 (Qdenga). These vaccines differ in their efficacy profiles, age indications, and safety considerations, particularly with respect to baseline serostatus.

A third live attenuated candidate vaccine TV003 (Butantan Dengue Vaccine) is now in the late stage of clinical development, showing promising protection[7].

Currently, no dengue vaccines are registered for use in Sri Lanka.

1) CYD-TDV

The first dengue vaccine to be licensed was a tetravalent dengue vaccine (TDV), also known as the chimeric yellow fever dengue vaccine (CYD-TDV). All four live attenuated recombinant dengue viruses is contained in CYD-TDV by replacing the prM and E proteins of the attenuated yellow fever 17D vaccine virus genome with the corresponding dengue virus genes. CYD-TDV was registered in

Mexico in December 2015 followed by the Philippines and Brazil. Subsequently, it was available in several countries in Asia and Latin America[8].

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[9]. While the vaccine may offer protection for individuals who have already had one previous infection of dengue, it increases the risk of severe disease in individuals who were dengue-naïve at the time of vaccination.

The WHO therefore, recommended a pre-vaccination screening strategy for CYD-TDV, allowing only dengue-seropositive individuals to be vaccinated[5]. Due to this programmatic inconvenience of pre-vaccination screening and its cost implications, the use of CYD-TDV has been limited. The manufacturer has decided not to further produce this vaccine, and it will be discontinued from use[10].

2) TAK 003

TAK-003 is a second-generation live-attenuated dengue vaccine developed using a dengue virus serotype-2 (DENV-2) backbone. In this construct, the prM and envelope genes of DENV-1, DENV-3, and DENV-4 were inserted into the DENV-2 backbone to produce three chimeric viruses, collectively generating a tetravalent formulation capable of inducing immunity against all four dengue serotypes (tetravalent).

A large multicenter phase 3 randomised controlled trial was conducted in Latin America and Asia, including Sri Lanka. A total of 20,099 healthy children aged 4–16 years were enrolled and randomised in a 2:1 ratio to receive either two doses of TAK-003 or placebo, administered three months apart[11].

Sri Lanka contributed approximately 2,100 participants, recruited from the catchment populations of four major medical institutions across the Colombo and Gampaha districts, providing robust local data relevant to

dengue-endemic settings. The large dengue outbreak in Sri Lanka in 2017, driven predominantly by dengue virus serotype 2, coincided with the phase 3 clinical trial of TAK-003 vaccine, which contained an active surveillance period of 4.5 years[12].

Efficacy

The pivotal trials conducted in dengue-endemic countries concluded that the overall vaccine efficacy of TAK-003 against virologically confirmed dengue (VCD) due to any serotype was 61% from a follow-up period of 57 months after the first dose. Vaccine efficacy for hospitalisation against VCD due to any serotype was 84%[10]. TAK-003 demonstrated efficacy against all four serotypes among baseline seropositive subjects and against DENV-1 and DENV-2 in baseline seronegative subjects. There was no efficacy in baseline seronegative subjects against DENV3 and DENV4 (Table)[13].

Table 1: Estimates of vaccine efficacy of TAK-003 after 57 months from 1st dose

Efficacy against VCD	Any serotype	DENV-1	DENV-2	DENV-3	DENV-4
Baseline seropositive	64%	56%	80%	52%	71%
Baseline seronegative	54%	45%	88%	-16%	-106%
Hospitalisation in seropositive	86%	67%	96%	74%	*
Hospitalisation in seronegative	79%	78%	100%	-88%**	*

* Insufficient sample size (inadequate power)

** 95% CI -573-48

The Phase 3 trial was not sufficiently powered to rule out a risk of vaccine-enhanced disease in seronegative subjects exposed to DENV-3 and DENV-4, as the number of cases due to these 2 dengue serotypes had been relatively small during the trial period. Although not statistically significant, there were higher rates of symptomatic and

hospitalised DENV-3 cases seen among seronegative vaccinated participants than among seronegative unvaccinated participants.

An effectiveness study is planned to assess the impact of TAK-003 against hospitalised dengue. It is intended to evaluate the impact of TAK-003 on severe/hospitalised cases due to DENV-3 and DENV-4. The proposed study is expected to be conducted in Asia in areas known to have circulation of DENV-3 and DENV-4[14].

Indications

The WHO recommends the use of TAK-003 in children aged 6–16 years in settings with high dengue transmission intensity. In contrast, WHO does not currently recommend its use in children under 6 years of age, given the lower vaccine efficacy observed in this age group. Notably, dengue seropositivity among children aged 4–6 years is generally low, even in highly endemic countries. Furthermore, WHO advises against programmatic deployment of TAK-003 in low to moderate transmission settings until the efficacy–risk profile for DENV-3 and DENV-4 in seronegative individuals is more comprehensively understood[13].

TAK-003 is expected to confer greater benefit in individuals who are seropositive before vaccination. However, in high-transmission settings, the WHO does not recommend the use of pre-vaccination screening strategies to restrict vaccination only to seropositive individuals. Additionally, a specific age-stratified dengue seroprevalence threshold above which vaccination should be introduced has not yet been precisely defined. Nonetheless, vaccine impact is anticipated to increase with rising baseline seroprevalence, with stronger performance expected among seropositive population groups.

Threshold cut-offs for minimal seroprevalence to initiate vaccination is expected to be decided by individual countries. As a proxy, seroprevalence of > 60% could be considered an indicator of high dengue transmission. In addition, a mean age of peak dengue-associated hospitalisation of <16 years could be considered an indicator of high dengue transmission.

Dosage and administration

TAK-003 is administered as a two-dose schedule at 0 and 3 months, with a minimum interval of three months between doses. Each dose consists of 0.5 mL given subcutaneously, preferably in the upper arm in the deltoid region[15].

In the Phase 3 trial, a booster dose was administered 54 months after the second dose to participants who were 4–11 years of age at initial enrolment. Although waning immunity was observed over the five-year follow-up period, no definitive data currently exist on the clinical benefit of booster administration. Consequently, a booster dose is not recommended currently.

A protective immune response induced by TAK-003 may not develop in all vaccine recipients for all four dengue virus serotypes, and immunity may wane over time. Moreover, it remains uncertain whether partial protection could be associated with an increased risk of severe dengue. Accordingly, vaccinated individuals should be advised to seek prompt medical care if they experience dengue-like symptoms or any warning signs suggestive of severe disease.

Duration of protection

A mathematical modelling analysis evaluating the impact of routine vaccination with TAK-003 demonstrated high protection against virologically confirmed dengue (VCD) and dengue-related hospitalisation caused by DENV-2, and moderate protection against VCD and hospitalisation due to DENV-1, in both seropositive and seronegative individuals. For DENV-3, the model predicted a negative outcome in seronegative individuals[14].

In the pivotal Phase 3 clinical trial, Sri Lanka reported a high efficacy for the TAK-003 vaccine at the end of three years, with an efficacy of 84.4%, during a period when DENV-2 was the predominant circulating serotype. Subsequently, by the end of the 4.5-year follow-up, vaccine efficacy in Sri Lanka declined, likely due to the emergence and gradual replacement of DENV-2 by DENV-3 in the study areas, which may have impacted vaccine efficacy[16].

Contraindications

- A history of anaphylaxis to any component of the vaccine
- Congenital or acquired immune deficiency
- Symptomatic HIV infection / asymptomatic HIV infection with evidence of impaired immune function

Vaccine is not recommended for pregnant and breastfeeding women. Pregnancy should be avoided for at least one month following vaccination.

Adverse effects

- Commonly reported reactions were injection site pain and erythema, headache, myalgia, malaise, and fever.
- Other reactions include nasopharyngitis, pharyngotonsillitis, arthralgia, injection site swelling, injection site bruising, injection site pruritus, and influenza-like illness[15].

Storage

2-8 °C. Do not freeze.

Use of dengue vaccine in outbreaks

TAK-003 has not been studied as an intervention for dengue outbreak control. Furthermore, the vaccine is not expected to have a significant population-level impact on the course of an ongoing outbreak.

A vaccine effectiveness study of TAK-003 conducted among adolescents aged 10-14 years during the 2024 dengue outbreak in Brazil demonstrated that the vaccine had provided individual-level protection against symptomatic dengue and dengue-related hospitalisation during an outbreak predominantly caused by dengue virus serotypes 1 and 2[17].

WHO Position

The WHO states that vaccination against dengue should be considered as part of a comprehensive, integrated strategy that includes effective case management, robust vector control measures, community

education, and meaningful community engagement to reduce disease transmission and burden.

Although TAK-003 offers significant protection, it does not prevent all dengue infections. Therefore, a scientifically sound, evidence-informed decision on its introduction requires the establishment of a national-level Technical Working Group (TWG) to evaluate evidence and provide recommendations. This TWG should consist of a multi-sectoral team of experts in immunisation, infectious diseases, and public health to provide technical guidance, oversight, and coordination in the decision-making process.

New vaccine candidates - TV003/TV005

Two promising single-dose live attenuated tetravalent dengue vaccine candidates named TV003 and TV005 were developed by the National Institutes of Health (NIH), USA. Both vaccines share the same components, but the dosing for serotype 2 is different[10].The vaccine contains all 4 DENV serotypes with three full-length DENV-1, -3 and -4 serotypes and chimeric DENV-2 which contains DENV-4 backbone with the prM and E genetic components of DENV-2[18]. According to the results of phase 1 and 2 trials this vaccine performed well and was

A Phase 3 trial of the live-attenuated dengue vaccine TV003 (Butantan-DV) conducted in Brazil evaluated a single-dose regimen in more than 16,000 children and adults aged 2-59 years. Over a two-year follow-up period, the vaccine demonstrated an overall efficacy of 79.6% against symptomatic, virologically confirmed dengue (VCD), irrespective of baseline serostatus. Efficacy varied by prior dengue exposure, reaching 89.2% in seropositive individuals and 73.5% in dengue-naïve participants. Serotype-specific analyses showed high efficacy against DENV-1 (~89.5%) and moderate efficacy against DENV-2 (~69.6%). Reliable efficacy estimates for DENV-3 and DENV-4 could not be determined, as these serotypes did not circulate widely in Brazil during the study period[7].

At five years post-vaccination, overall vaccine efficacy against VCD declined to 65.0% regardless of serostatus. Efficacy remained higher in participants with prior dengue exposure (77.1%) compared with those

without prior exposure (58.9%), indicating a gradual waning of protection over time, especially among seronegatives[20].

Brazil's health regulatory agency (Anvisa) has approved the Butantan dengue vaccine for use in individuals aged 12-59 years (an age range that begins 10 years above the youngest participants in its pivotal Phase 3 clinical trial), paving the way for its future deployment in public health efforts to combat rising dengue cases[21].

The NIH has licensed its technology to partners committed to advancing the clinical development programme. Consequently, a Phase 3 clinical trial (V181-005) has been initiated in dengue endemic areas in Asia-Pacific region[22].

References

1. World Health Organization. *Guidelines for the clinical evaluation of dengue vaccines in endemic areas*. Department of Immunisation, Vaccines and Biological, WHO Geneva. 2008. Available from: https://apps.who.int /iris/handle/10665/69850.
2. Guzman MG, et al. Secondary infection as a risk factor for dengue hemorrhagic fever/dengue shock syndrome: an historical perspective and role of antibody-dependent enhancement of infection. *Archives of Virology*. 2013; 158:1445-59.
3. World Health Organization, Regional Office for South-East Asia. *Comprehensive guidelines for prevention and control of dengue and dengue haemorrhagic fever, Revised and expanded edition*. WHO Regional Office for South-East Asia. (SEARO Technical Publication Series No. 60); 2011. https://apps.who.int/iris/handle/10665/204894.
4. Tissera HA, et al. Severe Dengue Epidemic, Sri Lanka, 2017. *Emerging Infectious Diseases*. 2020; 26(4):682–91. https://doi.org/10.3201/eid2604.
5. Malavige GN, et al. Changing epidemiology of dengue in Sri Lanka-Challenges for the future. *PLOS Neglected Tropical Diseases*. 2021;15(8):e0009624; doi: 10.1371/journal.pntd.0009624.
6. Jeewandara C, et al. The burden of dengue in children and risk factors of transmission in nine districts in Sri Lanka. *Journal of Medical Virology*. 2024; 96(1):e29394; doi: https://doi.org/10.1002/jmv.29394.

7. Kallàs EG, et al. Live attenuated, tetravalent Butantan-dengue vaccine in children and adults. *New England Journal of Medicine. 2024; 390: 397-408. DOI: 10.1056/NEJMoa*2301790
8. Wilder-Smith A, et al. Deliberations of the strategic advisory group of experts on immunisation on the use of CYD-TDV dengue vaccine. *Lancet Infectious Diseases*. 2019; 19(1): e31-8. https://doi.org/10.1016/S1473-3099(18)30494-8.
9. Sanofi Pasteur. Sanofi updates information on dengue vaccine. 2017. https://www.sanofi.com/en/media-room/press-releases/2017/2017-11-29-17-36-30 [Accessed May 29, 2020].
10. Wilder-Smith A, et al. Dengue Vaccine Development and Deployment into Routine Immunisation. *Vaccines.* 2025; 13(5):483. https://www.mdpi.com/ 2076-393X/13/5/483
11. Biswal S, et al. Efficacy of a tetravalent dengue vaccine in healthy children and adolescents. *New England Journal of Medicine.* 2019; 381(21):2009–19.
12. Fernando L, et al. Role of the dengue vaccine TAK-003 in an outbreak response: Modeling the Sri Lanka experience. *PLOS Neglected Tropical Diseases***.** 2024; 18(8): e0012376. https://doi.org/10.1371/journal.pntd.0012376.
13. WHO position paper on dengue vaccines – May 2024.Weekly epidemiological record, World Health Organization. https://www.who.int/publications/i/item/ who-wer-9918-203-224
14. SAGE working group on dengue vaccines and the WHO secretariat. Background paper on dengue vaccines, 6 October 2023. https://terrance.who.int/mediacentre /data/sage/SAGE_eYB_ Sept2023.pdf [Accessed April 2024]
15. Takeda. QDENGA Summary of Product Characteristics. https://www.ema. europa.eu/en/documents/product-information/qdenga-epar-product-information_en.pdf [Accessed November 2025].
16. Tricou V, et al. Long-term efficacy and safety of a tetravalent dengue vaccine (TAK-003): 4.5-year results from a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet Global Health.* 2024; 12(2):e257-e70); DOI: 10.1016/ S2214-109X(23)00522-3
17. Ranzani OT, et al. Effectiveness of the TAK-003 dengue vaccine in adolescents during the 2024 outbreak in São Paulo, Brazil: a test-negative, case–control study. *Lancet Infectious Diseases*. 2025; S1473-3099(25)00382-2. doi: 10.1016/S1473-3099(25)00382-2.

18. Kirkpatrick BD, et al. Robust and balanced immune responses to all 4 dengue virus serotypes following administration of a single dose of a live attenuated tetravalent dengue vaccine to healthy, Flavivirus-naive adults. *Journal of Infectious Diseases*. 2015; 212(5):702–710. https://doi.org/10.1093/infdis/jiv082.
19. Whitehead SS. Development of TV003/TV005, a single dose, highly immunogenic live attenuated dengue vaccine; what makes this vaccine different from the Sanofi-Pasteur CYD vaccine? *Expert Review of Vaccines*. 2016; 15(4):509–517. https://doi.org/10.1586/14760584.2016.1115727.
20. Nogueira ML. Five-year efficacy and safety of a live, attenuated tetravalent dengue vaccine produced by Butantan: Results from a Phase 3 clinical trial in children, adolescents, and adults. Presented at ASTMH 2025; November 9-13, 2025. Toronto, Ontaria, Canada; Session 59,6645.
21. Butantan Institute. Butantan-DV. São Paulo: Butantan Institute; 2025 Nov 26. https://www.butantan.gov.br/press-release-dengue-vaccine
22. MSD. MSD Initiates Phase 3 Study Evaluating Dengue Vaccine Candidate. Rahway, NJ: MSD; 12 Jun 2025. https://www.msd.com/news/msd-initiates-phase-3-study-evaluating-dengue-vaccine-candidate/

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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 characterised 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 species 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. Generalised 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. Localised tetanus is a rare form of disease occurring in adults with partial immunity. It could progress to generalised 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 genus Bordetella, including *B parapertussis* and less commonly *B bronchiseptica* are associated with cough-like illness resembling that of classic pertussis. Neither natural infection nor any pertussis vaccine confers lifelong immunity. 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 immunisation 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, 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 over 7 years and adults.

Types of vaccines

Vaccines given 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 given for children over 7 years and above

- Tdap - Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (reduced dose of diphtheria toxoid is designated as "d" and "ap" for acellular pertussis)
- Td - Tetanus toxoid, reduced diphtheria toxoid; also called adult Td, aTd, and adult dT ("d" denotes reduced diphtheria toxoid)

DTP vaccine is now combined with other vaccines to have 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

WHO prequalified hexavalent DTwP+HepB+HiB+IPV vaccine is also available in Sri Lanka since March 2024.

DTP vaccination schedule

In Sri Lanka, the primary vaccination starts at 2, 4 and 6 months and a booster dose is given at 18 months[1]. However, the 3-dose vaccination series could be started at 6 weeks with a minimal interval of 4 weeks between doses, then a booster dose at age 15–18 months.

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

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

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

This is the vaccine used in high-income countries for primary course of immunisation against diphtheria, tetanus, pertussis, hepatitis B, inactivated polio and *H influenzae* type b; recommended for all infants on completion of 2, 4 and 6 months of age and a booster dose at 18 months.

(iii) 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 primary course of immunisation with pentavalent, DTwP is used as a booster at 18 months.

For unimmunised older children up to the age of 7 years, primary vaccination series could be offered 6-8 weeks apart with a booster dose after one year from the last dose[2].

(iv) Diphtheria and tetanus vaccine (DT)

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

DT can be used for primary immunisation, when immunisation against pertussis antigen containing vaccine (DTP) is contraindicated.

(v) Diphtheria and tetanus vaccine for adults and adolescents (aTd)

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

(vi) Tetanus and reduced antigen diphtheria & 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 TdaP containing vaccines as primary vaccination[1]. CDC guideline advises to use Tdap at 11-12 years, 19 years and for pregnant mothers at 27-36 weeks of gestation and thereafter, every 10 years[2,3].

Many countries in the world today use Tdap during pregnancy to prevent neonatal tetanus and pertussis in the infant.

Dosage and Administration

For all DTP and 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 to 18 months, approximately 95 percent 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].

Whole cell 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 disease 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 randomised controlled trials and 3 cohort studies, revealed that the pooled efficacy of wP vaccine against pertussis disease in children was 78%[4].

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

Effectiveness

The effectiveness of diphtheria, tetanus and pertussis immunisation is demonstrated by the sharp decline of these diseases after the introduction of DTP to the routine immunisation 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% and 94% 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].

Duration of immunity

The protection provided by diphtheria, tetanus and whooping cough vaccines decreases over time, necessitating booster doses in childhood, adolescence, and adulthood[9]. Many scientific reports indicate that in pertussis, immunity persists for 10 and 20 years following natural infection and between 10 and 12 years following whole cell vaccination, as compared to about 3 to 5 years following immunisation with acellular vaccine[12].

A study in Sri Lanka had shown that the lowest median anti pertussis toxin (PT) IgG titres 1.43 IU/ml (minimal protective titre-5 IU/mL), were seen between 8-11 years and after 11 to 24 years, 8.57% of individuals showed significantly high anti PT IgG levels, suggesting recent Bordetella infections among them[13]. This illustrates that in Sri Lanka, there is hardly any protective immunity for pertussis in children over 11 years after completing primary vaccination and a single booster at 18 months. There is a very high risk for infants <6 months to contract the disease from infected adults. Repeated wP vaccines increased reactogenicity in the recipients. Therefore, only DT is given at 5 years of age 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 or Tdap at five years and Tdap at 10 years.

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 has not been reported. Severe allergic reaction to tetanus is 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 pertussis vaccines. Children <7 years of age who have a contraindication to pertussis immunisation may receive DT. If DTwP is the responsible vaccine, DTaP could be used instead.

Precautions

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

Precautions for administration of DTP or DT include:

- Guillain-Barré syndrome (GBS) <6 weeks after previous dose of tetanus toxoid-containing vaccines. 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 immunisation 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 characterised by severe pain, swelling, 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 (immunisation should be administered upon recovery).
- In children with progressive or unstable neurologic disorder, including infantile spasms, uncontrolled seizures, or progressive encephalopathy; DTP should be deferred only until the neurologic status is clarified and stabilised[16].

Conditions incorrectly perceived as contraindications or precautions

Vaccines could be administered in the following instances[16]

- Fever ≥40.5 °C (105 °F)
- Family history of seizures
- Family history of sudden infant death syndrome
- Family history of 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 can 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 Events

Mild adverse events

They are common and consist of local reactions and systemic reactions such as 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 immunisation[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, fretfulness, 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 reaction (>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 fourth or fifth dose of DTaP[26]. It is defined as swelling and redness involving more than half the circumference of the limb or over 10 cm in diameter, and it typically resolves on its own within a few days without serious complications. While it can cause concern and is sometimes misdiagnosed as cellulitis, pain is generally mild. 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 swelling of the entire limb were a common occurrence.

- **Arthus-type reaction**

Arthus-type reaction is also considered as a severe local reaction due to an immune complex-mediated hypersensitivity to diphtheria or tetanus toxoid containing vaccines.

Severe systemic reactions

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.

Seizure

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)

A case definition defines an HHE as the sudden onset of limpness and reduced responsiveness and pallor or cyanosis [27]. Although, HHE occurs most frequently after whole-cell pertussis vaccine, the reaction has been documented to occur after other vaccines, including diphtheria, tetanus, *H influenzae* type b and hepatitis B[22]. The reported rates following a whole cell pertussis vaccine range 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 has 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 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. Majority of anaphylaxis reported in the literature is due to DTwP rather than DTaP. The offending constituent in many cases turns out to be the wP component. Rarely tetanus toxoid containing vaccines too could cause anaphylaxis.

Special circumstances

Natural diphtheria or tetanus infection

Natural immunity is not conferred by tetanus and diphtheria because the amount of toxin produced during a natural infection is often too low to trigger a strong immune response. For tetanus, the body doesn't produce enough antibodies to neutralize the toxin, and for diphtheria, the toxin's mechanism can evade typical immune system processes. Children with diphtheria or tetanus infection should receive a diphtheria or tetanus toxoid-containing vaccine (e.g. DTaP, DTwP, DT) during their convalescence, even if they were completely immunised 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 variable protective immunity from 10-20 years[12]. DTP should be used to complete childhood immunisation, if the child is younger than seven years.

Life course approach to vaccination

Primary objective of vaccination is to protect the public from vaccine preventable infection throughout life from fetus till death. To achieve this goal, protective immunity has to be sustained at desired level throughout life. As protective immunity from the initial primary DTP vaccination series wanes overtime, every person should receive regular DTP boosters after the 4 primary doses to maintain protection against

these three diseases. Unprotected adults could contract the disease, disseminating the pathogen risking the most vulnerable children in the community. However, due to increased reactogenicity with repeated boosters, it is recommended to give reduced doses of diphtheria and acellular pertussis components as boosters (Tdap).

Recent evidence consistently indicates that maternal immunisation with aP-containing vaccine during the third trimester of pregnancy is safe[31] and highly effective in protecting infants from pertussis and that it may have a high impact on morbidity and mortality in infants too young to be vaccinated. Most countries in the world have switched from tetanus toxoid to Tdap vaccine for pregnant mothers at 27-36 weeks of gestation to protect the newborn from tetanus and the young infant from pertussis. Likewise, Tdap boosters are given at 3-5 years and 8-10 years to boost waning protective immunity in teenage population. Many countries including US, Canada, Austria, Australia and Belgium have gone one step further. Their new guidelines recommend Tdap vaccination every 10 years to achieve robust herd immunity to the entire population throughout life[32]. Recent study in India highlights the urgent need for Tdap boosters in their country[33].

Future recommendations

Based on the current literature and practices of many countries in the world, it is high time to reconsider DTP vaccine strategy in our NIP. As a first step of trying to achieve lifelong immunity, we need to change the 5- and 10-year boosters in our NIP to Tdap and switch to Tdap for pregnant mothers instead of tetanus toxoid.

References:

1. https://www.epid.gov.lk/storage/post/pdfs/en_6403b42a75fa4_Doc2.pdf.
2. Hall E, et al. eds.14th edition Pink Book: Washington. D.C, Public Health Foundation 2021.www.cdc.gov.\/vaccines/pubs/pink book/index.htm.
3. Use of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccines: Updated Recommendations of the Advisory Committee on Immunisation Practices United States, 2019 *Morbidity and Mortality Weekly Report.* January 24, 2020; 69 (3):77-83.

4. Jefferson T, et al. Systematic review of the effects of pertussis vaccines in children. *Vaccine*. 2003; 21:2003–2014.
5. Zhang L, et al. Acellular vaccines for preventing whooping cough in children. *The Cochrane Database of Systematic Reviews*. 2014; (9):CD001478. doi: 10.1002/14651858.CD001478.pub6.
6. Liko J, et al. Do pertussis vaccines protect against *Bordetella parapertussis? Clinical Infectious Diseases*. 2017; 64(12):1795-1797.
7. Pertussis vaccines: WHO position paper - September 2015.*Weekly Epidemiology Record*. 2015; 90(35):433-58.
8. Zerbo O, et al. Acellular pertussis vaccine effectiveness over time. *Pediatrics*. 2019; 144(1):e20183466. doi: 10.1542/peds.2018-3466.
9. Fulton TR, et al. Protective effects of contemporary pertussis vaccines: a systematic review and meta-analysis. *Clinical infectious diseases*. 2016; 62(9):1100-1110.
10. Barlow RS, et al. Vaccinated children and adolescents with pertussis infections experience reduced illness severity and duration. *Clinical Infectious Diseases*. 2014; 58(11):152–9.
11. Martin SW, et al. Pertactin-negative *Bordetella pertussis* strains: evidence for a possible selective advantage. *Clinical Infectious Diseases*. 2015; 60(2):223-227.
12. Burdin N, et al. What is wrong with pertussis vaccine immunity? The problem of waning effectiveness of Pertussis Vaccines. *Cold Spring Harbor Perspectives in Biology*. 2017; 9(12):a029454. doi: 10.1101/cshperspect.a 029454.
13. Sigera S, et al. Seroprevalence of *Bordetella pertussis* specific Immunoglobulin G antibody levels among asymptomatic individuals aged 4 to 24 years: a descriptive cross-sectional study from Sri Lanka: *BMC Infectious Diseases*. 2016; 16:729.
14. Rieber N, et al. Differences of humoral and cellular immune response to an acellular pertussis booster in adolescents with a whole cell or acellular primary vaccination. *Vaccine*. 2008; 26:6929-35.
15. Report from the SAGE Working Group on Pertussis vaccines 26–27 August 2014 meeting, Geneva, Switzerland.
16. Liang JL, et al. Prevention of Pertussis, Tetanus, and Diphtheria with Vaccines in the United States: Recommendations of the Advisory Committee on Immunisation Practices (ACIP). *Morbidity and Mortality Weekly report*. Recommendations and reports. 2018; 67(2):1-44.

17. DuVernoy TS, et al. Hypotonic-hyporesponsive episodes reported to the Vaccine Adverse Event Reporting System (VAERS), 1996-1998. *Pediatrics*. 2000;106(4):e52.
18. Centers for Disease Control and Prevention. Vaccine Information Statements. Diphtheria, tetanus, and pertussis (DTaP). Available at: https://www.cdc. gov/vaccines/hcp/vis/vis-statements/dtap.html [Accessed on May 10, 2018].
19. Trofa AF, et al. Immunogenicity and safety of an inactivated hepatitis A vaccine when coadministered with Diphtheria-tetanus-acellular pertussis and *Haemophilus influenzae* type B vaccines in children 15 months of age. *Paediatric Infectious Diseases Journal*. 2011; 30(9):e164-169. Doi: 10.1097/INF.0b013e3 1821b8a7d.
20. Gasparini R, et al. Safety and immunogenicity of a quadrivalent meningococcal conjugate vaccine and commonly administered vaccines after co-administration. *Pediatric Infectious Diseases Journal.* 2016; 35(1):81-93.
21. Kimberlin DW, et al. Pertussis (whooping cough). In: Red Book: 2018 Report of the Committee on Infectious Diseases, 31st ed, American Academy of Pediatrics, Itasca, IL 2018. P.620.
22. Cody CL, et al. Nature and rates of adverse reactions associated with DTP and DT immunisations in infants and children. *Pediatrics.* 1981; 68:65–60.
23. Long S, et al. Longitudinal study of adverse reactions following diphtheria tetanus pertussis vaccine in infancy. *Pediatrics*. 1990; 85:294–302.
24. Mark A, et al. Subcutaneous versus intramuscular injection for booster DT vaccination of adolescents. *Vaccine*. 1999; 17:2067–2072.
25. Rennels MB, et al. Safety of a fifth dose of diphtheria and tetanus toxoid and acellular pertussis vaccine in children experiencing extensive, local reactions to the fourth dose. *Paediatric Infectious Diseases Journal*. 2008;27(5):464-465.
26. Rennels MB, et al. Extensive swelling after booster doses of acellular pertussis-tetanus-diphtheria vaccines. *Pediatrics.* 2000; 105(1):e12.
27. Buettcher M, et al. Hypotonic-hyporesponsive episode (HHE) as an adverse event following immunisation in early childhood: Case definition and guidelines for data collection, analysis, and presentation. *Vaccine*. 2007;25:5875–5881.

28. Vermeer-de Bondt P, et al. Rate of recurrent collapse after vaccination with whole cell pertussis vaccine: follow-up study. *British Medical Journal*. 1998; 316:902-903.
29. Le Saux N, et al. Canadian Paediatric Society/ Health Canada Immunisation Monitoring Program-Active (IMPACT). Decrease in hospital admissions for febrile seizures and reports of hypotonic-hyporesponsive episodes presenting to hospital emergency departments since switching to acellular pertussis vaccine in Canada: a report from IMPACT. *Pediatrics*. 2003; 112(5):e348. doi: 10.1542/peds.112.5.e348. PMID: 14595075.
30. Reyes IS, et al. Alleged cases of vaccine encephalopathy rediagnosed years later as Dravet syndrome. *Pediatrics.* 2011; 128(3):699-702.
31. Donegan K, et al. Safety of pertussis vaccination in pregnant women in UK: observational study. *British Medical Journal.* 2014; 349:g4219.
32. https://www. cdc.gov/vaccines/hcp/current-vis/tdap.html
33. Irulappan M, et al. Pertussis in India: Vaccine-driven evolution, waning immunity, and the urgent need for Tdap boosters. *Indian Journal of Medical Microbiology*. 2025; 55:100846. doi: 10.1016/j.ijmmb.2025. 100846.

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CHAPTER 9

HAEMOPHILUS INFLUENZAE TYPE B VACCINE

Introduction

Haemophilus influenzae type b (Hib) is a leading cause of severe bacterial meningitis, pneumonia and sepsis in young children. Prior to Hib vaccine introduction, Sri Lanka had one of the highest recorded incidences of Hib meningitis in Asia[1,2]. With growing antibiotic resistance limiting treatment options, immunisation became crucial for preventing Hib disease. Sri Lanka introduced the Hib vaccine (as a pentavalent DTwP-HepB-Hib combination) into the National Immunisation Programme in 2008[2].

By the end of 2023, 193 of 194 WHO member states had incorporated Hib vaccination into their routine infant immunisation schedules. Global coverage with three doses of Hib vaccine is estimated around 77% as of 2023, although coverage remains uneven across regions. For example, the WHO European Region has over 94% Hib3 coverage, while the Western Pacific Region is only around 33% (largely due to limited use of Hib vaccine in a few populous countries). The WHO South-East Asia Region, which includes Sri Lanka, has achieved high Hib coverage (over 80%)[3]. In Sri Lanka, sustained immunisation efforts have yielded Hib3 coverage around 96% even during the COVID-19 pandemic years[4,5].

Types of Vaccine

All currently licensed Hib vaccines are conjugate vaccines composed of the Hib capsular polysaccharide (polyribosylribitol phosphate, PRP) chemically linked (conjugated) to a protein carrier. Conjugation transforms the PRP antigen into a T-cell dependent form, inducing robust antibody production in infants and long-lasting immunological memory[6]. Four main protein carriers have been used in Hib conjugate vaccines:

- CRM197 (diphtheria toxin mutant) – PRP-CRM_{197} conjugate
- Tetanus toxoid – PRP-T conjugate
- Outer membrane protein of *Neisseria meningitidis* – PRP-OMP conjugate
- Diphtheria toxoid – PRP-D conjugate (this older formulation was less immunogenic in infants <18 months and has been withdrawn from the market).

The protein carriers themselves are non-toxic and non-immunogenic in the amounts used, and they do not confer protection against diseases like diphtheria, tetanus, or meningococcal infection. Hib conjugate vaccines are available either as monovalent formulations or as part of combination vaccines**,** in both liquid and lyophilized presentations.

Common combination formulations that include Hib antigen are:

- **Pentavalent (DTwP-HepB-Hib):** a 5-in-1 vaccine combining diphtheria, tetanus, whole-cell pertussis, hepatitis B, and Hib. (Sri Lanka's national program uses this pentavalent vaccine in infancy.)
- **Hexavalent (DTaP-IPV-HepB-Hib):** a 6-in-1 vaccine combining diphtheria, tetanus, acellular pertussis, inactivated polio, hepatitis B and Hib. This formulation, used in some countries, reduces the number of injections by including IPV and acellular pertussis.
- **Hexavalent (DTwP-IPV-HepB-Hib):** a 6-in-1 vaccine combining diphtheria, tetanus, whole cell pertussis, inactivated polio, hepatitis B and Hib. This formulation, used in some countries, reduces the number of injections by including IPV and pertussis.
- **DTwP-Hib (Tetravalent):** combined diphtheria, tetanus, whole-cell pertussis and Hib (used in certain settings, such as boosters or where hepatitis B is given separately).
- **Hib-Meningococcal conjugate:** combination of Hib with meningococcal polysaccharides. For instance, a Hib-MenC conjugate is given at 12–15 months in some schedules (e.g. the Hib/MenC booster in the UK) to protect against both Hib and *Neisseria meningitidis* group C. A novel Hib-MenAC conjugate

vaccine is also under development and has shown safe, immunogenic results in infants[6].

(Note: Other routine paediatric vaccines, such as pneumococcal conjugate vaccines, are administered separately from Hib vaccines; there are currently no licensed Hib+PCV combination vaccines).

Efficacy

Immunogenicity

Hib conjugate vaccines are highly immunogenic in infants. Over 95% of infants develop protective anti-PRP antibody levels after completing the primary vaccination series (2 or 3 doses, depending on the product)[7]. Immune responses are strong even in young infants starting at 6 weeks of age. Hib vaccines also induce immunity in older children and adults if administered, although routine use is focused on infants and toddlers.

Clinical Efficacy

All Hib conjugate vaccines have demonstrated excellent efficacy in preventing invasive Hib disease. Clinical trials and observational studies indicate vaccine efficacy in the order of 95–100% against Hib meningitis and other invasive infections[7]. Countries that have introduced Hib vaccines and achieved high coverage have seen near-elimination of Hib meningitis in children. Notably, Hib vaccination also significantly reduces nasopharyngeal carriage of Hib, conferring herd immunity to unvaccinated contacts[8].

Duration of Protection

Although anti-PRP antibody levels can decline in the years after the primary series, vaccinated children remain protected during the period of highest risk (under 5 years of age) due to immune memory. All conjugate formulations (monovalent or combined) show comparable immunogenicity and efficacy in healthy children[9]. However, some studies have noted that Hib antibody titers can be slightly lower when the Hib antigen is given in combination with acellular pertussis vaccines (DTaP-based combinations), compared to administration

with whole-cell pertussis or separately with DTaP. Despite this, the efficacy in preventing disease remains high for all approved combination vaccines.

Special Populations

Hib conjugate vaccines are immunogenic even in children with impaired immunity such as infants and children with asplenia (functional or anatomical), sickle-cell disease, HIV infection, or those who have undergone chemotherapy or splenectomy. However, in significantly immunocompromised patients (such as advanced HIV infection or active malignancy), antibody responses may be attenuated. Because of this, additional booster doses (see below) may be considered to ensure adequate protection in these groups. Importantly, natural infection with Hib does not always induce lasting immunity in young children, so even those who have recovered from invasive Hib disease before the age of 2 years should receive the full vaccination course starting about 1 month after the onset of the illness.

It should be noted that Hib vaccines protect only against serotype b strains of *H influenzae*. These do not prevent disease caused by non-typeable *H influenzae* or other capsulated serotypes (such as type a, which is emerging in some regions). Thus, vaccination has no direct effect on otitis media, bronchitis or pneumonia caused by non-type b *H influenzae*, and those infections may still occur in vaccinated populations.

Indications

Primary infant immunisation

Hib vaccine is indicated for all infants and young children as a routine immunisation. The vaccine series should be started at the age of 6 weeks or as soon as possible thereafter (typically by 2 months of age). Routine vaccination of children under 5 years has the greatest impact on reducing Hib disease, as the incidence is highest in infants and toddlers[10]. In Sri Lanka and most countries, Hib vaccine is included in the infant immunisation schedule, with doses given at the age of 2, 4, and 6 months (as part of the pentavalent DTP-HepB-Hib).

Catch-up vaccination

Hib vaccination is generally not required for healthy children older than 5 years, because the risk of invasive Hib disease in immunocompetent individuals ≥5 years is very low. However, any child 1–5 years of age who missed the routine infant series should receive at least one dose of Hib vaccine to confer protection[11].

- 6–11 months of age – two doses 4 weeks apart
- 12–14 months of age - two doses 8 weeks apart
- 15–59 months of age – a single dose

Interrupted or delayed schedule

If a child's Hib vaccination schedule is interrupted or delayed, it should be resumed (not restarted) and completed as soon as possible with the appropriate number of doses for the child's current age. For example, if an infant started the series but missed the 6-month dose, administer a dose when possible and continue the schedule; there is no need to repeat doses already received.

Special risk groups

Certain groups of children are at an increased risk of invasive Hib infection or may have poorer outcomes if infected. It is recommended to ensure Hib immunisation (or complete it as early as possible) in the following groups, regardless of the child's current age**:**

- Anatomical or functional asplenia including those who have had splenectomy
- Sickle-cell disease
- Immunoglobulin deficiency syndromes (especially less severe Ig deficiencies – refer Chapter 33)
- Hodgkin disease (in remission)
- Following chemotherapy (after recovery)
- Nephrotic syndrome (in remission)
- HIV infection

- Cochlear implant-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 immunised individuals 5 years of age and older do not require a dose (see Chapter 35).

National policies differ, but in general, older children or adults with asplenia or other high-risk conditions who have never received Hib vaccine may be offered a one-time Hib vaccination. In Sri Lanka, routine Hib vaccination is not given beyond 5 years of age in healthy individuals, but high-risk older children (e.g. asplenia) may be considered for immunisation on a case-by-case basis[10].

Post-Hib Disease

Children under 2 years of age who recover from invasive Hib disease (e.g. meningitis) should still receive the full Hib vaccine series, because natural infection may not induce reliable immunity in this age group. Vaccination in such cases should begin approximately one month after the onset of the illness. The number of doses required depends on the child's age when starting vaccination after the illness (e.g. if <12 months old, complete the 3-dose primary series; if 12–24 months old, one dose is sufficient if at least one Hib dose was given before illness).

Dose, schedules and administration

Hib vaccines are given intramuscularly. The standard paediatric dose is 0.5 mL IM for all conjugate Hib vaccine preparations[12]. The anterolateral thigh is the preferred injection site in infants, or the deltoid muscle in older children. Hib vaccines may be administered concurrently with other routine childhood vaccines (such as DTP, polio, measles), but always using a separate syringe and at a separate injection site. Hib vaccines should never be mixed in the same syringe with another vaccine. An immunisation series that was started with one type of conjugate Hib vaccine may be completed with a different Hib-containing product if necessary; the vaccines are interchangeable in terms of immunogenicity[13].

Primary series

Available evidence suggests that at least three doses are needed to achieve high levels of long-term protection. Several Hib immunisation schedules are in use globally, all of which provide a primary series in infancy with or without a booster in the second year of life. Acceptable schedules include:

- 3 primary doses + 0 booster (3p+0): Three doses in infancy (e.g. at 6, 10, 14 weeks or 2, 4, 6 months), with no routine Hib booster later.
- 3 primary doses + 1 booster (3p+1): Three doses in infancy (as above) followed by a booster dose at age 12–18 months.
- 2 primary doses + 1 booster (2p+1): Two doses in infancy (e.g. at 2 and 4 months) followed by a booster at 12–15 months of age.

WHO recommends choosing the schedule based on the local epidemiology of Hib disease and programmatic considerations. In countries where the peak incidence of severe Hib disease occurs in early infancy (under 6 months of age), a 3p+0 schedule with doses starting at 6 weeks of age (e.g. 6, 10, 14 weeks) can confer early protection by completing the series as soon as possible. Sri Lanka follows a 3-dose primary series without a booster, with Hib given at 2, 4 and 6 months of age (as part of the pentavalent vaccine). This schedule aligns with the national DTP schedule and provides protection during the vulnerable first year of life[10].

In settings where Hib disease burden persists into later childhood or where immunity from infancy may wane (e.g. some industrialised countries), a booster dose in the second year of life is often added (3p+1 or 2p+1 schedules). WHO recommends that if a booster is used, it be given at age 12–18 months (commonly at 12-15 months). The booster serves to raise antibody levels and extend protection through the preschool years. Many high-income countries (and some middle-income countries) have adopted a 2p+1 schedule (e.g. 2, 4, and 12 months) or a 3p+1 schedule (e.g. 2, 4, 6, and 15 months) to maximise herd immunity and eliminate carriage. In the UK, for instance, the initial use of a 3p+0 schedule in the 1990s led to a small resurgence of Hib disease in 1–3-year-olds; this was rectified by introducing a 12-

month booster, which successfully sustained the protection[14]. Likewise, countries such as South Africa observed additional reductions in Hib incidence after adding a booster dose at 18 months[15].

In Sri Lanka, the current evidence indicates that the 3-dose infant regimen has been highly effective (with very low incidence of Hib disease and high coverage), therefore a booster dose is not presently included in the routine schedule. However, should Hib disease re-emerge, or coverage decline, health authorities may re-evaluate the need for a booster in the future.

Contraindications

Hib vaccines are safe and well-tolerated. Contraindications are minimal and similar to those for other inactivated vaccines:

- Severe allergic reaction (anaphylaxis) to a previous Hib vaccine dose, or to any component of the vaccine including the toxoid carrier proteins. Such reactions are exceedingly rare.
- Age <6 weeks: Younger infants may not mount an adequate response and there is a theoretical risk of inducing immunologic tolerance.
- Moderate or severe acute illness: Vaccination should be postponed in cases of moderate-to-severe illness with fever. Minor illness is not a contraindication[12].

Adverse effects

Adverse effects following Hib vaccination are uncommon and mostly mild. The vaccine's safety profile has been excellent across decades of use and billions of doses[16]. A meta-analysis of trials in the 1990s confirmed no significant increase in serious adverse events with Hib conjugate vaccines compared to placebo[7]. Post-licensure surveillance has similarly found no unexpected safety concerns[17].

Local reactions

Approximately 5–30% of vaccine recipients may experience minor injection-site reactions, such as redness, swelling, or pain at the site. These local reactions are usually mild and self-limited, resolving within

24–48 hours. They tend to be more common with combination vaccines (e.g. DTP-Hib) due to the other components (like pertussis) rather than the Hib antigen itself.

Systemic reactions

Mild systemic symptoms are infrequent. Fever >38°C within 1–2 days of vaccination is reported in 2-10% of infants. Other potential general symptoms include irritability, fussiness, loss of appetite, drowsiness, or short-lived vomiting/diarrhoea. Serious systemic reactions are very rare.

Storage

2-8 °C. Do not freeze.

References

1. Watt JP, et al. Burden of disease caused by *Haemophilus influenzae* type b in children younger than 5 years: global estimates. *Lancet.* 2009; 374(9693):903-11.
2. Batuwanthudawe R, et al. Incidence of childhood *Haemophilus influenzae* type b meningitis in Sri Lanka. *International Journal of Infectious Diseases.* 2010; 14: e:372-e376.
3. Rachlin A, et al. Routine vaccination coverage — worldwide, 2021. *Morbidity and Mortality Weekly Report.* 2022; 71(44):1396-1400.
4. Kaur G, et al. Routine vaccination coverage — worldwide, 2022. *Morbidity and Mortality Weekly Report.* 2023; 72(43):1155-61.World Health Organization. Immunisation coverage [Internet]. Geneva: WHO; 2023. Available from: https://www.who.int/news-room/fact-sheets/detail/immunisation-coverage Accessed 01 Apr 2025.
5. Slack MP, et al. Invasive *Haemophilus influenzae* infections after 3 decades of Hib protein conjugate vaccine use. *Clinical Microbiology Reviews.* 2021; 34(3): e0002821.Obonyo CO, et al. Efficacy of *Haemophilus influenzae* type b vaccination of children: a meta-analysis. *European Journal of Clinical Microbiology and Infectious Diseases.* 2006; 25(2):90-7.
6. Nanduri S, et al. *Haemophilus influenzae* type b vaccines. In: Plotkin S, et al, editors. Plotkin's Vaccines. 7th ed. Philadelphia (PA): Elsevier; 2018.

7. Oliver SE, et al. *Haemophilus influenzae* type b. In: Hall E, et al, editors. Epidemiology and Prevention of Vaccine-Preventable Diseases. 14th ed. Washington, DC: Public Health Foundation; 2021. p. 111-20.
8. Ginige S, editor. Immunisation Handbook. 3rd ed. Epidemiology Unit, Ministry of Health, Sri Lanka; 2012
9. Centers for Disease Control and Prevention. Child and Adolescent Immunisation Schedule by Age: Catch-Up Immunisation Schedule. Atlanta, GA: CDC; 2024. https://www.cdc.gov/vaccines/hcp/imz-schedules/child-adolescent-age.htmlAccessed 1st April 2025
10. *Haemophilus influenzae* type b (Hib) vaccine: WHO position paper – July 2013. *Weekly Epidemiological Record.* 2013; 88:413-28.
11. American Academy of Pediatrics. Interchangeability of vaccine products. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, editors. Red Book: 2021–2024 Report of the Committee on Infectious Diseases. 32nd ed. Ithaca (IL): American Academy of Pediatrics; 2021; 34-35
12. Ramsay M, et al. Hib vaccine: impact of the booster dose introduced in the UK. London: London School of Hygiene & Tropical Medicine; 2012
13. von Gottberg A, et al. Impact of conjugate *Haemophilus influenzae* type b (Hib) vaccine introduction in South Africa. *Bulletin of the World Health Organization*. 2006; 84(10):811–8.
14. World Health Organization. WHO Expert Committee on Biological Standardisation. WHO technical report series: report no. 897. Geneva: World Health Organization; 2000.
15. Centers for Disease Control and Prevention. Hib surveillance reports. Atlanta (GA): Centers for Disease Control and Prevention; 2023. Available from: https://www.cdc.gov/
16. World Health Organization. Global vaccine safety initiative. Geneva: World Health Organization; 2022. Available from: https://www.who.int

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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 < l6 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 could occur, especially among men who have sex with men (MSM).

Epidemiology

HAV affects an estimated 1.5 million people annually, worldwide, with seroprevalence varying by region[1]:

- High-endemic areas (e.g. Sub-Saharan Africa, South Asia) see most infections in early childhood, with 90% of individuals having anti-HAV IgG by the age of 10 years. Transmission is via poor sanitation and person-to-person contact.
- Medium-endemic areas (e.g. Asia, Latin America) have higher disease rates in late childhood and young adulthood, with 50%+ seroprevalence by the age of 15 years. Transmission occurs through contaminated food and water.

- Low-endemic areas (e.g. Western Europe, North America) have low disease rates, with infections mainly affecting susceptible individuals, and 50%+ seroprevalence by the age of 30 years.
- Very low-endemic areas (e.g. Northern Europe) have less than 50% seroprevalence by the age of 30 years.

Anti-HAV seroprevalence is decreasing in many parts of the world, including Asia, shifting infections toward adolescents and adults[2].

Sri Lanka is a country with an intermediate prevalence of hepatitis A[3]. Sri Lanka experiences outbreaks of hepatitis A, which has become a significant health problem[4]. The 2009 hepatitis A outbreak in Sri Lanka highlights a critical public health concern, especially given the scale of the incident and its impact on the population. It shows the potential risk of future outbreaks due to epidemiological shifts of hepatitis A infection in Sri Lanka[5].

Travellers to Sri Lanka are advised to be immunised against hepatitis A before travel.

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, Canada and Australia for travellers.

Efficacy

- Pre-exposure – 94-95% (The duration of protection is estimated to be as long as 25 years[7])

- Post-exposure - 96%[7]

Indications

- For individuals over 12 months of age

Recommended for

- food handlers
- children, adolescents and high-risk persons during outbreaks of hepatitis A
- persons with an 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 immunisation or a combination of the two methods could be used for post-exposure prophylaxis.

Human normal immunoglobulin (HNIG)

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/HIV infection with a CD4 count <200 cells per μL) and those at risk of severe complications (chronic liver disease, including chronic hepatitis B or C infection).

HNIG has shown 80-90% efficacy in preventing infection when administered IM within 2 weeks after exposure to HAV[6]. It is not available in Sri Lanka at present.

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 past 14 days[6]. The vaccine is preferred over HNIG as it gives long term protection[7]. 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 due to a rapid response[8].

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 is comparable in terms of effectiveness, is less expensive and easier to implement than the standard 2-dose schedule. However, the double dose schedule is still recommended[6]. A 2-dose schedule is preferred for high-risk patients and immunocompromised individuals[6].

Hepatitis A vaccines (both the monovalent and the combined) could be administered simultaneously with other vaccines. This could be safely administered to the immunocompromised[6]. Hepatitis A vaccines are not routinely recommended for pregnant or breastfeeding women. However, they could receive the vaccines if necessary[7]. Immunocompromised individuals and elderly patients show a reduced immune response to hepatitis A vaccination[6].

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[8].

Storage

2-8 ºC. Do not freeze.

References:

1. Girish V, et al. Hepatitis A. Last Update: October 6, 2024 https://www.ncbi.nlm. nih.gov/books/NBK459290.
2. World Health Organization. Regional Office for South-East Asia. 2017. Regional action plan for viral hepatitis in South-East Asia: 2016-2021. World Health Organization. Regional Office for South-East Asia. https://apps.who.int/%20iris/ handle/10665/258735
3. Wijewantha HS. Liver Disease in Sri Lanka. *Euroasian Journal of Hepatogastroenterolgy.* 2017; 7(1):78–81. doi:10.5005/jp-journals-10018-1217. https://pmc.ncbi.nlm.nih.gov/articles/PMC5663780/#B8
4. Dahanayaka NJ, et al. Clinical features and transmission pattern of hepatitis A: an experience from a hepatitis A outbreak caused by two cocirculating genotypes in Sri Lanka. *American Journal of Tropical Medicine & Hygiene.* 2016; 95(4):908–914. doi: 10.4269/ajtmh.16-0221.

5. Dahanayaka NJ, et al. Massive hepatitis A outbreak in Sri Lanka in 2009: an indication of increasing susceptibility and epidemiological shift? *Sri Lankan Journal of Infectious Diseases*. 2013; 3(2):28-30 doi: http://dx.doi.org/ 10.4038%20/sljid.v3i2.5640.
6. WHO position paper on hepatitis A vaccines - October 2022. *Weekly Epidemiological Record.* No 40, 2022; 97:493–512.
7. Victor JC, et al. Hepatitis A vaccine versus immune globulin for postexposure prophylaxis. *New England Journal of Medicine*. 2007; 357(17):1685-94. doi: 10. 1056/NEJMoa070546.
8. Lamabadusuriya, SP. First reported case of probable anaphylaxis following administration of Hepatitis A vaccine in Sri Lanka. *Sri Lanka Journal of Child Health*, 2020; 49(2):197. DOI: http://doi.org/10. 4038/sljch.v49i2.8977.

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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.

Chronic HBV infection is defined as persistence in serum for at least 6 months of any one of the following: hepatitis B surface antigen (HBsAg), HBV DNA, or hepatitis B e antigen (HBeAg)[1]. 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%[2]. WHO estimates that 254 million people were living with chronic hepatitis B infection in 2022, with 1.2 million new infections each year. In 2022, hepatitis B resulted in an estimated 1.1 million deaths, mostly from cirrhosis and primary liver cancer[3].

The rate of progression from acute to chronic hepatitis B is primarily determined by the age at 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%[2]. 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%[4]. Many studies have been carried out in determining prevalence among selected populations and rates have remained below 2%[5]. A more recent national survey conducted using a multi-stage cluster sampling method on 2538 five-year-old children and 1266 pregnant women showed that the HBsAg carriage to be 0% in both groups[6]. Sri Lanka has a policy of immunising healthcare workers (HCW) who are at risk of acquiring HBV occupationally.

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[7].

Hepatitis B vaccine for infants had been introduced nationwide in 190 countries by the end of 2024. Global coverage with 3 doses of hepatitis B vaccine is estimated at 84%. In addition, 117 countries have introduced the WHO recommended birth dose to newborns within the first 24 hours of life and global coverage is 45%[8].

Types of vaccine

It is a recombinant vaccine and contains HBsAg as 10 to 40 μg of HBsAg protein/mL with alum as an adjuvant. 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

For adult patients with renal insufficiency, a vaccine containing a higher antigen dose (40ug/dose) compared to the standard hepatitis B vaccineis recommended[1].

Efficacy

Protective efficacy is determined by the presence of anti-HBs antibodies. Protective efficacy is higher in infants compared to adults[2]. 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.

Ninety percent of vaccinated persons remain protected for at least 30 years[2]. 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[2]. 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, ageing, smoking, obesity and diabetes, are associated with reduced immunogenicity following vaccine administration. Patients with chronic disease should be vaccinated early in the disease process[2].

Indications for assessing post vaccination antibody response

- people at risk of occupationally acquired infection e.g. healthcare 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. Some recommend using a different vaccine product for the second series of vaccination[1]. Alternatively, after the first series, 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 titre is <10 mIU/ml after the second series they are known as non-responders. Anyone who does not respond to revaccination should be tested for HBsAg[8]. The healthcare workers who are non-responders need to be evaluated after all high-risk exposures.

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

Indications[1,8]

- All newborn babies, within 24 hours of birth
- All children, adolescents and adults if not vaccinated at birth
- 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
    - 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/mL) is required to induce a protective antibody response in immunocompromised and haemodialysis patients[2].

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 3 doses of hepatitis B containing combination vaccines administered during the same visits as the first three doses of DTP containing vaccines[2]. The birth dose of the hepatitis B vaccine can be co-administered with BCG vaccine and should be given at different injection sites[9]. However, currently the NIP in Sri Lanka administers three doses of the vaccine to all infants at 2, 4 and 6 months of age and no birth dose is included.

Newborns of mothers who are HBsAg positive should receive both 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[1]. Breastfeeding of an infant by an HBsAg-positive mother poses no additional risk of acquisition of HBV infection by the infant with appropriate administration of HepB vaccine and HBIG[1].

Children and adults: 3 doses of vaccine can be given at any age at 0, 1, and 6 months schedule.

Travellers and high-risk groups: WHO recommends 0, 7, 21 days and booster at 12 months for travellers[2].

Chronic kidney diseases: A vaccine dose of 40 µg should be administered at 0, 1, 2, and 6 or 12 months[10]. 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[10].

Booster doses: Routine booster doses of HepB vaccine are not recommended for children and adults with normal immune status. Annual anti-HBs testing and booster doses when anti-HBs concentrations decrease to <10 mIU/mL should be considered for immunocompromised people (e.g. HIV-infected people, hematopoietic stem cell transplant recipients, and people receiving chemotherapy) if they have an ongoing risk for HBV exposure[1].

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[2].

Storage

2-8 ^{0}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[1]

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 hours 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 at birth and HBV vaccine at birth and 2, 4, 6 months as per national immunisation programme or
- HBIG at birth and HBV vaccine at birth, 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.

During follow up of these infants, testing should not be performed before 9 months of age to maximise likelihood of detecting late onset HBV infection.

It is being planned by the Epidemiology Unit of Sri Lanka to screen pregnant women for HbsAg carriage with a view to preventing mother to child transmission of HBV infection

Sexual partners of persons with acute hepatitis B virus infection[1]

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

Household contacts of persons with acute hepatitis B virus infection[1]

Prophylaxis of an infant <12 months of age with HBIG and hepatitis B vaccine at 0, 1 and 6 months is indicated if the mother or primary caregiver 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[1]

This group should be tested for HBV markers (HBsAg, HBsAb & 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[‡]

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 (HCP) after occupational percutaneous and mucosal exposure to blood and body fluids[11]

Healthcare personnel status	**Post-exposure testing**		**Post-exposure prophylaxis**		**Post-vaccination serologic testing[†] For anti HBs**
	Source patient (HBsAg)	**HCP (anti-HBs)**	**HBIG***	**Vaccination**	
Documented responder[§] after complete series (≥3 doses)	No action needed				
Documented non-responder[¶] after 6 doses	Positive/ unknown	—**	HBIG x2 separated by 1 month	–	No
	Negative	No action needed			
Response unknown after 3 doses	Positive/ unknown ***	<10mIU/ mL**	HBIG x1	Initiate revaccination	Yes
	Negative	<10mIU/ mL	None		

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

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 <10 mIU/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. Total anti-HBc at baseline and HBsAg and total anti-HBc at approximately 6 months.*

**** 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*

References

1. American Academy of Pediatrics. *Red Book: 2024–2027 report of the Committee on Infectious Diseases*. Itasca (IL): American Academy of Pediatrics; 2024.
2. World Health Organization. WHO position paper on hepatitis B vaccines. *Weekly Epidemiological Record*. 2017;92(27):369–392.

3. World Health Organization. Hepatitis B. 2025 Jul 23 [cited 2026 Feb 10]. Available from: https://www.who.int/news-room/fact-sheets/detail/hepatitis-b%20[Accessed%2010.02.2026].
4. Premaratne EDRG, et al. Sero-epidemiology of hepatitis B and C in Colombo district. In: *Proceedings of the 116th Anniversary Academic Sessions of the Sri Lanka Medical Association*; 2003 Mar 26–29; Sri Lanka. p. OP-35.
5. Noordeen F, et al. A review of hepatitis B virus infection in Sri Lanka. *Sri Lankan Journal of Infectious Diseases*. 2015;5(2):42–50. doi:10.4038/sljid.v5i2.8087.
6. Epidemiology Unit, Ministry of Health, Sri Lanka. Viral hepatitis B sero-prevalence survey among pregnant mothers and 5-year-old children in Sri Lanka – 2022. Sri Lanka: Ministry of Health; 2022.
7. Bond WW, et al. Survival of hepatitis B virus after drying and storage for one week. *Lancet*. 1981; 1:550–551. doi:10.1016/S0140-6736(81)92877-4.
8. World Health Organization. Immunisation coverage. 2024. Available from: https://www.who.int/news-room/fact-sheets/detail/immunisation-coverage [Accessed on 10.02.2026].
9. Orenstein WA, et al. Hepatitis B vaccines. In: Plotkin SA, Orenstein WA, Offit PA, editors. *Plotkin's Vaccines*. 8th ed. Philadelphia: Elsevier; 2023.
10. UK Health Security Agency. Hepatitis B. In: *Immunisation against infectious disease (The Green Book)*. London: UK Health Security Agency; 2013 [updated 2025 Jun 11]. Chapter 18.
11. Centers for Disease Control and Prevention (CDC). Guidance for evaluating health-care personnel for hepatitis B virus protection and for administering postexposure management. *Morbidity Mortality Weekly Report*. 2013 Dec 20;62(10).

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CHAPTER 12

HUMAN PAPILLOMAVIRUS VACCINE

Introduction

Human papillomavirus (HPV) is the most common sexually transmitted infection (STI) worldwide. While the majority of HPV infections are asymptomatic and resolve spontaneously within 1-2 years, persistent infection with HPV may result in disease, such as invasive cervical cancer, cancers of the vulva, vagina, penis, anus, head, neck and oropharynx, as well as anogenital warts and respiratory papillomatosis[1].

Over 200 different HPV genotypes have been identified, with 40 HPV genotypes being transmitted sexually. These are classified into high risk (HR) and low risk (LR) types, based on their potential to cause cancer. Currently 12 HR types are identified which cause cancer in humans (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59). Type 68 is classified as probably causing cancer. Type 16 and 18 are responsible for 71% of cervical cancers and 87% anal squamous cell carcinoma. LR genotypes are associated with anogenital warts and laryngeal papillomatosis, with type 6 and 11 being the most commonly associated types[1].

The most common HPV related cancer in women is cervical cancer, which is the 4th most common cancer in women globally. Approximately 661,000 new cases and 348,000 deaths occur annually. Over 90% of these deaths occur in low- and middle-income countries[2]. Cervical cancer is the fifth most common cancer among Sri Lankan women, accounting for 6% of all female cancers[3].

Types of vaccines

The 2020 WHO Global Strategy to Accelerate the Elimination of Cervical Cancer as a Public Health Problem, recommends that HPV vaccines should be included in all national immunisation programmes and should reach 90% of all girls by age 15 by 2030[4].

There are three types of HPV vaccines, based on the number of HPV types included; bivalent, quadrivalent and nonavalent. All vaccines are prepared, using recombinant DNA and cell-culture technology. These vaccines are composed of highly purified L1 capsid proteins, which are the major structural proteins of the human papillomavirus. When produced in expression systems, these L1 proteins self-assemble into virus-like particles (VLPs) non-infectious, non-replicating structures that closely resemble the native virus in shape and size but do not contain any viral DNA. The bivalent vaccines contain VLPs for two HPV types (16 and 18), quadrivalent vaccines contain VLPs for four HPV types (6, 11, 16 and 18) and the nonavalent vaccine contain VLPs for nine HPV types (6, 11, 16, 18, 31, 33, 45, 52 and 58). All HPV vaccines induce strong and specific immune response without any risk of causing HPV infection[5].

In addition to the VLPs, the vaccines contain adjuvants to enhance the immune response. e.g. aluminum hydroxide and monophosphoryl lipid A (MPL), aluminum hydroxyphosphate sulfate[1].

All HPV vaccines are indicated for use in females aged 9 years or older and are licensed for use up to 26 or 45 years of age (according to the type of vaccine). Some HPV vaccines are also licensed for use in males. All are intended to be administered, if possible, before the onset of sexual activity, i.e. before exposure to HPV. The primary purpose of all currently licensed HPV vaccines is the prevention of cervical premalignant lesions and cancers caused by HR HPV types. Therapeutic HPV vaccines are under consideration for development in the future[1].

Currently two vaccines are in use in Sri Lanka, a bivalent vaccine in the private sector and a quadrivalent vaccine in the National Immunization Programme.

Efficacy

HPV vaccines are highly immunogenic, producing antibody titres 1- 4 logs higher than natural infection. The highest immune responses are seen in girls aged 9-15 years. Intramuscular administration promotes strong, lasting humoral immunity. In clinical trials, seropositivity rates

for HPV16 and HPV18 reached 100% and 98% respectively, among women aged 18-45 years, 66 months after 3 doses of a bivalent HPV vaccine[6]. The seropositivity rates for the quadrivalent vaccine remained high (>94%) for all 4 HPV types, 14 years post-vaccination[7]. Two-dose schedules in girls aged 9–14 years, showed non-inferior immune responses to 3-dose schedules in young women aged 15-26 years. Review of randomised controlled trials comparing efficacy and safety of HPV vaccine in females showed high-certainty evidence of protection against cervical precancer in adolescent girls and young women aged 15 to 26. In addition, there was moderate-certainty evidence of protection against cervical precancer in women older than 26 years, who were negative for HPV16/18 on enrollment[8].

High efficacy has been observed in a HPV naïve population for all licensed vaccines in studies that used HPV disease endpoints, including HPV infection, high grade cervical, vulval, vaginal lesions and cervical cancer[8,9,10]. The efficacy is higher when the vaccine is administered at an earlier age[8,11,12].

The quadrivalent and nonavalent vaccines provide high level protection against anogenital warts in men and women and anogenital precancerous lesions in susceptible men, when administered at 16–26 years. Vaccine efficacy studies showed that, among HPV-naive individuals, the quadrivalent vaccine confers almost 100% protection against anogenital warts associated with HPV6 and HPV11. Among vaccinated young women regardless of their prior HPV exposure, efficacy against all anogenital warts was 62%[13]. Additionally, widespread vaccination has led to herd protection, with declines in genital warts and oral HPV infections observed even in unvaccinated populations[14].

More recently, evidence from randomised trials, post-hoc analyses, and observational studies indicates that a single dose of HPV vaccine could provide similar efficacy and effectiveness against initial and persistent HPV16/18 infection as multidose regimens. The seropositivity following a single dose has been shown to persist for up to 10 years[15].

HPV vaccines are highly immunogenic in people living with HIV, with seroconversion rates of 94–100% after 3 doses. Antibody levels decline

over time but remain high for at least 2-4 years. The bivalent vaccine generally produces stronger responses than the quadrivalent vaccine, especially for HPV18. Immune responses are lower in those with low CD4 counts or detectable plasma HIV viral loads. No strong data exist for 1 or 2-dose schedules in PLWH, but early results suggest single-dose effectiveness may be promising[16,17].

Indications

For the
prevention of:

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

In addition, the quadrivalent vaccine is indicated for the prevention of anogenital warts (condylomata acuminata).

Dosage and administration

0.5 mL IM

Target groups for the prevention of cervical cancer:

- Primary target group -

  Girls aged 9-14 years. Achieving over 80% coverage in girls also reduces the risk of HPV infection for boys

- Secondary target groups -
  - Females ≥15 years-26 years, boys, older males or men having sex with men (MSM).
  - Vaccination for adults aged >26 years should only be offered following careful evaluation by a clinician.
    - HPV vaccination of people in this age range provides less benefit.
    - Persons who are in a long-term, mutually monogamous sexual partnership are not likely to acquire a new HPV infection.

- Although new HPV infections are most commonly acquired in adolescence and young adulthood, some adults are at risk for acquiring new HPV infections. At any age, having a new sex partner is a risk factor for acquiring a new HPV infection.

- HPV vaccines are not licensed for use in adults aged >45 years.

Vaccination schedule:

- **2 dose schedule:** given at 0 and 6 months for primary target group from 9-14 years
- **3-dose schedule**: recommended for recipients who start the series at ages 15 or above and immunocompromised persons
  - at 0, 1 month and 6 months for bivalent HPV vaccine
  - at 0, 2 months and 6 months for quadrivalent and nonavalent HPV vaccines

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

Vaccination of special populations

Immunocompromised women and men, including those living with HIV and children and adolescents who have faced sexual abuse, are at increased risk of HPV-related disease. It is recommended that these individuals are considered for vaccination against HPV as a priority as part of the public health programme. Immunocompromised or HIV-infected persons (regardless of age or antiretroviral therapy status) should receive at least two HPV vaccine doses (minimum 6 months interval) and where possible, three doses (at 0, 1 and 6 months).

Use in pregnancy

HPV vaccine is not recommended to be administered 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.

Contraindications and Precautions

- Severe allergic reactions to a previous dose or to a component of the vaccine
- A moderate or severe acute illness is a precaution to vaccination, and vaccination should be deferred until symptoms of the acute illness improve.
- A minor acute illness (e.g. diarrhoea or mild upper respiratory tract infection, with or without fever) is not a reason to defer vaccination.

Safety

HPV vaccines do not contain live virus, antibiotics or preservatives, making them non-infectious and safe.

Local reactions:

- Overall local adverse events were reported in 39–87% of recipients of bivalent or quadrivalent HPV vaccine. Common reactions are injection site reactions such as pain, redness and swelling, and usually resolves within 3-4 days.
- Bivalent vaccine may result in more adverse events at the injection site than quadrivalent vaccine.

Systemic reactions:

- Common systemic adverse events include headache, dizziness, myalgia, arthralgia and gastrointestinal symptoms (nausea, vomiting, abdominal pain). These are generally mild and self-limiting.
- Post vaccination syncope has been reported. This is described as a preventable event after injection among adolescents and could be minimised and its complications avoided, with appropriate preparation.
- Immunisation stress-related responses (ISRR) associated with HPV vaccine administration have been observed, and are of 4 main types: Vaso vagal syncope, acute anxiety or panic reactions,

Psychogenic seizures or pseudo seizures, mass psychogenic illness. ISRRs are transient, benign and preventable with proper education, setting, and post-vaccination observation.

Storage

2-8 ^{0}C and protected from light. Do not freeze.

Cervical cytology screening

While HPV vaccination is a primary prevention intervention, it does not eliminate the need for screening later in life (since the existing vaccines do not protect against all HR HPV types and limited impact on disease in women older than vaccine-eligible groups). Screening and treatment of cervical precancerous lesions is highly successful in preventing cervical cancer and the Global Strategy for Cervical Cancer Elimination recommends that 70% of women should be screened with a high-performance test by age 35 and again by age 45. Therefore, cervical cytology screening, diagnosis and treatment of pre-cancerous lesions and cancers and HPV vaccination should be considered as part of a coordinated and comprehensive strategy to prevent cervical cancers.

References

1. World Health Organization. Human papillomavirus vaccines: WHO position paper, December 2022 *Weekly Epidemiology Record*. 2022; 97(50):645–72. Available from: https://www.who.int/publications/i/item/who-wer9750-645-672
2. Bray F, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*. 2024; 74(3):229–63. doi: 10.3322/caac.21834.
3. National Cancer Control Programme, Ministry of Health. Cancer incidence & mortality data Sri Lanka 2021. Colombo: Ministry of Health; 2023.
4. World Health Organization. Global strategy to accelerate the elimination of cervical cancer as a public health problem [Internet]. Geneva: World Health Organization; 2020 [Accessed 2025 May 14]. Available from: https://iris. who.int/handle/10665/336583.

5. World Health Organization. Considerations for human papillomavirus (HPV) vaccine product choice [Internet]. Geneva: World Health Organization; 2024 [cited 2025 May 14]. Available from: https://iris.who.int/handle/10665/376546.
6. Schiller JT, et al. A review of clinical trials of human papillomavirus prophylactic vaccines. *Vaccine*. 2012; 30(Suppl 5): F123–38.
7. Kjaer SK, et al. Final analysis of a 14-year long-term follow-up study of the effectiveness and immunogenicity of the quadrivalent human papillomavirus vaccine in women from four Nordic countries. *eClinical Medicine*. 2020; 23:100401.
8. Arbyn M, et al. Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. *Cochrane Database Systematic Reviews*. 2018; 5:CD009069.
9. Qiao YL, et al. Efficacy, safety, and immunogenicity of an Escherichia coli-produced bivalent human papillomavirus vaccine: an interim analysis of a randomised clinical trial. *Journal of the National Cancer Institute.* 2020; 112:145-153.
10. Xu L, et al. Prophylactic vaccination against human papillomaviruses to prevent vulval and vaginal cancer and their precursors. *Expert Reviews on Vaccines*. 2019;18(1):1157-1166.
11. Drolet M, et al. Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis. *Lancet*. 2019; 394:497–509.
12. Palmer T, et al. Prevalence of cervical disease at age 20 after immunisation with bivalent HPV vaccine at age 12-13 in Scotland: retrospective population study. *British Medical Journal* 2019; 365:1161.
13. McCormack PL. Quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine (Gardasil®): a review of its use in the prevention of premalignant anogenital lesions, cervical and anal cancers, and genital warts. *Drugs*. 2014; 74(11):1253–1283.
14. Bollerup S, et al. Significant reduction in the incidence of genital warts in young men 5 years into the Danish human papillomavirus vaccination program for girls and women. *Sexually Transmitted Diseases*. 2016; 43:238e42.
15. Whitworth HS, et al. Efficacy and immunogenicity of a single dose of human papillomavirus vaccine compared to no vaccination or standard three and two-dose vaccination regimens: a systematic review of evidence from clinical trials. *Vaccine.* 2020; 38(6):1302-1314.

16. Toft L, et al. Comparison of the immunogenicity and reactogenicity of Cervarix and Gardasil human papillomavirus vaccines in HIV-infected adults: a randomised, double-blind clinical trial. *Human Vaccines and Immunothe rapeutics*. 2014; 209:1165-1173.
17. Faust H, et al. Human papillomavirus neutralising and cross-reactive antibodies induced in HIV-positive subjects after vaccination with quadrivalent and bivalent HPV vaccines. *Vaccine.* 2016; 34(13):1559-1565.

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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]. Influenza significantly increases morbidity, hospitalisations, and mortality, particularly among vulnerable populations. The associated economic burden is substantial, driven by lost productivity, varying healthcare costs depending on disease severity, hospitalisation, and antiviral treatment, as well as the added strain on healthcare systems during peak seasons[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[5]. Vaccination is currently the only effective means of reducing the burden of influenza in the community.

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 are still the most commonly used vaccines[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[6]. Both northern and southern hemisphere vaccines are 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 (a type of inactivated vaccine that contains an influenza virus that has been disrupted (split) into smaller fragments using a detergent) / subunit (contains purified parts of the pathogen that are antigenic, or necessary to elicit a protective immune response)

- 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

- Cell culture-based inactivated influenza vaccine (ccIIV3) for persons ≥ 6 months

- High-dose inactivated influenza vaccine (HD-IIV3) for persons ≥ 65 years
- Adjuvanted inactivated influenza vaccine (aIIV3) for persons ≥ 65 years

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, similar to 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)[7].

Vaccine effectiveness of IIV over five influenza seasons (from 2011–2016) between a reference group of adults aged 18–49 years and elderly (65–74 years, ≥ 75 years, and ≥ 65 years) found an overall VE of 48% (95% CI: 41; 54) against H1N1 in the adults and of 49% in the elderly, of 55% and 62% against B viruses, and of 21% and 14% against H3N2, respectively[8]. Overall, it has been estimated that IIVs are able to reduce the risk of influenza in children aged 2–16 years from 30% to 11%, and LAIVs from 18% to 4% in children aged 3–16 years[9].

Influenza vaccination prevents infection in pregnant women, as well as in their newborns through transfer of maternal antibodies. The pooled estimate from 3 randomised 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[10].

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 - preferably ≥ 2 weeks before departure
- 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 immunocompromised
- Pregnant women

  Pregnant and postpartum women are at higher risk of severe illness and complications. Influenza vaccine containing the killed virus is safe and recommended in all trimesters[11].
- 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 – Two doses one month apart. Half adult dose (0.25 mL) IM anterolateral aspect of thigh/deltoid.
  - 3-8 years – 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 – half adult dose (0.25 mL) IM anterolateral aspect of thigh/deltoid
  - > 3 years – adult dose (0.5 mL) IM deltoid muscle
- Over 65 years
  - High-dose inactivated influenza vaccine (HD-IIV3)
  - Adjuvanted inactivated influenza vaccine (aIIV3)

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

- 2-50 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
- Adults ≥ 50 years
- 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 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[12].

Adverse effects

Inactivated vaccines

- Local reactions, minimal – pain, erythema or induration
- Systemic effects – low grade fever and body aches lasting for 1-2 days
- Guillain–Barré syndrome – very rare[13]

LAIV

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

Coadministration

IIVs do not appear to interfere with concomitantly administered vaccines of the routine childhood immunisation programme. 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[14].

Storage

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

References

1. Vaccines against influenza: WHO position paper. *Weekly Epidemiological Record.* 2022; 97:185–208 http://www.who.int/wer
2. Somes MP, et al. Estimating the annual attack rate of seasonal influenza among unvaccinated individuals: a systematic review and meta-analysis. *Vaccine.* 2018; 36(23):3199-3207.

3. https://www.who.int/news-room/feature-stories/detail/the-burden-of-influenza[Accessed:2nd Sep 2025].
4. Tyrrell CS, et al. Influenza: epidemiology and hospital management. *Medicine* 2021; 49(12): 797 – 804.
5. Jayasinghe C, et al. Influenza surveillance activities in Sri Lanka. Proceedings of the 1st South East Asia Regional Group Meeting of the International Epidemiological Association, Colombo, Sri Lanka, 19-21 September 2019.
6. https://www.who.int/teams/global-influenza-programme/vaccines/vaccine-in-tropics-and-subtropics. [Accessed: 2nd Sep 2025]
7. https://www.cdc.gov/flu-vaccines-work/php/effectiveness-studies/index. html[Accessed:02.09.2025].
8. Trombetta CM, et al. Influenza Viruses and Vaccines: The role of vaccine effectiveness studies for evaluation of the benefits of influenza vaccines. *Vaccines* 2022; 10, 714.
9. Jefferson, T. et al. Vaccines for preventing influenza in healthy children. *Cochrane Database Systematic Reviews*. 2018; 2:CD004879
10. Quach THT, et al. Influenza vaccine efficacy and effectiveness in pregnant women: systematic review and meta-analysis. *Maternal and Child Health Journal.* 2020; 24: 229-40.
11. Safety of influenza vaccines. Atlanta, GA: Centers for Disease Control and Prevention, 2024 https://www.cdc.gov/flu/vaccine-safety/vaccine-pregnant. html [Accessed Sep 2025].
12. Su JR, et al. Anaphylaxis after vaccination reported to the Vaccine Adverse Event Reporting System, 1990-2016. *Journal of Allergy and Clinical Immunology.* 2019; 143(4):1465-1473.
13. Lotte Levison, et al. Guillain–Barré syndrome following influenza vaccination: A 15year nationwide population based case–control study. *European Journal of Neurology*. 2022;29(11):3389–3394.
14. Nolan T, et al. Safety and immunogenicity of concurrent administration of live attenuated influenza vaccine with measles-mumps-rubella and varicella vaccines to infants 12 to 15 months of age. *Paediatrics* 2008; 21(3): 508–516.

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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 100,000 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]. It is an infection of the central nervous system characterized by coma, seizures, paralysis, abnormal movements etc. It 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. Death occurs in one third of cases and serious sequelae in 40% of survivors[4,5].

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 prioritised over vaccination of pigs and mosquito control measures[2]. Substantial progress has been made with introduction and strengthening of JE immunisation programmes in

Asia[5]. WHO recommends that JE vaccination be integrated into national immunisation programmes in all areas where JE disease is recognised as a public health problem[2]. In some areas, other factors probably have contributed to the decline, including industrialisation and urbanisation, reducing *Culex* mosquito breeding sites, widespread use of agricultural pesticides and centralised pig farming[5].

JEV is not spread from person to person through direct contact. Humans are considered as dead-end hosts in the JEV transmission cycle, because they do not develop a level or duration of viraemia sufficient to infect mosquitoes[5]. 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].

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

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

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

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

Produced in primary hamster kidney cell (BHK) culture[1]. 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[6,7]. It is a freeze-dried preparation and is WHO pre-qualified. In the National Immunisation Programme all children are immunised 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 neutralising antibodies after a single dose[7]. It does not contain any adjuvant or preservative. This freeze-dried vaccine is licensed for use in 15 countries which include Sri Lanka, Australia, Thailand, Philippines, Singapore, Malaysia, Bangladesh and Indonesia. This vaccine is WHO pre-qualified.

- **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. It does not contain any preservatives, antibiotics or stabilisers. It is a WHO pre-qualified vaccine.

- **Inactivated mouse brain derived vaccine**

This vaccine is prepared from a suspension of mouse brain infected with JEV. Nakayama strain - Freeze dried or liquid vaccine. Vietnam is the only country that continues to use a mouse brain derived JE vaccine.

Efficacy

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

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[8]. In a multicentre randomised control trial involving previously primed 2–5year olds and naïve 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[9].

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

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

Dosage and administration

- **Live attenuated vaccine**

Primary immunisation - 0.5 mL, SC.

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. Because protection of several years has been demonstrated after a single dose, WHO does not currently recommend a booster dose[1]. 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 JE vaccine[11].

- **Live recombinant yellow fever–Japanese encephalitis chimeric vaccine**

One dose of 0.5 mL is administered SC for individuals aged above 9 months. 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. A booster dose could be given for adults if required, after 5 years (manufacturer's recommendation, 2017).

- **Inactivated Vero cell derived vaccine**

Primary schedule varies by age.

2-35 months - 0.25 mL, IM

≥3 years - 0.5 mL, IM

Primary series consists of 2 doses administered 28 days apart. Persons who are at ongoing risk or likely to be re-exposed to JEV, should receive a booster dose 12-24 months after the primary immunisation[5].

Immunisation of travellers visiting JE endemic countries:

Vaccines should be considered for travellers if they have an increased risk for JEV exposure based on travel duration, season, location, activities and type of accommodation[3,4] (refer Chapter 30).

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 33)
  - Leukaemia, lymphoma and other malignancies (ref. 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^{0}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^{0}C
- Stable neurological conditions e.g. cerebral palsy, Down syndrome
- Treatment with topical steroids or systemic use of steroids at low dosages, less than 0.5 mg/Kg body wt.[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 ^{0}C. Avoid exposure to direct sunlight. The liquid vaccine should not be frozen.

References

1. JE vaccine. WHO position paper: *Weekly Epidemiological Record.* 2015; 90:69–88.
2. Japanese encephalitis. WHO Fact Sheet: 6th August 2024.
3. Hills SL, et al. Japanese encephalitis vaccine: Recommendations of the Advisory Committee on Immunisation Practices. *Morbidity and Mortality Weekly Report.* Recommendations and Reports. 2019; 68(2):1-33.
4. Halstead SB, et al. Japanese encephalitis vaccine. In: Halstead BS, et al. (eds) *Plotkin's Vaccines*. 7th ed. Philadelphia, PA: Elsevier; 2018. 511-545.

5. Halstead SB, et al. Japanese encephalitis vaccines. In: Orenstein AW, et al. (eds) *Plotkin's Vaccines*. 8th ed. Philadelphia, PA: Elsevier; 2023.577–607.
6. Immunisation Handbook. National Expanded Programme of Immunisation Sri Lanka. Epidemiological Unit, Ministry of Health 2012; 3rd edition: 87-94.
7. Halstead SB, et al. Japanese encephalitis: New options for active immunisation. *Clinical Infectious Diseases*. 2010; 50(8):1155-1164.
8. Feroldi E, et al. Primary immunisation of infants and toddlers in Thailand with Japanese encephalitis chimeric vaccine in comparison with SA-14-14-2: a randomised study of immunogenicity and safety. *Paediatric Infectious Diseases Journal*. 2014; 33(6):643 – 649.
9. Chokephaibulkit K, et al. Safety and immunogenicity of a single administration of live-attenuated Japanese encephalitis vaccine in previously primed 2-5 year olds and naïve 12-24 month olds. A multicentre randomised controlled trial. *Paediatric Infectious Diseases Journal*. 2010**;** 29(12):1111–1117.
10. Kaltenbock A, et al. Immunogenicity & safety of "Ixiaro" in phase III study in healthy Indian children between 1-3 years of age. *Vaccine.* 2010; 28(3):834 -839.
11. Wijesinghe PR, et al. Immunogenicity of live attenuated Japanese encephalitis SA 14-14-2 vaccine among Sri Lankan children with previous receipt of inactivated JE vaccine. *Vaccine.* 2016; 34(48):5923–5928.

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CHAPTER 15

MEASLES, MUMPS AND RUBELLA VACCINE

Measles, mumps and rubella (MMR) is a live attenuated combined vaccine which prevents measles, mumps, rubella and congenital rubella syndrome (CRS).

In Sri Lanka, monovalent measles vaccine was first introduced in 1984 for infants at the age of 9 months as a single dose. MR vaccine was introduced as a second dose of 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 the 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.

Measles

Measles is one of the most highly contagious of all infectious diseases where a human being is the only host for the virus. The incubation period is approximately 10 days, but varies from 7 to 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 characterised 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 spots) may be detected. Case fatality rates are higher among children younger than 5 years, the immunocompromised and in the severely malnourished, including in vitamin A deficiency as well[1,2].

The measles elimination programme (2000-2023) has prevented an estimated 60.3 million deaths due to measles. However, despite the commitment from all six WHO regions, no region had successfully achieved or maintained measles elimination by the end of 2023. During

the COVID-19 pandemic, estimated global coverage with the first dose of measles-containing vaccine (MCV1) had declined to 81%, which was the lowest level since 2008. Subsequently, MCV1 coverage improved to 83% in 2022 but it remained unchanged in 2023. It was also revealed that from 2022 to 2023, estimated measles cases increased by 20% worldwide, indicating that a number of countries experienced large outbreaks of measles. The suboptimal coverage has left millions of children, particularly in low-income countries, unprotected. It was re-emphasised to ensure 2 doses of MCV to all children and strengthen surveillance to prevent further outbreaks[2,3].

The measles outbreak which occurred in Sri Lanka in 2023 was predominantly driven by unvaccinated individuals[3]. It was recommended to enhance immunisation coverage, through targeted catch-up immunisation campaigns focusing on high-risk groups, alongside culturally sensitive educational initiatives to prevent such outbreaks[3].

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 wild type of measles, characterised by behavioral and intellectual deterioration and seizures[1].

Mumps

Mumps generally occurs during childhood. It is caused by an 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].

Despite the significant reduction of the incidence of mumps due to vaccination, a majority of countries have failed to reach the status of elimination. A study evaluating mumps vaccination over three decades showed the possibility of re-emergence of the disease among young adult vaccinees[4].

Complications

Recent studies have shown that complications could occur at the rate of 10-40%. The most common complication was orchitis, followed by meningitis. Less common complications include pancreatitis, encephalitis, deafness, mastitis, oophoritis and Bell's palsy[5,6]. Orchitis occurs in 15-30% of unvaccinated males and nearly 10% among the vaccinated[5]. Orchitis typically occurs 10 days after the onset of parotitis and is most often unilateral. Young pubertal and post-pubertal males (15-34 years) are at the highest risk (2.7%). Damage caused to testicular tissue by the mumps virus results in subfertility (13%) while infertility remains to be a rare complication[7]. Other complications include pancreatitis (2%), febrile seizures (2%) and meningitis (2%). Any individual who experiences hearing loss with mumps should be evaluated by an ENT specialist for potential cochlear damage[5,6].

Mumps during the first trimester of pregnancy is associated with an increased incidence of spontaneous abortions[7,8].

Rubella

Rubella is an acute viral infection which generally results in a mild disease in children and adults. It is caused by a Togavirus 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. About 25-50% of infections are subclinical[9]. 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 feto-placental barrier resulting in

teratogenicity. Rubella virus (RV) infection in pregnancy may lead to miscarriage or stillbirth. More importantly, primary RV infection may lead to serious birth defects, CRS. Congenital heart defects (such as patent ductus arteriosus and branch pulmonary artery hypoplasia/stenosis), cataracts, and sensorineural hearing loss are the classic triad. The WHO estimates that approximately 100,000 congenital rubella syndrome cases occur annually. The risk of congenital effects in the first trimester is estimated as 80%, with the risk falling to 10-20% by the 16th week of gestation[1,10].

Introduction of rubella vaccination in the NIP has resulted in > 96% reduction in reported rubella cases and a corresponding > 98% reduction in CRS cases in Sri Lanka[11].

Type 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

Regardless of the universal implementation of the two-dose trivalent MMR vaccine in the past two decades, outbreaks of all three diseases continue to occur even among countries with high vaccine uptake[12]. A recent systematic review showed that the estimated overall seroconversion rates were 96·0% for measles, 93·3% for mumps when excluding the Rubini strain, 91·1% for mumps when including the Rubini strain, and 98·3% for rubella. Estimated overall annual waning rates were 0·009 for measles, 0·024 for mumps, and 0·012 for rubella[12].

A Cochrane review (2020) had revealed that the effectiveness of MMR vaccine was 96% in the prevention of measles, over 86% for mumps with the 2nd dose and 89% in the prevention of rubella, after a single dose[13].

A seroprevalence study conducted in Thailand has shown that there was a decline in long term sero-protection against measles and mumps, but not for rubella after two doses of MMR at 9 months and 2.5 years[14].

The ACIP recommended to administer a third dose of vaccine for healthcare workers who were previously vaccinated with two doses of MMR vaccine, who belong to a group at increased risk of mumps infection in the event of an epidemic[15].

Indications

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

Catch-up vaccination

- Previously unvaccinated children and adults - 2 doses of MMR ≥ 4 weeks apart[15]
- Persons who have received one dose of measles - 2 doses of MMR ≥ 4 weeks apart
- Persons who have received one dose of measles and one dose of MR/MMR - 1 dose of MMR

Post-exposure prophylaxis

One dose of MMR should be administered to an unvaccinated person within 72 hours of exposure to a person with infectious measles, and the second dose should be given ≥ 4 weeks later.

During mumps outbreaks, a third dose of MMR is recommended for persons identified by public health authorities as being part of a group or population at increased risk for acquiring mumps because of an outbreak[15,16].

Dosage and administration

0.5 mL SC. Could also be given IM

Contraindications

- Pregnancy
- Persons with immunodeficiency, HIV/AIDS (refer Chapter 34)
- 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, mutton etc.) or cow's milk should be evaluated by a specialist before immunization.
- Vaccination should be deferred in persons with an acute febrile illness
- MMR either should be administered ≥ 2 weeks before 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[16] (refer Chapter 35).

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 and thrombocytopaenic purpura had been reported among vaccinated populatons[17,18]. Concerns raised 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[19].

Storage

2-8 ^{0}C

MMRV Vaccine

Since 2005, a 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[20]. MMRV is currently unavailable in Sri Lanka.

References

1. Kimberlin DW, et al. Red Book: 2024 Report of the Committee on Infectious Diseases. Itasca, IL: American Academy of Paediatrics; 2024.
2. Minta AA. Progress toward measles elimination-worldwide, 2000–2022. *Morbidity and Mortality Weekly Report*. 2023; 72. doi:10.15585/mmwr.mm 7147a1
3. Kalubowila K, et al. Factors influencing the unexpected measles outbreak of 2023 in Colombo, Sri Lanka. *Journal of the College of Community Physicians of Sri Lanka*. 2025; 30(4).
4. Frost JR, et al. Genomic characterisation of three Canadian mumps outbreaks demonstrates endemic transmission in Canada. *Viruses*. 2024; 16(8):1280.
5. Mir NY, et al. Clinical course, complications, immunisation status and outcome of mumps in children. *International Journal of Community Medicine and Public Health.* 2023;10(3):1076–1080.
6. Hamad BJ, et al. Mumps and sterility: a comprehensive review. *Teikyo Medical Journal*. 2021; 44(6):2725–2735.
7. Nyawale H, et al. High mumps virus IgG seropositivity among women with spontaneous abortion attending health care facilities in Mwanza, Tanzania. *Tanzanian Journal of Health Research*. 2024; 25(3):1176 –1183.
8. Kaleelullah RA, et al. Teratogenic genesis in fetal malformations. *Cureus*. 2021; 13(2).
9. Winter AK, et al. Rubella. *Lancet.* 2022; 399(10332):1336–1346.
10. Vynnycky E, et al. Estimates of the global burden of congenital rubella syndrome, 1996–2019. *International Journal of Infectious Diseases*. 2023; 137:149–156.

11. Gamage D, et al. Impact of rubella vaccination on elimination of congenital rubella syndrome in Sri Lanka: progress and challenges. *WHO South East Asia Journal of Public Health*. 2015; 4(2):189–196. doi:10.4103/2224-3151.206689
12. Shah N, et al. A review of safety and immunogenicity of a novel measles, mumps, rubella (MMR) vaccine. *Human Vaccines and Immunotherapy*. 2024; 20(1)2302685.
13. Di Pietrantonj C, et al. Vaccines for measles, mumps, rubella, and varicella in children. *Cochrane Database of Systemic Reviews*. 2020; (4).
14. Angsuwatcharakon P, et al. High seroprevalence of rubella in Thai children with a 2-dose MMR national immunisation policy. *Vaccine*. 2021; 39(42):6206–6209. doi:10.1016/j.vaccine.2021.08.079
15. Issa AN. Advisory Committee on Immunisation Practices recommended immunisation schedule for children and adolescents aged ≤ 18 years—United States, 2025. *Morbidity and Mortality Weekly Report*. 2025;74.
16. Centers for Disease Control and Prevention (CDC). Vaccines and immunisation: contraindications and precautions for healthcare providers. 2024.
17. Shepersky L, et al. Mumps in vaccinated children and adolescents: 2007–2019. *Paediatrics*. 2021;148(6).
18. Rodriguez-Nava G, et al. MMR vaccine adverse drug reactions reports in the CDC WONDER System, 1989–2019. *Open Forum of Infectious Diseases*. 2020; 7(8): ofaa211.
19. Gabis LV, et al. The myth of vaccination and autism spectrum. *European Journal of Paediatric Neurolology*. 2022; 36:151–158.
20. Bellavite P, et al. Adverse events following measles-mumps-rubella-varicella vaccine: an independent perspective on Italian pharmacovigilance data. *F1000Research*. 2020; 9:1176. doi:10.12688/f1000research.26523.2

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CHAPTER 16

MENINGOCOCCAL VACCINE

Introduction

Neisseria meningitidis is a Gram-negative, non-spore-forming, encapsulated, diplococcus (paired, round) bacterium that can cause meningitis and septicaemia. It is a common commensal of the human upper respiratory tract but can also cause invasive meningococcal disease (IMD). It is classified into13 serogroups based on their capsular polysaccharides. Serogroups A, B, C, W135, X, and Y are the most common causes of invasive disease where vaccines are targeted.

N meningitidis is transmitted through aerosols. Overcrowding 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 laboratory exposures, 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.

There are several studies focusing on several aspects of *N meningitidis*, including its genetic characteristics, epidemiology, and treatment options. One key area is the emergence of antimicrobial resistance, with studies highlighting the need for broader control strategies. Additionally, research is exploring the relationship between carriage and invasive disease, while concentrating on the impact of vaccines on both disease and carriage.

Meningococci may be present asymptomatically in up to 30% of the population for periods exceeding 2 years. Factors associated with higher carriage rate were age $\leq$ 22 years, previous tonsillectomy, cigarette smoking, drinking alcohol and attending parties, pubs and

clubs. Female gender and sharing a household with children aged 0-9 years were associated with lower carriage. The most frequent genogroups were capsule null locus (*cnl*), group B and group Y and the most commonly identified clonal complexes (cc) were cc198 and cc23. Persistent carriage with the same meningococcal strain for 12 months was observed in two subjects[1].

Meningoccci adhere to epithelial surfaces in the nasopharynx to form microcolonies which resemble biofilms that help them to persist under adverse conditions. *N meningitidis* has 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 could cross the blood-brain barrier causing meningitis.

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

In Sri Lanka, according to data from the National Reference Laboratory, Medical Research Institute, eleven cases of IMD had been reported in children and adults from Western, Eastern, Northern and North-Central Provinces with no recent overseas travel. Meningococcaemia, skin rash, meningitis and sepsis were the common clinical manifestations observed. The meningococcal isolates belonged to serogroups B and C[4]**.** Majority of the isolates were intermediate-susceptible to penicillin. Some strains showed resistance to quinolones (ciprofloxacin, levofloxacin). All cases are reported to epidemiology unit to control potential outbreaks.

Vaccination is the mainstay of infection prevention. In countries where the disease occurs less frequently (< 2 cases per 100,000 population /year), meningococcal vaccination is recommended for defined risk groups. In particular, the continued absence of serogroup X and predominance of serogroup B in many regions outside the African meningitis belt indicate the need for widespread vaccination against serogroup B in addition to serogroups ACWY in these regions. The newly available pentavalent ACWYX vaccine, provides protection against serogroup X and is expected to be utilised only in specific regions[5].

WHO recommendations on meningococcal vaccines and vaccination that apply to all countries globally, are planned for 2025[5].

Types of vaccine[3]

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[3]

MenACWY vaccines are protein conjugate vaccines.

- Meningococcal groups A, C, W and Y polysaccharide diphtheria toxoid conjugate vaccine (MenACWY-D) is licensed for use from 9 months to 55 years of age
- Meningococcal groups A, C, W and Y oligosaccharide diphtheria CRM197 conjugate vaccine (MenACWY-CRM) is licensed for use from 2 months to 55 years of age
- Meningococcal groups A, C, W and Y polysaccharide tetanus toxoid conjugate vaccine (MenACWY-TT) is licensed for use from 6 weeks of age

Serogroup B vaccines

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

- MenBFHbp is based on a surface-exposed lipoprotein named 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 outbreak conditions.

- MenB-4C contains 4 antigenic components (FHbp fusion protein, NadA, NHBA fusion protein, and outer membrane vesicle). It is administered as a 2-dose series (0, 1 month).
- When MenACWY-D is administered 30 days after diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine, it interferes with the immune response for all four meningococcal serogroups. Therefore, it should be administered either before or at the same time as DTaP for children for whom quadrivalent meningococcal vaccine is indicated.
- MenACWY-D should not be given concomitantly or within 4 weeks of the pneumococcal conjugate vaccines. Competition between carrier proteins may lead to interference with antibody response to certain serotypes in the PCV vaccine. As children < 2 years of age with functional or anatomical asplenia or HIV are at an increased risk of invasive pneumococcal disease, they should not receive the MenACWY-D vaccine. They may be given the MenACWY-CRM vaccine instead as it does not interfere with the response to PCV.

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 immunisation 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 condition 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

Meningococcal vaccination is not recommended for post-exposure prophylaxis following exposure to a single case[4].

Special considerations

- Pregnancy

Although not extensively studied in pregnant women, MenACWY and MenB vaccines may be administered to pregnant women when there is an increased risk of disease.

- Asplenia

Use of MenACWY vaccine (beginning in infancy) and MenB vaccine (beginning at 10 years of age) can be considered on a case-by-case basis for children with either primary or secondary splenic dysfunction. When surgical splenectomy is planned, Hib, pneumococcal, and meningococcal vaccine history should be reviewed, and the needed vaccines should be administered at least 2 weeks before surgery. If splenectomy is performed on an emergency basis or if the needed vaccines were not administered before splenectomy, it should be administered 2 weeks after surgery.

- Clinical microbiology staff

Those who are routinely exposed to isolates of *N. meningitidis* are at increased risk of severe meningococcal disease if exposed to a clinical isolate and should be vaccinated with MenACWY and MenB[3].

- Travel

MenACWY is recommended for use in people age $\geq$ 2 months travelling to areas where there is a high burden of meningococcal disease, such as sub-Saharan Africa or other areas with ongoing

meningococcal outbreaks. Completion of the entire series is preferred prior to travel.

Booster doses are recommended for people who are at continuous or repeated increased risk of meningococcal infection.

Table 1. Dosage and administration of conjugate vaccines

Age groups/ categories	Available preparations	Dose and route	Remarks
Pregnancy	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)
	Men B		During B serotype outbreaks and with high risk only when benefits outweigh the risks
2 months – 10 years	Men ACWY-CRM or Men ACWY-D	0.5 mL IM	Not recommended for routine use (refer Table 2 for recommended groups)
Primary			
11-21 Years	Men ACWY-CRM or Men ACWY-D	0.5 mL IM single dose	If not vaccinated before
Booster			
Adolescent	Men ACWY-CRM or Men ACWY-D	0.5 mL IM single dose	Recommended if 1st dose taken before 16 years
During outbreaks			
16-22 years	MenB-FHbp or MenB-4C	0.5 mL IM	1 or 2 doses one month apart based on outbreak situation
>22 years	Men ACWY-CRM or Men ACWY-D	0.5 mL IM single dose	refer Table 2 for recommended groups

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

	Available preparations	Dose and route
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 At risk during a community outbreak attributable to a vaccine serogroup	Men ACWY-CRM*	0.5 mL IM at 2, 4, 6 and 12 months
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	MenACWY-CRM	Additional dose of Men ACWY 3 years after 1ry immunisation Boosters should be repeated every 5 years thereafter

>7 years of age		Additional dose of Men ACWY 5 years after 1ry immunisation Boosters should be repeated every 5 years thereafter
2-55 years with following high-risk conditions, not immunised previously Persistent complement deficiencies Functional or anatomic asplenia HIV infection	MenACWY-CRM or MenACWY-D**	0.5 mL IM 2 doses 8-12 weeks apart
10 years or older with following high-risk conditions not immunised previously: who have 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*	MenB-4C MenB-FHbp	0.5 mL IM 2 doses 1 month apart

*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
**MenACWY-D may be used at least 4 weeks after completion of pneumococcal vaccine doses

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.

Storage

2-8 °C.

References

1. Rouphael NG, et al. *Neisseria meningitidis*: biology, microbiology, and epidemiology. *Methods in Molecular Biology* 2012; 799:1-20. doi: 10.1007/978-1-61779-346-2
2. American Academy of Paediatrics, 2018-2021, Red Book, Report of the Committee of Infectious diseases, 31st edition, Itaska, ISSN-1080-0131, ISBN 978-161002-146-3, MA0858
3. Karunanayake L, et al. Antimicrobial susceptibility and serotypes of *Neisseria meningitidis* and *Streptococcus pneumoniae* in Sri Lanka: Experience from the National Reference Laboratory. *Asian Pacific Journal of Tropical Medicine* 2022; 15(3): 114-20.
4. Meningococcal vaccines: WHO position paper on the use of multivalent meningococcal conjugate vaccines in countries of the African meningitis belt. *Weekly Epidemiological Record*. 2024, Nos,1/2, 2024,99,1-10, http;//www. who.int/wer

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CHAPTER 17

PNEUMOCOCCAL VACCINE

Introduction

Streptococcus pneumoniae remains a leading cause of vaccine-preventable morbidity and mortality worldwide, particularly among children under five years, older adults, and individuals with chronic medical conditions or are immunocompromised. The human upper respiratory tract is the natural reservoir for *S pneumoniae*. The carriage of *S pneumoniae* in the nasopharynx, even in the absence of symptoms, is a crucial factor in the transmission of this pathogen. Pneumococcal disease manifests as invasive pneumococcal disease (IPD) including bacteraemic pneumonia, meningitis, and sepsis as well as non-invasive disease, notably community-acquired pneumonia (CAP), otitis media, and sinusitis[1].

Globally, in 2000, prior to widespread introduction of the pneumococcal conjugate vaccine (PCV), about 14.5 million episodes of serious pneumococcal disease were estimated to occur. The WHO estimated that approximately 800,000 children were dying each year of pneumococcal disease, with 90% of these deaths occurring in developing countries[2]. In adults, pneumococcus remains one of the commonest causes of severe bacterial pneumonia requiring hospitalisation. In 2022, adults in the USA aged ≥ 65 years had incidence and mortality rates secondary to pneumococcal diseases of 17.2 and 2.7 per 100,000 population, respectively[3]. Pneumococcal meningitis is associated with high case fatality rates (10–30%) and significant long-term neurological sequelae among survivors[4].

In Sri Lanka, pneumococcal disease contributes significantly to childhood pneumonia admissions and adult CAP, although precise national incidence data are limited due to under-diagnosis, aetiological agents for pneumonia not being notifiable and restricted routine serotyping. Hospital-based studies and regional surveillance indicate that pneumococcus remains an important pathogen in paediatric

meningitis, sepsis, and pneumonia in elderly, with rising concern regarding antimicrobial resistance[5,6,7].

Historical development of pneumococcal vaccines

More than 100 pneumococcal serotypes have been identified, based on the capsular structure, though a smaller subset causes the majority of invasive disease. About 5-10% of healthy adults and 20-40% of healthy children are colonized with *S pneumoniae*[8].

Early attempts to prevent pneumococcal disease focused on capsular polysaccharide vaccines, reflecting the organism's polysaccharide capsule as the major virulence determinant. The first multivalent pneumococcal polysaccharide vaccine was introduced in the 1970s, culminating in the 23-valent pneumococcal polysaccharide vaccine (PPSV23) in 1983. A population-based retrospective cohort study in USA of more than 47,000 persons 65 years of age or older, showed effectiveness of PPSV23 in significantly reducing pneumococcal bacteraemia. While PPSV23 has a broad serotype coverage, its inability to induce T cell dependent immune responses limited effectiveness in infants and young children and resulted in poor immunological memory. Also, PPSV23-conferred protection may be lower in adults aged ≥ 75 years and in individuals who were vaccinated over 5 years before disease onset[9].

The development of PCVs in which capsular polysaccharides are chemically linked to protein carriers represented a major breakthrough. Conjugation transformed the immune response into a T cell dependent process, enabling robust immunity in infancy, immune memory, and reduction in nasopharyngeal carriage, thereby conferring herd protection[10]. However, the effects of PCV on nasopharyngeal carriage of pneumococcus may wane with time[11].

Pneumococcal conjugate vaccines are licensed for use in young children. The 7-valent vaccine (PCV7), introduced in 2000, included serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, which were responsible for the majority of IPD in young children in North America at the time of its introduction[12]. It has now been phased out and replaced by newer higher-valent vaccines. PCV10, licensed between 2008 and 2009 in

Canada, Australia, and Europe, expanded coverage by adding serotypes 1, 5, and 7F to those included in PCV7. PCV13, licensed in 2009 by the European Medicines Agency and in Chile, further broadened protection by incorporating serotypes 3, 6A, and 19A. Both PCV10 and PCV13 are eligible for the Pneumococcal Advance Market Commitment, with manufacturers committed to supplying these vaccines to Gavi-eligible countries[13]. PCV15 was licensed for adults in 2021 and children in 2022 based on phase 3 trials demonstrating non-inferior immunogenicity to PCV13 for shared serotypes and superior responses to the additional serotypes 22F and 33F, with a comparable safety profile[14]. PCV20 was released in 2021 for adults and approved in 2023 for children to address serotype replacement and residual disease burden5[15].

Circulating serotypes pre and post vaccine

Serotype distribution varies geographically and over time, influenced by vaccine use and antimicrobial pressure[16]. Over time, non-vaccine type serotypes fill in the biological gap in nasopharyngeal colonisation created by PCV and subsequent replacement disease continues to reduce the overall impact of PCV immunisation.

Estimates of the proportion of IPD among young children showed that a limited number of serotypes seem to cause most IPD worldwide. The number of serotypes accounting for ≥ 70% of IPD ranged from 6 in North America to 9 in Africa and 11 in Asia. Seven serotypes (1, 5, 6A, 6B, 14, 19F, and 23F) were the most common globally, the seven most common in both Africa and Asia, and accounted for 58-66% of IPD in every region. Based on the year 2000 WHO Global Burden of Disease Project incidence and mortality estimates, the seven global serotypes (1, 5, 6A, 6B, 14, 19F, and 23F) account for approximately 9 million cases and 500,000 deaths due to pneumococcal disease in children < 5 years of age[16]. Following PCV introduction, non-vaccine serotypes such as 19A, 3, 6C, 8, 10A, 12F, 22F, and 33F have emerged in some regions. South Asian data indicate persistence of serotypes 1, 5, 14, 19F, with increasing relevance of 19A and 3[17].

Potential impact of pneumococcal vaccination in Sri Lanka

Surveillance data from Sri Lanka indicate that IPD in children is predominantly caused by vaccine-type serotypes, including 19F, 14, 23F and 6B, with substantial antimicrobial resistance, particularly to penicillin, macrolides and co-trimoxazole reported among isolates[5,6,17]. Studies of nasopharyngeal carriage similarly demonstrate high prevalence of these serotypes, with approximately 80% coverage by PCV13 formulations[7]. These findings align with regional South Asian data and support the public health value of introducing PCVs into the national immunisation programme (NIP).

Countries that have incorporated PCVs into NIPs have demonstrated rapid and sustained declines in antibiotic-resistant pneumococcal infections, pneumococcal morbidity and mortality in several settings[18]. This includes marked reduction in IPD among vaccinated children and substantial herd immunity benefiting unvaccinated age groups, including older adults. Modelling studies suggest PCVs are among the most cost-effective childhood vaccines, particularly when the indirect effects are considered[19].

PCV10 is estimated to cover approximately 60% of pneumococcal serotypes reported from Sri Lankan IPD and carriage studies. PCV10 covers the historically dominant paediatric serotypes in Sri Lanka (19F, 14, 6B, 23F, 1, 5), explaining its expected effectiveness against childhood IPD. Of note, it also provides long lasting cross-protection against 6A which is an important cause of IPD[20]. PCV13 increases estimated coverage to 75–85%, mainly through inclusion of 6A, 3 and 19A, which are common in carriage studies and are associated with antimicrobial resistance (notably 19A). PCV20 offers the broadest coverage (over 90%), supporting the incremental public health benefit of higher-valent conjugate vaccines, particularly relevant for adult and elderly IPD and future-proofing against serotype replacement (e.g. 8, 12F, 22F, 33F).

Cost-effectiveness, access and global supply

Cost remains a major barrier to PCV introduction in many LMICs. Global initiatives such as Gavi, the Vaccine Alliance, have facilitated

access through tiered pricing and pooled procurement, enabling widespread PCV rollout.

A major success story is PCV10 manufactured in India, which has substantially reduced vaccine cost. Developed in collaboration with PATH and the Bill & Melinda Gates Foundation, it has received WHO prequalification in December 2019. This made it the third PCV option available for Gavi, the Vaccine Alliance-eligible countries, at a highly competitive price of around US$2 per dose. This affordability was critical in expanding access to millions of children in low- and middle-income countries who previously couldn't afford other cost-prohibitive options. It was introduced in India phase-wise, beginning in high-burden states, and the rollout was completed nationwide by 2021[21]. The 10 serotypes in PCV 10 (including drug resistant serotype 19A) were specifically chosen to target those causing the most morbidity and mortality in Africa, Asia, and Latin America, maximising public health benefits where the need is greatest.

For Sri Lanka, incorporation of PCV into the NIP would likely result in substantial reductions in childhood pneumonia, antibiotic use, and hospitalisations, with long-term economic benefits.

Recommendations for use

Children

- **Routine infant immunisation** with a PCV is recommended.
- **Catch-up vaccination** is advised for unvaccinated or partially vaccinated children. Those with high-risk conditions e.g. chronic lung disease, congenital heart disease, asplenia should be given PCV20 alone or PCV10, PCV13 or PCV15 followed by PPSV23 when over 2 years.

Adults

- Adults aged 65 years and those aged 19-64 years with risk factors, should receive pneumococcal vaccination.
- Strategies include PCV alone for newer high valency vaccines PCV20 or PCV10, PCV13 or PCV15 followed by PPSV23, depending on vaccine availability and national guidance.

Types of vaccine

1) **Pneumococcal Polysaccharide Vaccine (PPSV23)-** contains purified polysaccharide for 23 capsular types of pneumococci

   Serotypes covered**:** 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F

Indications:

- Adults ≥ 65 years
- Persons ≥ 2 years with chronic disease or immunocompromising conditions
    - Asplenia or severe dysfunction of the spleen
    - Splenectomy – in elective splenectomy, at least two weeks prior to surgery
    - 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
    - Coeliac disease

Dosage and administration:

Single 0.5 mL dose IM or SC

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)

Storage:

2–8 °C. Do not freeze

Efficacy:

Effective against IPD in adults; limited effect on non-bacteraemic pneumonia

Contraindications:

Severe allergic reaction to previous dose

Adverse events*:*

Local reactions such as pain, erythema, induration, muscle pain, fatigue, headache, decreased appetite, low grade fever

Precautions:

- Acute febrile illness. Postpone vaccination until the person is well.
- Reduced immunogenicity in young children

2) Pneumococcal Conjugate Vaccines

- Pneumococcal Conjugate Vaccine – PCV10

  Serotypes covered: 1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F, and 23F
- Pneumococcal Conjugate Vaccine – PCV13

  Serotypes covered: 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F, 3, 6A, 19A
- Pneumococcal Conjugate Vaccine – PCV15

  Serotypes covered**:** 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F,3, 6A, 19A, 22F, 33F

Indications:

- Children under 5 years old, typically starting at 2 months of age
- Selected high-risk older children*
- Adults ≥ 65 years, and high-risk adults*

* Moderate-to-severe persistent asthma, heart disease, diabetes, immune deficiencies e.g. HIV, cancer, or taking immunosuppressive medications, blood disorders (sickle cell disease, other haemoglobinopathies), asplenia or splenic dysfunction, cochlear implants, cerebrospinal fluid leaks

Schedule:

0.5 mL IM per dose

- For infants
    - India - a 2 dose primary series at 6 weeks and 14 weeks, and a booster at 9 months
    - USA - a 3 dose primary series at 2, 4, 6 months, and a booster dose at 12-15 months
    - UK - a single dose at 4 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 one year later (for immunocompromised minimum interval of 8 weeks)

Storage:

2–8 °C. Do not freeze.

Efficacy:

Proven reduction in IPD and CAP in adults[11]

Advantages:

Strong immune memory, herd protection

Contraindications:

- Severe allergic reaction to previous dose
- Adverse reaction to the diphtheria toxoid component

Precautions:

Vaccine should be postponed during acute febrile illnes

Adverse events:

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

References

1. van der Poll T, at al. Opal SM. Pathogenesis, treatment, and prevention of pneumococcal pneumonia. *Lancet*. 2009; 374:1543–56.
2. O'Brien KL, et al. Burden of disease caused by *Streptococcus pneumoniae* in children younger than 5 years: global estimates. *Lancet*. 2009;374:893–902.
3. Kobayashi M, et al. Expanded recommendations for use of pneumococcal conjugate vaccines among adults aged ≥ 50 years: recommendations of the Advisory Committee on Immunisation Practices—United States, 2024. *Morbidity and Mortality Weekly Report*. 2025;74:1–8.
4. McIntyre PB, et al. Effect of vaccines on bacterial meningitis worldwide. *Lancet*. 2012;380:1703–11.
5. Batuwanthudawe R, et al. Surveillance of invasive pneumococcal disease in Colombo, Sri Lanka. *Clinical Infectious Diseases*. 2009; 48 Suppl 2:S136–40.
6. Karunanayake L, et al. Antimicrobial susceptibility and serotypes of *Neisseria meningitidis* and *Streptococcus pneumoniae* in Sri Lanka: experience from the National Reference Laboratory. *Asian Pacific Journal of Tropical Medicine*. 2022;15:114–20.
7. Vidanapathirana G, et al. Pneumococcal colonisation among healthy and hospitalised vaccine-naive Sri Lankan children. *Vaccine*. 2020;38:7308–15.
8. Hausdorff WP, et al. Epidemiological differences among pneumococcal serotypes. *Lancet Infectious Diseases*. 2005;5:83–93.

9. Niederman MS, et al. Efficacy and effectiveness of a 23-valent polysaccharide vaccine against invasive and noninvasive pneumococcal disease and related outcomes: a review of available evidence. *Expert Review of Vaccines*. 2021;20:243–56.
10. Davis SM, et al. Impact of pneumococcal conjugate vaccines on nasopharyngeal carriage and invasive disease among unvaccinated people: review of evidence on indirect effects. *Vaccine*. 2013;32:133–45.
11. van Deursen AMM, et al. Impact of the 13-valent pneumococcal conjugate vaccine on pneumococcal carriage in the Community Acquired Pneumonia Immunisation Trial in adults (CAPiTA study). *Clinical Infectious Diseases*. 2018;67:42–49.
12. Black S, et al. Efficacy, safety, and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. *Pediatric Infectious Diseases Journal*. 2000;19:187–95.
13. Centers for Disease Control and Prevention. Licensure of 13-valent pneumococcal conjugate vaccine for adults aged 50 years and older. *Morbidity Mortalality Weekly Report*. 2012;61:394–5.
14. Martinón-Torres F, et al. A Phase III, multicenter, randomised, double-blind, active comparator-controlled study to evaluate the safety, tolerability, and immunogenicity of V114 compared with PCV13 in healthy infants (PNEU-PED-EU-1). *Vaccine*. 2023; 41:3387–98.
15. Essink B, et al. Pivotal Phase 3 randomised clinical trial of the safety, tolerability, and immunogenicity of 20-Valent Pneumococcal Conjugate Vaccine in Adults Aged >/=18 Years. *Clinical Infectious Diseases*. 2022; 75:390–98.
16. Johnson HL, et al. Systematic evaluation of serotypes causing invasive pneumococcal disease among children under five: the pneumococcal global serotype project. *PLoS Medicine*. 2010; 7:e1000348
17. Kim SH, et al. Changing trends in antimicrobial resistance and serotypes of *Streptococcus pneumoniae* in isolates in Asian countries: an Asian Network for Surveillance of Resistant Pathogens (ANSORP) study. *Antimicrobial Agents Chemotherapy*. 2012; 56:1418–26.
18. Whitney CG, et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. *New England Journal of Medicine*. 2003; 348:1737–46.
19. Chen C, et al. Effect and cost-effectiveness of pneumococcal conjugate vaccination: a global modelling analysis. *Lancet Global Health*. 2019; 7:e58–67.

20. Rinta-Kokko H, et al. Long-term impact of 10-valent pneumococcal conjugate vaccination on invasive pneumococcal disease among children in Finland. *Vaccine*. 2018;36:1934–40.
21. Kumar P, et al. Chronicling the journey of pneumococcal conjugate vaccine introduction in India. *Vaccines (Basel)*. 2025; 13.

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CHAPTER 18

POLIOMYELITIS VACCINE

Introduction

Poliomyelitis is a contagious viral disease caused by poliovirus, resulting in acute flaccid paralysis. Poliovirus 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. After an incubation period of 3 to 35 days, generalised symptoms such as fever, headache, vomiting and muscle pain occur. Irreversible paralysis is reported in 1 in 200 infected persons. Among them, 5-10% has a risk of dying due to respiratory failure. The paralysis could 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 poliovirus (WPV) and paralysis could 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 eradicated globally 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 poliovirus 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 case was reported 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 introduced 2-fractional doses of IPV

(which contains killed polio virus for all 3 antigenic types) together with bivalent OPV (which contains live attenuated poliovirus 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 combined with other antigens (hexavalent vaccine)
- Novel oral poliomyelitis (Sabin derived) monovalent type 2 vaccine (nOPV2) available for emergency use in countries experiencing outbreaks of vaccine derived polio type 2

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 & 3 of the polio virus. Three primary doses of bOPV produces immunity to types 1 & 3 in more than 95% of recipients and booster doses are expected to maximise 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 poliovirus and protecting from paralytic poliomyelitis by the development of a humoral antibody response[1].

Dosage and administration

- bOPV - 2 drops orally at 2, 4, 6, 18 months and 5 years.

  Additional doses could be given during mass campaigns if needed.

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

  Open vial policy is applicable to bOPV (Ref Chapter 39)

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

- fIPV - 0.1 mL intradermal at 2 & 4 months together with bOPV
- Hexavalent vaccine- IPV in combination with other antigens, should be administered intramuscularly, it is not given as fractional doses.
- When IPV is given in combination with other vaccines such as diphtheria, tetanus, pertussis and hepatitis B the vaccine should be administrated intramuscularly.

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 unimmunised close contacts[5]. VAPP risk is increased in persons with immunodeficiency and in under-immunized populations[2].

Individuals with history of VAPP should be given IPV only.

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-immunised. 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: 2-8 ^{0}C, up to 3 months. -20 ^{0}C, up to 2 years.

IPV: 2-8 ^{o}C, do not freeze

References

1. Global Polio Eradication Initiative. http://polioeradication.org/polio-today/polio-prevention/the-virus/ news-post/novel-oral-polio-vaccine-type-2-nopv2-granted-interim-emergency-use-listing-recommendation [Accessed 02/09/2025].
2. Sutter RW, et al. Poliovirus vaccine-live in Plotkin, SA, et al. Plotkin's Vaccines, 7th eds. 2018. Philadelphia: Elsevier 866-917.
3. South-East Asia Regional Certification Commission for Polio Eradication (SEA-RCCPE), Report of the Seventh Meeting, SEARO, New Delhi, 26-27 March 2014. https://apps.who.int/iris/handle/10665/206377. [Accessed 10/08/2025].
4. Polio Eradication and Endgame Strategic Plan 2013-2018, Polio Eradication Initiative, WHO. http://polioeradication.org/wp-content/uploads/2016/07/ PEESP_EN_A4.pdf [Accessed 02/09/2025].
5. Polio Vaccines: WHO position paper. *Weekly Epidemiological Record*. 2022; 97:277-300.
6. De Silva R, et al. Prevalence of prolonged and chronic poliovirus excretion among persons with primary immune deficiency disorders in Sri Lanka, *Vaccine*. 2012; 30(52):7561-7565.

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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, to date. RABV infection in rodents is uncommon and no human rabies cases have been reported following bites by rodents[3].

Human to human transmission of rabies has not been documented, except rarely as a result of infected tissue or organ transplantation[2].

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 localised 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 course of anti rabies vaccine
- if indicated, infiltration of rabies immunoglobulin (RIG) in and around the wound/s[3]

In-spite of offering rabies PEP free of charge in most government hospitals of Sri Lanka, still around 20-25 human rabies deaths occur annually due to not seeking/delayed presentation for PEP by persons exposed to RABV. The WHO and its partners have endorsed a target of zero human rabies deaths from dog-transmitted rabies by 2030 ("Zero by 30")[1].

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

a) Pre-exposure prophylaxis (PrEP)

Pre-exposure immunisation 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 immunisation

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 should be administered 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 reduced as required. Comparative non-inferiority studies have shown ID and IM PrEP regimens could be shortened to 1 week, with a 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, irrespective of the date of the last dose of the vaccine:

- 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 is recommended to confirm that the animal remains healthy.
- 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].

b) Post- exposure prophylaxis (PEP)

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

Screening the patient – Categorisation 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 doe (goat)

Screening the animal

a) **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.

b) **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]. Therefore, 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 or exclusion of rabies[5].

*National Rabies Reference Laboratory, Medical Research Institute, Colombo 8

*Rabies Laboratory, Faculty of Veterinary Medicine & Animal Science, University of Peradeniya

*Rabies Laboratory, National Hospital, Galle

Management of the patient

Anti rabies PET, when indicated:

- **Major exposure:** rabies immunoglobulin (equine or human) followed by a course of ARV.
- **Minor exposure:** 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 & E, ICU etc.)[4].

The drug of choice in managing anaphylaxis is 1:1000 adrenaline 0.5 mL for an adult given IM immediately. Oral or parenteral steroids are best avoided as it could reduce the immune response. (Refer Chapter 38)

Administration of HRIG:

HRIG is a very costly biologic 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 within 6-8 hours of opening the vial, while being stored at 2-8^{0}C. 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 N-saline up to a maximum of 3 times.

A single monoclonal antibody (mAb) product against rabies, which was licensed in India in 2017, has been demonstrated to be safe and effective in clinical trials. This mAb neutralises a broad panel of globally prevalent RABV isolates. The comparative advantages of

mAb products include large-scale production with standardised quality, greater effectiveness than RIG, elimination of the use of animals in the production process, and reduction in the risk of adverse events[1]. Though there are several products including rabies monoclonal antibody cocktails being widely studied, they are still not available commercially in the market to be used for PEP.

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 immunisation 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)

- **This is the standard schedule used in government hospitals.**

  One dose (0.1 mL) 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 immunisation 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 6-8 hours stored at 2-8 ^{0}C[1]).
- Sterile 1 mL fixed needle-syringes should be used for administration of ID ARV to minimise 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.

a) With documented evidence of a full course of a potent and effective ARV

   If the animal is **proven rabid, suspected of rabies or unobservable:**

   For individuals who are not immunocompromised,

   - if the previous course of ARV is within 3 months, anti rabies PET is not 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.

b) With documented evidence of a partial course of ARV (3 doses on days 0, 3 & 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].

Precautions:

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 ^{0}C

References

1. Rabies Vaccines: WHO position paper, *Weekly Epidemiological Record*, 2018; 16 (93):201 -220.
2. Human rabies vaccines. *Immunisation Hand Book*, National programme on immunisation, Epidemiology Unit, Ministry of Health, 2012; (3): 118-125.
3. WHO Expert Consultation on Rabies, third report: *WHO Technical Report Series* No. 1012, Geneva, 2018 (ISBN 978-92-4-121021-8).
4. Protocol for Anti Rabies Post Exposure Therapy (PET). General Circular No. 01-50/2019 dated 16.08.2019. Ministry of Health. Sri Lanka.
5. Rupprecht CE, et al. *Laboratory Techniques in Rabies)* Fifth Edition, Volume 1, WHO. September 2018
6. WHO recommendations on rabies post exposure treatment and correct technique of intradermal immunisation against rabies. WHO/EMC/ 200.96.6.1997.
7. Perera KADN, et al. Immunogenicity study to determine the persistence of rabies neutralising antibodies in previously immunised patients and their booster response following anti rabies vaccine for a subsequent exposure. Proceedings of the 3rd Rabies in Asia Conference, Colombo, Sri Lanka. 2011; p39

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CHAPTER 20

RESPIRATORY SYNCYTIAL VIRUS (RSV) VACCINE

Introduction

Respiratory syncytial virus (RSV) is an enveloped, single-stranded, RNA virus that belongs to the genus *Orthopneumovirus* of the family *Pneumoviridae*[1]. The virus envelope contains two surface glycoproteins, G and F (fusion), which are important in facilitating virus entry. There are two major subtypes (A and B) of human RSV based on structural variations in the G protein. The RSV epidemics commonly occur during winter in countries having a temperate climate[2]. Seasonality is less defined in the tropics and sub-tropics[2]. The dominant circulating subtype may change over successive RSV seasons; however, there is no consistent association between the subtype and the severity of RSV disease[3].

RSV is a common cause of acute respiratory tract infections (ARTI) in all age groups. It usually causes a mild self-limiting respiratory infection in adults and children, but it could cause severe disease in infants and older adults, particularly with clinical risk factors. It could cause acute lower respiratory tract infection (LRTI), including pneumonitis, and bronchiolitis in infants. RSV causes significant morbidity and mortality globally in children less than 5 years of age, especially during the first 6 months of life, particularly in low and middle-income countries (LMICs)[4]. The virus is attributable for one in every 50 deaths in children aged 0-60 months and one in every 28 deaths in children aged 28 days to 6 months[4].

The clinical risk factors that predispose for severe RSV disease among infants include prematurity, congenital heart disease, chronic respiratory disease, chromosomal abnormalities, neuromuscular disorders, and immunodeficiency[5].

RSV is also considered to have a substantial morbidity and mortality among elderly, adults with comorbid conditions and immunocompromised patients. RSV mortality rates could be as high as 80% in immunocompromised patients who develop RSV pneumonitis[6].

The host immune response against RSV includes the production of neutralising antibodies and cell-mediated immunity[7]. The neutralising antibodies against F and G proteins of the virus prevents virus entry in to host cells. Even when the production of RSV neutralising antibody following RSV infection is robust, humoral immunity wanes over time. Reinfection during subsequent seasons is common. The cellular immune response to RSV infection is important for the clearance of virus-infected cells.

In Sri Lanka, a routine surveillance system for RSV does not operate currently and published data is limited. In a single-center study conducted among hospitalised children under 5 years of age from the year 2016 to 2018, the prevalence of RSV was found to be 28%[8]. Co-circulation of both RSV subtypes was detected in this study, with a predominance of RSV B. In another study that included children from 3 months to 5 years of age with severe or very severe pneumonia, RSV was detected as the commonest cause of community-acquired viral pneumonia[9].

In a study conducted in two paediatric units of dry and wet zones of Sri Lanka during 2013-2014, the incidence of RSV-associated ARTI was 29.76/100,000 person-years[10]. This was significantly higher for RSV than the rest of the viral ARTI[10]. This study concluded that RSV showed clear seasonal peaks in both wet and dry zones with a positive association with rainfall.

RSV immunisation

Immunisation against RSV could be achieved through either,

- Passive immunisation using monoclonal antibodies (mAbs) or through vaccination of pregnant mothers
- Active immunisation through vaccines

RSV monoclonal antibodies

Monoclonal antibodies (mAbs) have been an essential tool in RSV prevention, particularly in high-risk pediatric populations. They bind to the RSV glycoprotein F, and prevent virus entry. The F protein exists in pre-fusion and post-fusion conformations. The pre-fusion, being the more immunogenic form, is the primary target for neutralising antibodies[11]. Palivizumab, a humanised mAb, was the first mAb approved by the US FDA for RSV prophylaxis. Administered as monthly intramuscular injections during the RSV season, it has been shown to reduce RSV-related hospitalisations by approximately 55% in high-risk infants[12]. However, due to the cost and the requirement for repeated doses, a newer mAb with a longer half-life, nirsevimab was introduced. A single dose of nirsevimab would provide adequate protection for high-risk infants to survive their first RSV season. The phase 3 MELODY trial reported a 74.5% reduction in medically attended RSV lower respiratory tract infections in healthy term and late preterm infants[13]. A post-licensure surveillance conducted by the US Centers for Disease Control and Prevention (CDC) demonstrated effectiveness of 90% against RSV-associated hospitalisation[14]. Nirsevimab has been approved in several regions, including the US and Europe for use in all infants entering their first RSV season, making use of niresvimab as a strategy for universal infant prophylaxis against RSV[15]. Both mAbs against RSV are currently not available in Sri Lanka.

Types of vaccine

- Recombinant vaccine with RSV pre-fusion F protein (Abrysvo®)
- Recombinant adjuvanted vaccine with RSV pre-fusion F protein (Arexvy®)
- Messenger RNA (mRNA) vaccine for RSV F protein (mResvia®)

Currently, Abrysvo® and Arexvy® are licensed in the United Kingdom[15] and Australia[16]. All three products are licensed by the US FDA[17]. Out of these, Abrysvo® is recommended for pregnant women[15-17]. None of these vaccines are currently registered in Sri Lanka.

Efficacy

RSV pre-F vaccine (Abrysvo®)

- **Efficacy among newborns of mothers who received maternal RSV vaccination from 24 - 36 weeks of gestation:**

  Vaccine efficacy (VE) against severe RSV LRTI was 82.4% at 90 days and 70.0% at 180 days[18,19].

  VE against RSV LRTI after the first RSV season was 57.6% at 90 days and 49.2% at 180 days[18,19].

  A post hoc analysis of vaccination by gestational week suggests the possibility of higher VE against LRTI when the vaccine is given from 28 weeks of gestation[18].

- **Efficacy among adults aged 60 years or above**

  VE against RSV LRTI with ≥2 symptoms was 65.1% and with ≥3 symptoms 88.9%, for the first RSV season[20,21].

Adjuvanted RSV pre-F vaccine (Arexvy®)

This vaccine contains a pre-fusion F protein with an adjuvant (AS01E, a proprietary combination of saponin and monophosphoryl lipid A), which has shown to enhance immunogenicity, including T helper cell responses, over unadjuvanted formulations[22].

- **Efficacy among adults aged 60 years or above**

VE against RSV LRTI after the first RSV season (a median 6.7 months follow-up) was 82.6% VE against severe RSV LRTI, was 94.1% A VE of 69% was observed after three RSV seasons[23].

mRNA vaccine for RSV F protein (mResvia®)

- **Efficacy among adults aged 60 years or above**

VE was 78.7% against RSV-associated lower respiratory tract disease with at least two signs or symptoms and 80.9% against the disease with at least three signs or symptoms These analyses were performed after a median of 3.7 months of follow-up[24].

VE studies were conducted after a single dose of vaccine for all above vaccines. The trials included patients with chronic comorbid conditions, while excluding immunocompromised patients.

Indications

- **Older adults**

A single dose of RSV vaccine is indicated for adults ≥75 years.

The vaccine is also indicated in those below this age cut off if they have clinical risk factors for severe RSV disease[25.]

All three vaccines are licensed for use in individuals aged ≥60 years.

Arexvy® is also licensed for use in individuals 50 through 59 years of age who are at increased risk for LRTI caused by RSV**,** while Abrysvo® is licensed for use in individuals at increased risk,18 through 59 years of age.

At present, there are no recommendations for boosters.

- **Maternal vaccination**

Vaccination of the mother at least two weeks before delivery has been demonstrated to prevent LRTI caused by RSV in infants from birth to 6 months of age[20,21,26].

Administration of the vaccine is recommended starting from 28 weeks up to delivery[15-17].

Currently, there is insufficient data on the benefit of revaccination in subsequent pregnancies.

Dosage and Administration

All vaccines 0.5 mL IM

Contraindications

Vaccine should not be administered to individuals with a history of a severe allergic reaction (e.g., anaphylaxis) to any component of the same vaccine

Adverse Effects

Common side effects observed include:

- Injection site reactions (pain, redness, swelling)
- Fatigue
- Headache
- Muscle or joint pain
- Fever or chills
- Nausea

Most side effects are mild to moderate and self-limiting.

Warnings and Precautions

The results of a phase 3 observational trials and in post-marketing surveillance of older adults, suggest an increased risk of Guillain-Barré syndrome (GBS) during the 42 days following vaccination with both Abrysvo® and Arexvy®[27-29].

Storage

- **RSV pre-F vaccine (Abrysvo®)**[30]
  - Storage before reconstitution

    2-8 °C. Do not freeze
  - Storage after reconstitution

    Administer immediately or store at room temperature (15-30ºC) and use within 4 hours.
- **Adjuvanted RSV pre-F vaccine (Arexvy®)**[28]
  - Storage before reconstitution

    Store refrigerated at 2-8 °C. Do not freeze
  - Storage after reconstitution

    Administer immediately or store in the refrigerator between 2-8 °C or at room temperature (up to 25 °C) for up to 4 hours prior to use.
- **mRNA vaccine for RSV F protein (mResvia®)**[29]

- Frozen Storage ; -40 °C to -15 °C
- Storage after thawing
  - Pre-filled plastic syringes may be stored refrigerated between 2-8 °C for up to 90 days prior to use.
  - Pre-filled plastic syringes may be stored between 8-25 °C for a maximum of 24 hours

Discard the pre-filled syringe if not used within this period.

- Syringes should not be returned to the refrigerator after being thawed at room temperature.
- Do not refreeze once thawed. Do not shake.

References:

1. Vandini S, et al. Respiratory syncytial virus: the influence of serotype and genotype variability on clinical course of infection. *International Journal of Molecular Sciences* 2017; 8(08):1717. doi: 10.3390/ijms18081717.
2. Staadegaard L, et al. Defining the seasonality of respiratory syncytial virus around the world: National and subnational surveillance data from 12 countries. *Influenza and Other Respiratory Viruses* 2021; 15(6):732-741. doi: 10.1111/irv.12885.
3. Ciarlitto C, et al. Respiratory Syncytial Virus A and B: three bronchiolitis seasons in a third level hospital in Italy. *Italian Journal of Pediatrics* 2019; 45(1):115. doi: 10.1186/s13052-019-0704-0.
4. Li Y, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: a systematic analysis. *Lancet* 2022; 399(10340):2047-2064. doi: 10.1016/S0140-6736(22)00478-0.
5. Thorburn K. Pre-existing disease is associated with a significantly higher risk of death in severe respiratory syncytial virus infection. *Archives of Disease in Childhood* 2009; 94(2):99-103. doi: 10.1136/adc.2008.139188.
6. Falsey AR, Walsh EE. Respiratory syncytial virus infection in adults. *Clinical Microbiology Reviews* 2000; 13(3):371-84. doi: 10.1128/CMR.13.3.371.
7. Domachowske JB, etal. Respiratory syncytial virus infection: immune response, immunopathogenesis, and treatment. *Clinical Microbiology Reviews* 1999 ; 12(2):298-309. doi: 10.1128/CMR.12.2.298.

8. Divarathna MVM, et al. Epidemiology and risk factors of respiratory syncytial virus associated acute respiratory tract infection in hospitalised children younger than 5 years from Sri Lanka. *Frontiers in Microbiology* 2023; 14:1173842. doi: 10.3389/fmicb.2023.1173842.
9. Gonapaladeniya M, et al. Burden of Respiratory Syncytial Virus Associated Severe Pneumonia in Hospitalised Children. *International Journal of Pediatrics* 2021 Jun 30;2021:8269400. doi: 10.1155/2021/8269400.
10. Jayaweera JAAS, et al. Viral burden and diversity in acute respiratory tract infections in hospitalised children in wet and dry zones of Sri Lanka. *PLoS One* 2021; 16(12):e0259443. doi: 10.1371/journal.pone.0259443.
11. McLellan JS, et al. Structure-based design of a fusion glycoprotein vaccine for respiratory syncytial virus. *Science* 2013; 342(6158): 592–598.
12. IMpact-RSV Study Group. Palivizumab, a humanised respiratory syncytial virus monoclonal antibody, reduces hospitalisation from RSV infection in high-risk infants. *Pediatrics* 1998; 102(3 Pt 1):531-7.
13. Hammitt LL, et al. Nirsevimab for Prevention of RSV in Healthy Late-Preterm and Term Infants. *New England Journal of Medicine* 2022; 386(9):837-846. doi: 10.
14. Moline HL, et al. Respiratory Syncytial Virus Disease Burden and Nirsevimab Effectiveness in Young Children From 2023-2024. *JAMA Pediatrics* 2025 Feb 1;179(2):179-187. doi: 10.1001/jamapediatrics.2024.5572. Erratum in: JAMA Pediatr. 2025; 179(2):223. doi: 10.1001/jamapediatrics.2024.6442.
15. Chapter 27a: Respiratory syncytial virus (2025). In Ramsay M. (Ed.). Immunisation against infectious disease. UK Health Security Agency. 2021. Available at:https://assets.publishing.service.gov.uk/media/67bce1e6d157fd4b79addddd/Green_Book_on_immunisation_Ch27a_RSV_21_2_25.pdf Accessed on April 25, 2025
16. Centers for Disease Prevention and Control. Vaccines and Immunisations. Respiratory Syncytial Virus (RSV) Immunisations https://www.cdc.gov /vaccines/vpd/rsv/index.html Accessed on April 26, 2025.
17. Respiratory syncytial virus (RSV). In Australian Technical Advisory Group on Immunisation (ATAGI). Australian Immunisation Handbook, Australian Government Department of Health and Aged Care, Canberra. 2022. Available at: https://immunisationhandbook.health.gov.

au/contents/vaccine-preventable-diseases/respiratory-syncytial-virus-rsv#recommendations Accessed on April 25, 2025

18. Munjal I, et al. Protection Against Infant Illness with a Bivalent RSVpreF Vaccine in Pregnancy: Final Analysis. RSVVW '24. 2024 15 February 2024. Last modified 7 Mar 2024. Available at: https://drive.google.com /drive/folders/1I5jugJOyg2tqItokMNhDpHkGEHYSQnwxAccessed on Apri 27, 2025.
19. Simões EAF, et al. Efficacy, Safety, and Immunogenicity of the MATISSE (Maternal Immunisation Study for Safety and Efficacy) Maternal Respiratory Syncytial Virus Prefusion F Protein Vaccine Trial. *Obstetrics and Gynecology* 2025; 145(2):157-167. doi: 10.1097/AOG. 0000000000005816.
20. Walsh EE, et al. Efficacy and Safety of a Bivalent RSV Prefusion F Vaccine in Older Adults. *New England Journal of Medicine* 2023; 388(16):1465-1477. doi: 10.1056/NEJMoa2213836.
21. Pfizer Announces Positive Top Line Data for Full Season Two Efficacy of ABRYSVO® for RSV in Older Adults. Pfizer. Available at: https://www. pfizer.com/news/press-release/press-release-detail/ pfizerannounces-positive-top-line-data-full-season-two Accessed on April 27, 2025.
22. Leroux-Roels I, et al. Safety and Immunogenicity of a Respiratory Syncytial Virus Prefusion F (RSVPreF3) Candidate Vaccine in Older Adults: Phase 1/2 Randomised Clinical Trial. *Journal of Infectious Diseases* 2023; 227(6):761-772. doi: 10.1093/infdis/jiac327.
23. Gerber S. AReSVi-006 Pivotal Efficacy Study: Preliminary Updates from Season 3, Phase 3, Randomised, Placebo-Controlled, Multi-Country Study to Demonstrate Efficacy & Safety of Single & Annual Revaccination Doses in Adults 60 Years & Older, NCT04886596. GSK. Presented at US Advisory Committee on Immunization Practices, 24 October 2024. Available at: https://www.cdc.gov/acip/downloads/slides 2024-10-23-24/04-RSV-Adult-Gerber-508.pdf Accessed on April 28, 2025.
24. Das R. Update on Moderna's RSV Vaccine, mRESVIA (mRNA-1345), in Adults ≥60 Years of Age. Moderna. Presented at US Advisory Committee on Immunization Practices, June 26, 2024. Available at: https://www. cdc.gov/acip/downloads/slides-2024-06-26-28/04-RSV-Adult-Das-508.pdf Accessed on April 27, 2025.

25. Centers for Disease Control and prevention. Respiratory Syncytial Virus Infection. RSV Vaccine Guidance for Older Adults. Available at: https://www.cdc.gov/rsv/hcp/vaccine-clinical-guidance/older-adults.html Accessed on April 28, 2025.
26. Kampmann B, et al. Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants. *New England Journal of Medicine* 2023; 388(16):1451-1464. doi: 10.1056/NEJMoa2216480.
27. U.S. Food and Drug Administration. FDA Requires Guillain-Barré Syndrome (GBS) Warning in the Prescribing Information for RSV Vaccines Abrysvo and Arexvy. Last updated on 07/01/2025
    Available at: https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/fda-requires-guillain-barre-syndrome-gbs-warning-prescribing-information-rsv-vaccines-abrysvo-and Accessed on April 28, 2025.
28. U.S. Food and Drug Administration. GSK AREXVY package insert. Available at: https://www.fda.gov/media/167805/download? attachment Accessed on April 28, 2025.
29. U.S. Food and Drug Administration. Moderna MRESVIA package insert. Available at: https://www.fda.gov/media/179005/download? attachment Accessed on April 28, 2025.
30. U.S. Food and Drug Administration. Pfizer ABRYSVO package insert. Available at: https://www.fda.gov/media/168889/download Accessed on April 28, 2025.

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CHAPTER 21

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[3].

The World Health Organization (WHO) has recommended that rotavirus vaccine for infants should be included in all national immunisation 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 world-wide[4]. One hundred and twenty-six countries had introduced rotavirus vaccination into their national immunisation programmes by the year 2024, with four other countries introducing on a partial basis or for risk groups[5].

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[6]. 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. Thirty-two G types and 47 P types have been identified in group A[1]. 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[7,8].

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 to10 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]. In addition, there are domestically licensed rotavirus vaccines available in China and Vietnam[4].

Efficacy

The vaccine will prevent about 74-87% of all rotavirus gastroenteritis, >80% of severe cases, and about 95-100% of hospitalisations due to rotavirus[2].

Indications

Prevention of childhood gastroenteritis due to rotavirus

Dosage and administration

- **Human monovalent vaccine (2 doses)**

Liquid vaccine (oral suspension)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 (3 doses)**

Lyophilised and liquid forms, 2.5 mL (lyophilised) 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 four 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[2,9]. 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)[10].

Adverse effects

Diarrhoea, vomiting, otitis media and nasopharyngitis

Storage

2-8 °C. Protect from light.

References:

1. Bergman H, et al. Vaccines for preventing rotavirus diarrhoea: vaccines in use (Review*). Cochrane Database of Systematic Reviews* 2021, Issue 11. Art. No.: CD008521. DOI: 10.1002/14651858.CD008521.pub6
2. Rotavirus vaccines-WHO position paper. *Weekly Epidemiological Report*, No: 28, 16 July 2021.
3. Linhares AC, et al. Human Rotavirus Vaccine Study Group. Efficacy and safety of an oral live attenuated human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in Latin American infants: a randomised, double-blind, placebo-controlled phase III study. *Lancet* 2008; 371(9619):1181-9.
4. Sun ZW, et al. Association of rotavirus vaccines with reduction in rotavirus gastroenteritis in children younger Than 5 Years: A systematic review and meta-analysis of randomised clinical trials and observational studies. *JAMA Pediatrics*. 2021; 175(7):e210347. doi: 10.1001/jamapediatrics.2021.0347.
5. https://immunisationdata.who.int/global/wiise-detail-page/introduction-of-rotavirus-vaccine?YEAR= [Accessed 0on 04th June 2025].
6. Burke RM, et al. Current and new rotavirus vaccines. *Current Opinion in Infectious Diseases*. 2019; 32(5): 435–444. doi: 10.1097/QCO.0000000000000572
7. Palihawadana P, et al. Rotavirus infection among hospitalised children under five years of age with acute watery diarrhea in Sri Lanka. *Vaccine* 2018; 36(51):7846-7850
8. Chandrasena TGAN, et al. Surveillance of rotavirus in three hospital settings of Sri Lanka 2007-2010. *Proceedings of the 23rd Annual Scientific Sessions of the Sri Lanka College of Microbiologists*. The Bulletin of the Sri Lanka College of Microbiologists. August 2014, Vol 12, Issue 1

9. Yen C, et al. Rotavirus vaccination and intussusception – Science, surveillance, and safety: A review of evidence and recommendations for future research priorities in low- and middle-income countries. *Human Vaccine and Immunotherapeutics*. 2016; 12(10):2580–2589.
10. National Advisory Committee on Immunisation. Canadian Immunisation Guide: Part 4; Active Vaccines. https://www.canada.ca/en/public-health/services/ publications/healthy-living/canadian-immunisation-guide-part-4-active-vaccines/page-19-rotavirus-vaccine.html. 23/9/2021. [Accessed on 04/06/2025].

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CHAPTER 22

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 through mucous membranes. Spores germinate under anaerobic conditions and vegetative bacilli produce tetanospasmin[1]. Neonatal tetanus is caused by contamination of the umbilical stump. Tetanus does not spread from person to person[2]. The incubation period is between 3 to 21 days but extremes of 1 day to several months have been reported[3,4].

The disease is characterised by painful contraction and spasm of skeletal muscles. Muscle spasms initially involve 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. The disease course 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[3,4]. Protection against tetanus is antibody-dependent and could be achieved only through active (tetanus vaccine) or passive (tetanus-specific immunoglobulin) immunisation[4].

- Active immunisation with tetanus vaccine is indicated for all persons who have not been completely immunised. Adequate immunisation coverage is the key strategy for prevention of tetanus, as there is no place for herd immunity or natural immunity.
- Passive immunisation using tetanus antitoxin, preferably of human origin, is essential for treatment and occasionally for prophylaxis (e.g. in cases of contaminated wounds in incompletely immunised 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[2].

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[2]. If the vial contains clumps of material that cannot be re-suspended with vigorous shaking, it should not be used.

Tetanus toxoid containing vaccines (TTCV)[4,5,6]

Several preparations of vaccines contain tetanus toxoid as a component of a combination of vaccines and an age-appropriate vaccine should be selected for immunisation[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]. Though Sri Lanka has not implemented this strategy earlier, it is being considered to introduce Td (aTd) in the routine pregnancy and post exposure immunisation schedules in future [8,9].

Table 1: Tetanus toxoid containing vaccines (TTCV)[5]

	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 (for 5 years and above) Low antigenic diphtheria, tetanus and acellular pertussis vaccine	≥2 IU/dose	≥20 IU/dose	≥8 µg pertussis toxoid ≥8 µg filamentous haemagglutinin ≥2.5 µg pertactin/dose
aTd Diphtheria and tetanus vaccine for adolescents and adults	≥2 IU/dose	≥40 IU/dose	----------
TT (for adults) Tetanus toxoid	----------	≥40 IU/dose	----------
DTP-HepB- Hib Diphtheria, tetanus, pertussis, Hib, hepatitis 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]. Sri Lanka has successfully implemented a tetanus immunisation programme for pregnant women and achieved maternal and neonatal tetanus elimination status in 2016[11].

Indications for active immunisation against tetanus

1. Routine immunisation
2. Immunisation following an injury with risk of wound contamination
3. Immunisation during active tetanus disease

1. Routine Immunisation

The WHO recommends that all populations worldwide should be immunised 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 immunisation

National Immunisation Programmes (NIP) are recommended to initiate a tetanus vaccine course of 6 doses with 3 doses of TTCV (containing 40 IU of tetanus toxoid) as primary immunisation. e.g. DTwP, DTaP, DTP-HepB-Hib (pentavalent vaccine) or DTaP-HepB-Hib-IPV (hexavalent vaccine). Two booster doses of TTCV are recommended during childhood. The 3rd booster dose (6th dose, containing a minimum of 20 IU tetanus toxoid) should be completed by adolescence[7].

According to the NIP Sri Lanka, the primary series of TTCV is given in infancy on completion of 2nd, 4th and 6th months of life and the first booster is given on completion of 18 months (DTwP / DTaP /pentavalent / hexavalent). The second booster dose is given before

school entry on completion of 5 years of age (DT /DTaP/ Tdap) and the third booster (sixth dose of TTCV) is given after completion of 11 years of age as aTd or Tdap[8]. (refer Chapter 8 and Annexes 1 & II)

Routine immunisation of adolescents and adults

The 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]. 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, recruitment to military service, the medical examination before first employment or admission to higher education institutes.

Adolescents and adults with no past immunisation against tetanus should receive 5 doses of TT/TTCV (containing a minimum of 20 IU tetanus toxoid) 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[6,7,8]. Longer intervals between the 3rd and 4th doses (5 years) and the 4th and 5th doses (10 years) are preferred[2].

Routine immunisation of pregnant women to prevent maternal and neonatal tetanus

Evidence of previous tetanus immunisation should be verified before TT/TTCV is given during pregnancy. If there is no documented evidence of previous vaccination against tetanus, 2 doses of TT/aTd/Tdap should be given during the first pregnancy. One dose of TT/TTCV is recommended during each subsequent pregnancy, up to a total of 5 doses (Table 2)[12].

Table 2: Immunisation schedule for pregnant women[4,7,8,12]

For previously unvaccinated pregnant women		
1st dose	TT/aTd/Tdap	During 1st pregnancy, after 12 weeks of gestation
2nd dose	TT/aTd/Tdap	During 1st pregnancy, 6-8 weeks after the 1st dose (at least 2 weeks before delivery)
3rd dose*	TT/aTd/Tdap	During 2nd pregnancy, after 12 weeks of gestation
4th dose*	TT/aTd/Tdap	During 3rd pregnancy, after 12 weeks of gestation
5th dose*	TT/aTd/Tdap	During 4th pregnancy, after 12 weeks of gestation *Even when there are no subsequent pregnancies, the specified schedule of 5 doses of TTCV should be completed in order to ensure lifelong protection
		(3rd dose should be given at least 6 months later and 4th and 5th doses should be given at intervals of at least 1 year)[7].
For pregnant women with documented evidence of previous immunisation		
Booster doses indicated	TT/aTd/Tdap	If 6 doses of TTCV received as per NIP during childhood and adolescence and a gap of 10 years or more after the last TTCV – need one booster dose during the 1st pregnancy. If 4 doses of TTCV received during childhood – need one booster dose in first pregnancy and a 6th dose at least one year later or during next pregnancy. If 3 doses of TTCV received during childhood – need two booster doses in the first pregnancy and a 6th dose at least one year later or during next pregnancy.
Tetanus toxoid immunisation not indicated		
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		

2) Immunisation following an injury with risk of wound contamination[1,2,3,8]

- A history regarding tetanus immunisation should be taken before TT/TTCV is given for wound prophylaxis.
- For persons who have not been immunised against tetanus previously or whose vaccination status is unknown or uncertain, a primary course of 3 doses of TT/TTCV is recommended as follows – 1st dose immediately, 2nd dose 4–6 weeks later and 3rd dose after 6 months[8]. A minimum of 3 doses of TT/TTCV is required to produce effective immunity. A booster dose could be given once in 10 years[1].
- 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 immunisation with 5 doses of TTCV.
- Adults with a history of immunisation with only 5 doses of TTCV in childhood need 1 booster dose of TT/TTCV.
- Adults with documented evidence of immunisation 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 immunisation.
    - when the patient's previous tetanus immunisation history is unreliable.

3) Immunisation 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[1,10].

Dosage and administration

Dosage – 0.5 mL of tetanus toxoid or tetanus toxoid containing vaccine[2,4]

Route of administration[2,4]

- Infants - deep IM into antero-lateral aspect of thigh
- Older age groups – deep IM in the deltoid muscle

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[7].

Storage

2-8 ^{0}C, protected from light. Do not freeze[2].

References

1. Tejpratap S.P, et al. Tetanus. In: Epidemiology and Prevention of Vaccine-Preventable Diseases (Pink Book) 14th Edition; Centers for Disease Control and Prevention: August 2021; 315-328.
2. https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book-chapter30-Tetanus updated 02.06.2025 [accessed 27.10.2025].

3. Liang JL, et al. Prevention of Pertussis, Tetanus, and Diphtheria with Vaccines in the United States: Recommendations of the Advisory Committee on Immunisation Practices (ACIP). *Morbidity and Mortality Weekly Reports Recommendations and Reports* 2018; 67(No. RR-2):1–44.
4. Tetanus vaccines. WHO position paper. *Weekly Epidemiological Record.* 10th February 2017; 92:53-76.
5. WHO Expert Committee on Biological Standardization. *WHO Technical Report Series.* 980, 2014: 211–406.
6. Ensuring Sustained Protection Against Diphtheria: Replacing TT with Td vaccine. WHO/UNICEF Guidance Note; Version 12; September 2018; 1-12.
7. WHO - Protecting All Against Tetanus: Guide to sustaining maternal and neonatal tetanus elimination (MNTE) and broadening tetanus protection for all populations. Geneva: World Health Organization; 2019.
8. Guidelines on Immunisation against Tetanus; General Circular No 01-22/2010, Ministry of Healthcare and Nutrition, Sri Lanka.
9. Technical Report of the National Immunisation Summit 2025, Epidemiology Unit, Ministry of Health and Mass Media, Sri Lanka; 2025.
10. The immunological basis for immunisation series: module 3: Tetanus. Geneva: World Health Organization; 2018.
11. A Strategic Approach for Sustained Elimination of Maternal-Neonatal Tetanus in Sri Lanka; *Weekly Epidemiological Report;* 01st–07th Feb 2025.
12. Use of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccines: Updated Recommendations of the Advisory Committee on Immunisation Practices — United States, 2019*; Morbidity and Mortality Weekly Report* January 24, 2020; 69 (3).

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CHAPTER 23

TYPHOID VACCINE

Introduction

Enteric fever (the collective term for typhoid and paratyphoid fever) is a prolonged, bacteraemic, potentially life-threatening 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. The burden of disease due to typhoid fever is more important, globally[3] with, as of 2019, an estimated 9 million people acquiring typhoid and 110,000 dying from it annually[1].

S enterica serovar Typhi and *S enterica* serovar Paratyphi are exclusively pathogens of humans and the 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. Therefore, the risk is higher in populations that lack access to adequate sanitation and potable water and large epidemics may be seen.

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 prolonged 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 hospitalised 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[4]. 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 urgency of controlling the disease through effective vaccination complemented by population-level access to safe drinking water and adequate sanitation, health education and hygiene among food handlers.

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

Four types of safe and moderately efficacious vaccines against typhoid fever are available. The current typhoid vaccines do not protect against paratyphoid fever. In addition, there is a substantial burden of disease due to non-typhoidal *Salmonella* (NTS). Therefore, there is a strong case to develop bivalent vaccines protecting against both typhoid and paratyphoid and even combination vaccines against *S enterica* serovars Typhi, Typhimurium, Enteritidis, and Paratyphi A[5].

Typhoid Vi conjugate vaccines (TCV)

TCVs consist of the Vi polysaccharide of *S* Typhi conjugated to tetanus toxoid protein (Vi-TT).So as 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. Only TCV have been prequalified by the WHO[2,6,7].

Vi polysaccharide conjugated to recombinant *Pseudomonas aeruginosa* exotoxin A vaccine (Vi-rEPA)

A TCV consisting of Vi bound to a nontoxic recombinant exoprotein A of *Pseudomonas aeruginosa*.

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 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[6].

Typhoid Vi conjugate vaccine (TViCV)

A systematic review and meta-analysis published in 2024 showed that the pooled efficacy of a single dose of TViCV at 2 years post-immunisation was 83%. TViCV probably results in a large reduction in the incidence of typhoid fever among the participants aged 6 months-16 years, 1-2 years post-immunisation[7]. A study in Pakistan showed high rates of seroconversion after the administration of a single dose of TViCV that was sustained over 4 years of follow-up in a highly endemic setting. However, a steeper decline in antibody levels in the youngest children, who were less than 2 years of age at vaccination, was noted as well as a significant number of breakthrough infections occurring 2-3 years after vaccination[8].

Vi polysaccharide conjugated to recombinant *Pseudomonas aeruginosa* exotoxin A vaccine (Vi-rEPA)

The cumulative efficacy of two doses of Vi-rEPA vaccine at 2 years was 91%[7].

Unconjugated Typhoid Vi polysaccharide (ViPS) vaccine

The pooled efficacy against typhoid fever was 58%. Vi-PS probably reduces the incidence of typhoid fever among participants aged 2-50 years over the period of 1-3 years post-vaccination[7].

Oral typhoid vaccine (Ty21a)

The pooled efficacy against typhoid fever was 45%. Therefore, Ty21a vaccine probably reduces the incidence of typhoid fever among the participants aged 3-44 years over a period of 1-5 years post-vaccination[7].

Indications[2]

- WHO recommends programmatic use of typhoid vaccines, preferably TViCV. Decisions on the age of TViCV 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 immunisation programme. Vaccination is also recommended during outbreaks and may be considered during humanitarian emergencies
- 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 (TViCV)

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[2,6]. The vaccine is administered as a single, IM dose 0.5 mL and provides greater protection against typhoid fever than the other available vaccines. The need for boosting with TCV is still not clear[2]. Options that warrant careful consideration include adding a booster dose at school entry age or raising the age for administering the primary dose[8,9,10].

Unconjugated Typhoid Vi polysaccharide (ViPS) vaccine

Single 0.5 mL dose IM or SC in individuals ≥ 2 years. For travellers to endemic areas the vaccine should be administered at least 2 weeks before the anticipated exposure. ViPS vaccine elicits a T-independent antibody response that does not create immunologic memory to allow boosting of serum Vi antibody titres following an initial immunisation[6]. Re-immunisation 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[2,6].

Inter-changeability of vaccines

There are currently no data on the interchangeability or sequential use of the different typhoid vaccines.

Contraindications

- Known hypersensitivity reaction to any vaccine component
- No information is available on the safety of the typhoid vaccines in pregnancy. Use of the live attenuated Ty21a vaccine during pregnancy should be avoided[6]
- 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 illnes[6].

Adverse effects

No serious vaccine-attributable adverse events were observed in clinical trials with any of the vaccines[7]. Fever, pain and swelling were reported in approximately 1–10% of vaccinees[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 1cm 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[6].

Storage

2-8 ºC. Do not freeze

References

1. Stanaway JD, et al. The global burden of typhoid and paratyphoid fevers: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Infectious Diseases* 2019; 19: 369–81.
2. World Health Organization (WHO). Typhoid vaccines: WHO position paper, March 2018. *Weekly Epidemiological Record.* 2018;13(93) :153–72.
3. Als D, et al. Global Trends in Typhoidal Salmonellosis: A Systematic Review. *The American Journal of Tropical Medicine and Hygiene*. 2018;99(3_Suppl):10–19. doi:10.4269/ajtmh.18-0034.
4. Qamar FN, et al. Antimicrobial resistance in typhoidal salmonella: surveillance for enteric fever in Asia project, 2016–2019. *Clinical Infectious Diseases* 2020; 71 (suppl 3):S276–84.
5. MacLennan CA, et al. *Salmonella* Combination Vaccines: Moving Beyond Typhoid. *Open Forum Infectious Diseases*. 2023;10(Suppl 1):S58-S66. doi: 10.1093/ofid/ofad041. PMID: 37274529; PMCID: PMC10236507.
6. American Academy of Pediatrics. In: Kimberlin DW, et al. eds. Red Book: 2021 Report of the Committee on Infectious Diseases. Itasca, IL: *American Academy of Pediatrics*: 2021.
7. Batool R, et al. Efficacy of typhoid vaccines against culture-confirmed S*almonella* Typhi in typhoid endemic countries: a systematic review and meta-analysis. *The Lancet Global Health*. 2024; 12(4):e589 - e598.
8. Qamar FN, et al. Longevity of immune response after a single dose of typhoid conjugate vaccine against *Salmonella* Typhi among children in Hyderabad, Pakistan. *International Journal of Infectious Diseases*. 2024; 147:107187.

9. Vashishtha, VM, et al. Typhoid conjugate vaccines: is a single dose enough for durable protection? *Expert Review of Vaccines*, 2025; 24(1):194–205.https://doi.org/10.1080/14760584.2025.2476525
10. Qadri F, et al. 5-year vaccine protection following a single dose of Vi-tetanus toxoid conjugate vaccine in Bangladeshi children (TyVOID): a cluster randomised trial. *The Lancet*. 2024; 404(10461):1419-1429. doi: 10.1016/S0140-6736(24)01494-6.

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CHAPTER 24

VARICELLA VACCINE

Introduction

Chickenpox is caused by varicella zoster virus (VZV) and the disease is characterised by fever and a pruritic vesicular rash of generalised distribution. It is highly contagious, with an average incubation period of 14-16 (range 10-21) days after exposure, and is transmitted through airborne route, as well as through direct contact with skin lesions[1]. In temperate climates, in the absence of vaccination, the highest incidence of varicella occurs among children leading to > 90% of people being infected before adolescence[2]. The epidemiology in Sri Lanka, however, is similar to other tropical countries, where overall seroprevalence of 54.2% for anti-VZV IgG has been reported, in which 75% of the seropositivity has been noted in individuals more than 40 years[3].

Risk factors for severe varicella include age, immunocompromised status, and pregnancy. Although the incidence of varicella is highest among children, the risk for severe disease, both hospitalizations and deaths, is significantly increased during infancy and adulthood[4].

Complications of varicella include bacterial superinfection of lesions, neurologic complications including cerebellar ataxia, meningitis, and encephalitis. Thrombocytopaenia and rarer complications such as glomerulonephritis, arthritis, and hepatitis could occur. Primary viral pneumonia is uncommon among immunocompetent children but is the most common complication among adults and other high-risk populations. Rarely, varicella could be fatal[5].

Varicella during pregnancy could lead to serious maternal and fetal problems. Varicella could cause severe infection in pregnant women, often complicated by viral pneumonia, mainly in the third trimester of pregnancy. Maternal primary infection with VZV in the first or early second trimester could result in congenital varicella syndrome. Varicella infection in the third trimester could result in HZ in infancy or childhood. Perinatal varicella (if mothers develop varicella from 5 days

before delivery to 2 days after birth) could result in disseminated neonatal varicella, which is life threatening. Although rare, the devastating effects of congenital varicella syndrome and neonatal varicella emphasise the importance of protection against varicella for women of reproductive age[5].

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. A vaccine for prevention of herpes zoster is available, though not yet registered in Sri Lanka (refer Chapter 26).

As the VZV vaccine is a live attenuated vaccine, the vaccine virus also establishes latency similar to the wild type virus. The varicella vaccine strain could very rarely reactivate as HZ[2]. It is up to 5 times lower than in unvaccinated people infected with wild-type varicella[8].

Types of vaccine

All varicella vaccines contain the Oka strain of live attenuated VZV, lyophilised vaccine supplied with sterile diluent.

Efficacy

The effectiveness of 1 dose of varicella vaccine is reported as 72.5%[9]. A pooled 2-dose effectiveness against all manifestations of varicella of 92% has been reported[2]. 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[10].

Indications[11]

- 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 persons > 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

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 documented evidence of only one dose of the vaccine during childhood based on earlier guidelines, are recommended another dose of the vaccine.

> 12 Years

They should receive two 0.5 mL doses of varicella vaccine, 4-12 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[2]. 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].

Contraindications

- Those suffering from immunodeficiencies 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 (refer Chapter 33)
- 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 component of the vaccine such as fetal bovine serum and gelatin[13]

Precautions

- Patients on steroids < 2 mg/kg of body weight or < 20 mg/day for over 2 weeks (refer Chapter 33)
- 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

Adverse effects

- Mild pain, redness at site of administration
- Varicella type rash in 3% of recipients. These rashes are mostly maculopapular and occur within 2 weeks of immunisation
- 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 ^{0}C

References

1. Centers for Disease Control and Prevention. Chickenpox (varicella). Available from: https://www.cdc.gov/chickenpox/hcp/index.html [Accessed 06.01.2026].
2. Varicella vaccines: WHO position paper. *Weekly Epidemiological Record*. 2025 Nov 21;(47).
3. Munasingha HM, et al. Seroprevalence of varicella zoster virus in Colombo district, Sri Lanka. *Asian Pacific Journal of Tropical Medicine*. 2018; 11(1):53–57.
4. Galil K, et al. Hospitalisations for varicella in the United States, 1988 to 1999. *Pediatric Infectious Disease Journal*. 2002; 21:931–5.
5. Dooling K, et al. Clinical manifestations of varicella: disease is largely forgotten, but it's not gone. *Journal of Infectious Diseases*. 2022; 226(Suppl 4):S380–4. doi:10.1093/infdis/jiac390
6. Andrei G, et al. Advances and perspectives in the management of varicella-zoster virus infections. *Molecules*. 2021; 26(4):1132. doi:10.3390/molecules26041132
7. Dooling KL, et al. Recommendations of the Advisory Committee on Immunisation Practices for use of herpes zoster vaccines. *Morbidity and Mortality Weekly Report*. 2018; 67(3):103–8.
8. Australian Government Department of Health. People who have received varicella vaccine when it was indicated can consider zoster vaccine [Internet]. Available from: https://immunisationhandbook.health. gov.au/ recommen dations/people-who-have-received-varicella-vaccine-when-it-was-indicated-can-consider-zoster-vaccine [Accessed 06.01.2026].
9. Bayer O, et al. Meta-analysis of vaccine effectiveness in varicella outbreaks. *Vaccine*. 2007; 25(37–38):6655–60.
10. Marin M, et al. Twenty-five years of varicella vaccination in the United States. *Journal of Infectious Diseases*. 2022; 226 (Suppl 4):S375.
11. Centers for Disease Control and Prevention. Epidemiology and prevention of vaccine-preventable diseases. *The Pink Book.* 14th ed. Washington (DC): Public Health Foundation; 2021.
12. Lachiewicz AM, et al. Varicella-zoster virus post-exposure management and prophylaxis: a review. *Preventive Medical Reports*. 2019; 16:101016. doi:10.1016/j.pmedr.2019.101016.

13. de Silva R, et al. Sensitisation to bovine serum albumin as a possible cause of allergic reactions to vaccines. *Vaccine*. 2017; 35(11):1494–500.

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CHAPTER 25

YELLOW FEVER

Yellow fever (YF) is an arthropod-borne viral haemorrhagic fever prevalent in Sub-Saharan Africa and tropical South America. Non-human primates and humans act as reservoirs of the YF virus, which is transmitted through mosquito vectors belonging to *Aedes and Haemogogus species*[1]. However, despite the presence of the vector mosquitoes, locally acquired cases of YF have never been reported in Asia[2].

Three transmission cycles of the virus which are aetiologically and clinically identical, have been identified. The virus usually transmits between non-human primates through *Haemagogus* and *Aedes* mosquitoes in the sylvatic (jungle) life cycle, and humans become infected accidentally with travel to forest areas. The intermediate (savannah) cycle involves transmission of the virus to humans either from monkeys or humans, at jungle borders, through *Aedes* species of mosquitoes that breed both in the wild and around households. This usually results in sporadic cases. Humans act as the reservoir in the urban transmission cycle with human-to-human transmission of the virus, through *Aedes aegypti* mosquitoes that live in peri-domestic areas[1.] The urban cycle may result in large epidemics due to infected people moving to densely populated areas with little or no population immunity to YF[3].

In general, rural populations are at greatest risk of YF. However, urban populations are also at risk due to re-infestation of vector mosquitoes and increased population movement in and out of endemic areas[3,4]. Children are at the highest risk of infection in endemic regions since the natural immunity is acquired with age[3].

YF is a Group A notifiable disease in Sri Lanka. Cases of YF have not been reported from Sri Lanka to date, although the risk of transmission of the virus from imported cases remains a possibility due to the presence of the vector mosquito, *A aegypti*[5].

The incubation period of YF ranges between three to six days. A majority of the infected individuals will either not exhibit symptoms or have mild non-specific symptoms such as fever, headache, chills, nausea, vomiting, myalgia, backache and prostration, which improve within 3-4 days. However, approximately 12% of the patients enter a more toxic phase within 24 hours of recovering from the initial symptoms, characterised by jaundice, haemorrhagic manifestations, multi organ failure and shock. Around 30-60% of these patients succumb to the illness[1,4].

There is no specific antiviral treatment for YF. Vaccination is the most effective means of prevention, although control of mosquitoes and protection from mosquito bites also play roles in prevention of YF[3]. The 'Eliminate YF epidemics' (EYE) strategy 2017-2026, developed by the Global Alliance for Vaccines and Immunisation (GAVI), United Nations International Children's Emergency Fund (UNICEF) and World Health Organization (WHO), to end YF epidemics by 2026, aims to ensure universal access to YF immunisation and thereby, protect every person in at-risk countries against the disease[6].

Types of vaccine

All currently available YF vaccines are live attenuated vaccines of the 17D strain of the YF virus passaged in embryonated chicken eggs. The vaccine virus exists as two sub-strains; 17D-204 and 17DD which share 99.9% sequence homology. Only the 17D- 204YF vaccine is available in Sri Lanka.

The vaccine exists in the lyophilised form with a sterile diluent.

Efficacy[2,3,8]

A single dose of the vaccine confers immunity in 95-100% of the vaccine recipients. A single dose of the vaccine will produce protective antibody titres for several decades or probably lifelong in most recipients, with only a few exceptions.

Indications[2,3]

- Individuals who are nine months or older, and living in, or travelling to, countries that require an International Certificate of Vaccination or Prophylaxis (ICVP) for entry.
- Individuals who are nine months or older, and living in, or travelling to, areas/countries with a risk of YF transmission, although evidence of immunisation is not required for entry to these countries.

(An updated list of countries with a risk of YF transmission can be accessed through: *https://www.fitfortravel.nhs.uk/advice/disease-prevention-advice/yellow-fever/yellow-fever-risk-areas*)

- Laboratory workers handling infected material

Immunisation should take place 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, vaccination should still be considered in last minute travellers who should be counselled about the importance of following precautions against insect bites, and the possible implications of an invalid ICVP[2,3].

Reinforcing immunisation[2,3,7,8]

According to the WHO Strategic Advisory Group of Experts (SAGE) 2013, a single dose of the YF vaccine usually confers life-long protective immunity against YF, with a few exceptions. Thus, a routine booster dose of the vaccine is not indicated to maintain immunity. However, vaccine recipients belonging to these exceptions, who have a continuous risk of exposure should receive a second dose, as they may not develop long term protection with a single dose[2](Figure 1).

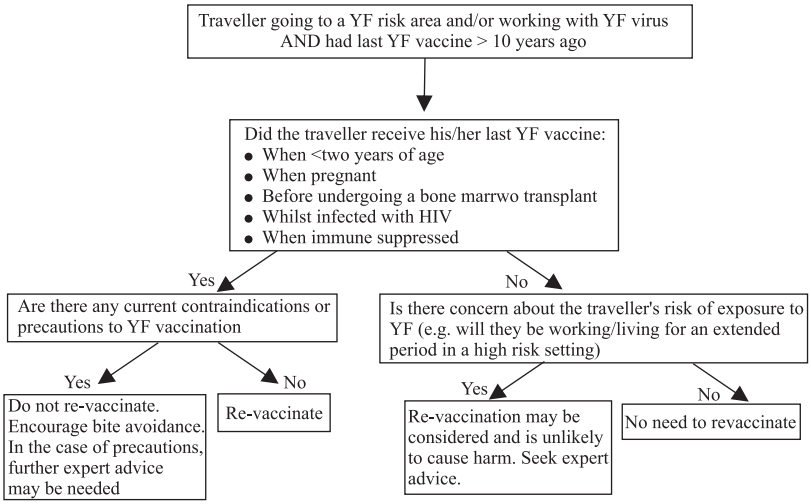


Figure 1. Reinforcing immunisation for travellers.

(Adapted From Chapter 24, SLMA Guidelines and Information on Vaccines, 2023)

In addition, the following categories should be considered for reinforcing immunisation[7].

- Laboratory workers who routinely handle wild-type YF virus.
- Travellers who received the vaccine at least 10 years previously and who will be in a higher risk setting based on season, location, activities, and duration of travel.

International certificate of vaccination or prophylaxis (ICVP)[1,2,9,10]

A proof of vaccination against YF is specified by the International Health Regulations (IHR) as a condition of entry to YF endemic countries. As per the IHR, an ICVP is issued by all countries as an official, internationally recognised document, at designated yellow fever vaccination centres (YFVC) approved by the WHO. 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 the IHR, as of 11th July 2016, Sri Lanka considers ICVP to be valid for life, beginning from the tenth day after the primary immunisation and immediately after re-immunisation[1,9,10].

The following criteria should be fulfilled for the ICVP to be valid,

- The vaccine should be approved by the WHO
- The signature of the clinician who supervised the vaccination should be included in the ICVP
- The official stamp of the designated YFVC where the vaccine was administered should be included in the ICVP

Dosage and schedule[2,11]

A single dose of 0.5 mL

The WHO recommends that the vaccine should contain not less than 3.0 $\log^{10}$ international units (IU) of the vaccine virus.

The dosage of the fractional YF (fYF) vaccine which is used off-label, as part of an emergency response during an outbreak should be determined according to the available vaccine product (e.g. 1/2 or 1/5). This is not considered equivalent to the full dose vaccination under the IHR for issuing an ICVP, thus will require revaccination with a standard dose[11].

Booster doses are not routinely recommended to maintain immunity, except under special circumstances (see reinforcing immunisation).

Administration[2,11]

Reconstitute immediately before use, with the sterile diluent provided.

Both the standard and the fractional doses of the vaccine should be administered as deep subcutaneous or intramuscular injections, to the lateral aspect of the upper arm, or the anterolateral aspect of the thigh in babies and very young children.

Once reconstituted, the vaccine should be used immediately or within a maximum period of 6 hours stored at 2-8^{0}C.

Contraindications

- Infants below 6 months of age
- Pregnant women – except during YF outbreaks when the risk of infection outweighs the vaccination risk

- A history of severe allergic reaction or anaphylaxis to a previous dose or any component of the YF vaccine
- A history of thymus disorder or thymectomy
- 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
- Patients who are immunosuppressed as a result of treatment (e.g. high dose of steroids, biologic therapy, radiotherapy, cytotoxic drugs)
- Patients aged 60 years or older who are travelling to areas where yellow fever vaccine is generally not recommended by the WHO
- Patients who have a first degree relative in the family history of YF vaccine - associated neurologic disease (YEL-AND) or YF vaccine-associated viscerotropic disease (YEL-AVD) following vaccination, that was not related to a known medical risk factor[2]

Approach for vaccination in patients with egg allergy[2,12]

- Assess whether the individual has already outgrown egg allergy
- If an ongoing egg allergy is present
    - Preschool children - could be vaccinated using the standard administration protocol in a hospital where facilities for management of anaphylaxis are available
    - Children of school age and above, and adults - desensitisation protocols should be followed with recommendations from an allergy specialist[2,12]

Vaccination following cardiac and thoracic surgery

Cardiac surgery - Consider formal documentation or evidence of presence of residual thymic tissue and the risk of acquiring YF, prior to offering the vaccine.

Thoracic surgery - Vaccination is contraindicated only if the patient has specifically had a thymectomy[2].

Individuals with contraindications for vaccination should be educated on the risk of acquiring YF and on mosquito avoidance methods. For those who intend to visit countries which require an ICVP against YF for entry, a letter of exemption should be issued by the YFVC or the practitioner treating the patient, clearly stating the contraindication for vaccination and signing off on official stationery with the issuing date. The letter requires stamping used by the YFVC to validate the ICVP. Reasons other than medical contraindications are not acceptable for exemption from vaccination.

The above document will only be valid for that particular travel and should be taken into consideration by the port health authorities upon entry to countries. However, the traveller should be advised that issuance of a waiver does not guarantee its acceptance by the country of destination.

Precautions[2,3,5]

A minor illness without fever or systemic disturbance is not considered a contraindication. If an individual is acutely unwell, immunisation should be postponed until recovery.

- ***Persons over 60 years of age:***
  The vaccine should only be offered if there is a significant and unavoidable risk of acquiring YF, since the risk of neurological and viscerotropic adverse events following vaccination increases with age.
- ***Pregnancy:***
  Pregnant women should be advised to avoid travel to high-risk areas due to the theoretical risk of receiving a live viral vaccine during pregnancy, with the possible risk of fetal infection. However, if travel is unavoidable, vaccination should be considered on an individual basis[2,3,13].
- ***Breast feeding:***
  Expert advice should be obtained when vaccinating breast feeding mothers with babies less than nine months of age, due to evidence of transmission of the live vaccine virus through breast milk to infants less than two months of age[2,5].

- ***Infants:***

  Infants aged six to nine months should be immunised only if the risk of YF during travel is unavoidable, since the risk of vaccine associated encephalitis is irreversibly proportionate with age. Immunisation should be carried out with expert opinion.

- ***Immunosuppression and HIV infection:***

  Unless the YF risk is unavoidable, asymptomatic HIV infected persons should not be immunised. However, the vaccine may be given safely to HIV infected persons with a CD4 count ≥ 200/µl and a suppressed viral load[2].

  Specialist advice should be sought before deciding on vaccinating patients on long term stable low dose corticosteroid therapy, either alone or in combination with low dose non-biological oral immune modulating drugs.

Adverse effects[2,3,4]

Mild adverse effects

Headache, myalgia, low-grade fever and soreness at the injection site may occur in 10-30% of recipients. The systemic side effects may last up to two weeks.

Severe adverse effects[2,3,4]

- Immediate severe hypersensitivity or anaphylactic reactions

  Most common in people with allergies to eggs or gelatin. The incidence of anaphylactic reactions is estimated to be in 1.3 per 100,000 vaccinations[2,3].

- YEL-AND

  A serious, but rarely fatal adverse event that usually occurs 3-28 days after vaccination due to direct viral invasion or autoimmune reactions. The clinical presentations include meningoencephalitis, Guillain-Barre syndrome, acute disseminated encephalomyelitis, bulbar palsy and Bell's palsy, which are usually followed by complete recovery. Almost all cases are detected in first time

vaccine recipients and is commoner in people aged more than 60 years of age[2,3].

- YEL-AVD

  Resembles severe YF with features of multi-organ system failure, with a fatality rate of more than 60%. It is caused by replication and dissemination of the vaccine virus. The onset of illness averages 3 days (range 1-8 days) after vaccination. It is also more common among persons aged more than 60 years of age.

  Both YEL-AND and YEL-AVD have been described in primary vaccine recipients with a rate of 8 per 1 million and 3 per 1 million vaccine doses respectively.

Storage

2-8 °C. Do not freeze. Do not expose to light.

References

1. Gershman MD, et al. Yellow Fever. In: Infectious diseases related to travel. CDC Yellow 2024. Centers for Disease Control and Prevention. https://wwwnc.cdc.gov/travel/yellowbook/2024/infections-diseases/yellow-fever
2. Yellow Fever. In; The Green Book -Immunisations against Infectious Diseases UK Health Security agency. 2020; 443-54. https://travelhealthpro.org.uk/media_lib/mlib-uploads/full/the-green-book-chapter-35-yellow-fever-march-2024.pdf
3. Vaccines and vaccination against yellow fever. WHO position paper. *Weekly Epidemiological Record.* 2013; 88(27):269-84.
4. Yellow fever, Fact sheet. WHO 2025. https://www.who.int/news-room/fact-sheets/detail/yellow-fever
5. Yellow Fever Vaccine–New Developments, Epidemiology Unit. *Weekly Epidemiological Report*. 2014; 41(10) https://www.epid.gov.lk/storage/post/pdfs/vol_41_no_10-english.pdf
6. Eliminate yellow fever epidemics (EYE) strategy 2017-2026, WHO 2025. https://www.who.int/initiatives/eye-strategy

7. Staples JE, et al. Yellow Fever Vaccine Booster Doses: Recommendations of the Advisory Committee on Immunisation Practices, 2015, *Morbidity and Mortality Weekly Report*. 2015; 64(23);647-650.
8. Rosenstein MD, et al. Long-term immunity after a single yellow fever vaccination in travelers vaccinated at 60 years or older: A 10-year follow-up study. *Journal of Travel Medicine*. 2021; 28(8): taab126.
9. Centers for Disease Control and Prevention, International Certificate of Vaccination or Prophylaxis (ICVP): Yellow Fever Vaccination Documentation. 2024. https://wwwnc.cdc.gov/travel/page/icvp.
10. Vaccination during international travel. Epidemiology Unit. 2025. https://www.epid.gov.lk/vaccination-during-international-travel.
11. Yellow fever vaccine: WHO position on the use of fractional doses June 2017, *Weekly Epidemiological Record*. 2017; 92 (25): 345-56.
12. Lopes F, et al. Safe administration of yellow fever vaccine in patients with suspected egg allergy. *Journal of Allergy and Clinical Immunology Global*. 2(3) :100089,March 2023.
13. Galang R, et al. Pregnant travellers, CDC Yellow book. 2024. https://wwwnc. cdc.gov/travel/yellowbook/2024/family/pregnant-travellers.

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CHAPTER 26

OTHER VACCINES OF INTEREST (Chikungunya, Ebola, malaria, mpox, zoster)

CHIKUNGUNYA VACCINE

Introduction

Chikungunya virus (CHIKV) is an alphavirus, which has emerged as a global public health threat over the past two decades. It is transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes. Following its re-emergence in the Indian Ocean region in 2004, large epidemics have spread across Asia, Africa, and the Americas, with occasional indigenous transmission in Europe. Attack rates of 30-75% have been documented in naïve populations, producing widespread morbidity and economic loss[1].

The disease typically causes an acute febrile illness followed by severe polyarthralgia, which may persist for months to years, impairing quality of life and workforce productivity. High fever with headache and photophobia occurs after a 2-7 day incubation period. Arthralgia/arthritis is symmetrical, often affecting distal joints. About 50% develop a maculo-papular or petechial rash. Post-viral arthritis or arthralgia may persist in up to 50% of patients[2].

With increasing global travel and expansion of *Aedes* mosquitoes into temperate regions, chikungunya is no longer a geographically restricted disease. Until 2023, prevention relied solely on vector control and avoidance strategies.

Types of vaccine

There are 2 chikungunya vaccines.

Live attenuated vaccine[3]

This is the first licensed vaccine for prevention of CHIKV infection. It is a live-attenuated virus with deletion of 60 amino acids in the nSP3 protein.

Virus like particle vaccine[4]

This is a recombinant vaccine containing purified virus-like particles (VLPs) consisting of CHIKV capsid protein (C) and envelope proteins E1 and E2.

Indications

Live attenuated vaccine[5]

Indicated for the prevention of disease caused by CHIKV in individuals 18 years of age and older who are at high risk of exposure

Virus like particle vaccine[4]

Recommended for the prevention of disease caused by CHIKV in individuals 12 years of age and older.

Efficacy

Live attenuated vaccine[3]

Phase III trials have shown significant levels of neutralising antibodies in > 96% of the participants for at least 180 days post-vaccination.

Virus like particle vaccine[6]

The immunogenicity of this vaccine has been assessed in two studies. The sero-response rate for 12 through 64 years of age was 97.8% and 87.3% for the 65 years and older age group. The sero-response rate at 183 days post-vaccination in Study 1 and study 2 were 85.5% and 75.5% respectively among vaccine participants.

Dosage and Administration

Live attenuated vaccine[5]

Single dose of 0.5 mL IM

Virus like particle vaccine[4]

Single dose of 0.8 mL IM

Contraindications

Live attenuated vaccine[5]

- Immunocompromised individuals
- Individuals with a history of a severe allergic reaction (e.g. anaphylaxis) to any component of the vaccine

Virus like particle vaccine[4]

History of a severe allergic reaction (e.g. anaphylaxis) to any component of the vaccine

Precautions

Live attenuated vaccine[5]

Transmission of vaccine virus to the fetus during pregnancy is not known.

Virus like particle vaccine[4]

Immunocompromised individuals, including individuals receiving immunosuppressive therapy, may have a diminished immune response.

Adverse effects

Live attenuated vaccine[5]

Injection site tenderness, headache, fatigue, myalgia, arthralgia, fever, nausea, syncope

It may cause serious, severe, or prolonged chikungunya-like illness especially in adults over 65 years of age. FDA has withdrawn this vaccine from the market[7] although EMA has reinstated this vaccine with a recommendation to give the vaccine when there is a significant risk of infection and after a careful consideration of the benefits and risks[8].

Virus like particle vaccine[4]

Injection site pain, fatigue, headache, myalgia

Storage

2-8 ^{0}C. Store in the original carton to protect from light. Do not freeze.

EBOLA VIRUS VACCINE

Introduction

Ebola diseases are rare but life-threatening infections caused by Ebola virus which belongs to the Filoviridae family, genus *Orthoebolavirus*. They are filamentous, enveloped, negative-stranded RNA viruses. There are three species which cause haemorrhagic disease in man; *Orthoebolavirus zairense* (EBOV) causing Ebola virus disease, *Orthoebolavirus sudanense* (SUDV) causing Sudan virus disease and *Orthoebolavirus bundibugyoense* (BDBV) causing Bundibugyo virus disease[9].

The virus is transmitted to humans during close contact with the body fluids of infected wild animals such as fruit bats, non-human primates, porcupines etc. It 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.

Outbreak control relies on a package of interventions including intensive supportive care of patients, infection prevention and control, disease surveillance and contact tracing, laboratory services, safe and dignified burials, vaccination if relevant, and social mobilization[9].

Ebola virus disease caused by EBOV 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). Case fatality rates have varied from 25-90%, which have been significantly reduced by early treatment and supportive care[9].

While there are licensed vaccines and therapeutics for Ebola virus disease, there is no approved vaccine or treatment for other Ebola diseases, such as Sudan virus disease or Bundinugyo virus disease[9].

Types of vaccine

There are two vaccines licensed and prequalified by WHO for Ebola virus disease.

rVSVΔG-ZEBOV-GP

The rVSVΔG-ZEBOV-GP vaccine is a live attenuated, recombinant, vesicular stomatitis virus-based vector expressing the envelope glycoprotein gene of Zaire Ebola virus[10].

Ad26.ZEBOV/MVA-BN-Filo vaccine[11]

This vaccine has 2 components delivered in 2 different doses, namely Ad26.ZEBOV and MVA-BN-Filo used as a prime-boost strategy to enhance immunogenicity. The Ad26.ZEBOV component is a monovalent vaccine based on adenovirus vector (Ad26) expressing the Ebola virus glycoprotein. The MVA-BN-Filo component is a multivalent vaccine based on modified vaccinia Ankara (MVA) vector expressing Ebola virus, Sudan virus, and Marburg virus glycoproteins and Tai Forest virus nucleoprotein, and is designed to provide immunity to all of these viruses.

Efficacy

An open-label, cluster-randomised, ring vaccination trial has shown the vaccine efficacy of rVSVΔG-ZEBOV-GP as 100%[12]. The effectiveness in the real world setting during an outbreak was estimated to be 84%[13] The duration of protection is unknown but has been shown to remain for at least 5 years[14].

Efficacy data for the Ad26.ZEBOV/MVA-BN-Filo vaccine are not available but it has shown high immunogenicity in Phase 2 clinical trials[15].

Indications

rVSVΔG-ZEBOV-GP vaccine is indicated for a “ring vaccination” strategy to protect persons at the highest risk during an outbreak of Ebola virus disease, including health care workers (HCW) and first line workers (FLW)[16].

A two-dose vaccine regimen, such as that of the Ad26.ZEBOV and MVA-BN-Filo vaccines, is not suitable in the context of vaccination for outbreak response, where rapid high levels of protection are important[16].

Dosage and administration

rVSVΔG-ZEBOV-GP vaccine - approved for use in individuals aged 1 year and older as a single intramuscular dose[11].

Ad26.ZEBOV/MVA-BN-Filo - authorised for use in 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[11].

Contraindications

Severe allergic reaction (e.g. anaphylaxis) to any component of rVSVΔG-ZEBOV-GP including rice protein[17].

Precautions

The vaccines should be administered with caution to people with thrombocytopaenia or any coagulation disorder because bleeding or bruising may occur after the vaccines are administered[17].

rVSVΔG-ZEBOV-GP - The effectiveness in immunocompromised individuals may be diminished and the administration of a live vaccine should be weighed with the risk[17].

Ad26.ZEBOV/MVA-BN-Filo - Generally well-tolerated among pregnant patients; however, the decision to vaccinate should take into account the elevated risk of Ebola virus disease in pregnant patients during outbreaks[17].

Adverse effects

Common adverse reactions to both vaccines include injection-site reactions, arthralgia, myalgia, rash, headache, fever and fatigue[11].

Storage

rVSVΔG-ZEBOV-GP should be stored frozen at -80 to -60 °C in the

original carton to protect from light. Do not re-freeze thawed vaccine[18]. Refer manufacturer's instructions.

Ad26.ZEBOV/MVA-BN-Filo – both vaccines should be stored at -85 °C to -55 °C. Refer manufacturer's instructions[19,20].

MPOX VACCINE

Introduction

Mpox is a viral zoonosis with symptoms similar to smallpox, although it is less contagious and causes less severe illness. Monkeypox 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[21,22]. Vaccination against smallpox is about 85% effective in preventing mpox and, today, young persons may be more susceptible to mpox due to cessation of the smallpox eradication campaign[21].

Mpox primarily occurs in rural central and west Africa, often in proximity to tropical rainforests. Small forest-living rodents are likely to be the natural reservoir of the virus with primates, including humans, being incidental hosts[22]. Animal-to-human transmission could occur from direct contact with the blood, body fluids, or cutaneous or mucosal lesions of infected animals.

Human-to-human transmission results 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. People with multiple sexual partners are at higher risk of acquiring mpox. Almost all cases during the 2022-2023 outbreak were seen among men, particularly men who have sex with men and those who have had recent sexual contact with a new partner or partners[23]. Transmission can also occur via the placenta from mother to fetus or during close contact during and after birth.

The incubation period is 2-21 days. Common symptoms are fever, rash, sore throat, headache, muscle aches, back pain and lymphadenopathy. 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. 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.

Mpox is usually a self-limited disease with symptoms lasting from 2-4 weeks. Severe cases occur more commonly among children, pregnant women and the immunocompromised. 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 ranges from 0-11% in the general population and is higher among young children. In recent times, the case fatality ratio has been around 3-6%[22].

Types of vaccine

Replication-competent vaccinia virus, second-generation (ACAM2000)

ACAM2000 is grown in cell culture rather than by the historical method of scarification on the sides of calves (*Bos taurus*). It is only licensed to prevent smallpox in the US[24].

Replication-deficient modified vaccinia Ankara, third-generation (Modified Vaccinia Ankara-Bavarian Nordic; MVA-BN)

It has been approved for the prevention of smallpox and monkeypox in the US in 2019[24]. MVA-BN is not licensed for use in children under the age of 18 years[21].

Attenuated, minimally replication-competent vaccinia virus, third-generation (LC16m18, available in Japan)

Vaccine is produced in cell culture using rabbit kidney cells.

Efficacy

A systematic review estimated vaccine effectiveness (VE) of 2 doses as 82%[24]. Post-exposure VE was estimated at 20%[25]. There are no studies that report directly on the vaccine effectiveness of LC16m8 or ACAM2000[21].

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. Mass vaccination is not recommended for mpox at this time[21].

Pre-exposure vaccination is recommended for individuals at high-risk of exposure to mpox in an outbreak. These include men who have sex with men (MSM) with multiple sexual partners, sex workers, health workers, laboratory personnel and outbreak response team members[21].

Post-exposure preventive vaccination (PEPV) is recommended for contacts of cases, ideally within four days of first exposure (and up to 14 days in the absence of symptoms)[21].

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[21].

Replication-deficient modified vaccinia Ankara, third-generation (Modified Vaccinia Ankara-Bavarian Nordic; MVA-BN)

Two subcutaneous doses are given 28 days apart.

Contraindications[21]

ACAM2000 - Infants, immunocompromised and pregnant persons and in individuals with skin conditions such as atopic dermatitis.

LC16m8 - Immunocompromised and pregnant women and in individuals with skin conditions such as atopic dermatitis.

Precautions[21]

ACAM2000 is a live vaccinia virus that could be transmitted to persons who have close contact with the vaccinee.

MVA-BN could be used in pregnant and lactating women when the benefits of vaccination outweigh the potential risks.

LC16m8 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[24].

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[24]. Serious adverse events with 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[24].

Storage

Frozen between -25 and -15 °C. The vaccine should be used immediately after thawing[21].

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 concern to public health and is responsible for high morbidity and mortality rates, worldwide. According to the WHO, globally in 2023, the number of malaria cases was estimated at 263 million and the number of deaths was 597,000 in 83 malaria endemic countries[26]. Approximately 95% of malaria cases and deaths occur in sub-Saharan Africa. Almost all malaria deaths are caused by *Plasmodium falciparum* and most occur in African children under 5 years of age[27].

Although strategies for disease control such as vector control, insecticide impregnated bed-nets, 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[28].

Types of vaccine

RTS, S/AS01

This is the first-ever approved vaccine for a human parasitic infection[27].

R21/Matrix-M[26]

Both vaccines, are WHO-prequalified and recommended for use. Both are pre-erythrocytic vaccines that prevent *P. falciparum* infection in children and subsequent illness and death; they are not designed to interrupt malaria transmission and there is no known cross protection with other *Plasmodium* species.

As of December 2025, 24 countries in Africa had introduced WHO-recommended malaria vaccines in their childhood immunization programmes.

Efficacy

RTS, S/AS01

Phase 3 trials have shown an efficacy of 24% for the 3-dose group and 19% for the 4-dose group.-The vaccine reduced malaria episodes by about 40% and severe malaria cases by about 30% over a four-year period[29].

R21/Matrix-M

The efficacy of a 4-dose schedule of R21/Matrix-M was 75% for clinical malaria cases during the 12-month period following the administration of 3 doses[27].

Indications

RTS, S/AS01 / R21/Matrix-M

Prevention of *P falciparum* malaria in children living in areas where malaria is endemic. Malaria vaccines should be provided as part of a

comprehensive malaria control strategy for the highest impact of control[26].

The vaccine is not recommended for adults or indicated in travellers to endemic areas[27].

Dosage and administration

RTS, S/AS01

0.5 mLIM into the deltoid[27]

R21/Matrix-M

0.5 mL, IM into the deltoid[27]

Malaria vaccines should be provided in a 4-dose schedule in children from 5 months of age. Minimum interval between any doses is 4 weeks. Fourth dose should be given 6-18 months after the third dose[27].

Contraindications

Severe hypersensitivity to a previous dose of malaria vaccine or hepatitis B vaccines or to any of the vaccine components[27].

Adverse effects

Both malaria vaccines are considered safe and well-tolerated. 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 vaccination was 2.5 per 1,000 doses in children for RTS,S/AS01 and 1 per 2800 doses for R21/ Matrix-M[27].

Storage

2–8 °C.

ZOSTER VACCINE

Introduction

Reactivation of varicella virus causes herpes zoster (HZ). 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[30]. HZ 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[31].

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[30]. The vaccine is formulated with a higher potency of 19,400 PFU, as the target group will have been previously infected with varicella
- Recombinant adjuvanted - 50 μg of recombinant VZV glycoprotein E (gE) formulated with AS01B adjuvant

Efficacy

The live attenuated 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[32]. However, the protection offered by this vaccine was shown to wane 5 years following vaccination[33,34].

The vaccine effectiveness of the recombinant vaccine for HZ was 73.9% and against PHN was 83.7%. The effectiveness was lower in those who were immunocompromised. The effectiveness remained at high levels 4 years after vaccination[35].

Indications[36]

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. However, as immunity wanes after 5 years and the severity is less in people < 70 years, UK recommends administration of the vaccine after 70 years. After 80 years, vaccination is not cost-effective as the vaccine effectiveness is less[37]. 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. A shorter vaccine schedule of 0 and 1-2 months is recommended for such persons.

Dosage and administration

- Live, attenuated – a single dose of 0.65 mL subcutaneous injection
- Recombinant – 2 doses of 0.5mL IM, 2-6 months apart

Contraindications

Live attenuated vaccine

- History of anaphylaxis to any component of the vaccine
- Immunosuppression or immunodeficiency
- Pregnancy

Recombinant vaccine

- History of anaphylaxis to any component of the vaccine
- Pregnancy – insufficient evidence

Adverse effects

HZ-like rash, erythema, pain/tenderness and swelling at the injection site, myalgia, fatigue, headache. An increased risk of Guillain-Barre syndrome has been reported with the recombinant vaccine[30].

Storage

2-8 ^{0}C.

References

Chikungunya Vaccine

1. Brito C, et al. Chikungunya: From Hypothesis to Evidence of Increased Severe Disease and Fatalities. *Viruses* 2025; 17(1):62.
2. Albarrán RH, et al. Chikungunya virus infection: A scoping review highlighting pediatric systemic and neurologic complications. *Seminars in Pediatric Neurology* 2025; 54:101213.
3. Ng LSP, et al. Live-attenuated chikungunya virus vaccine. *Cell*. 2024; 813.e1 187/4, http://dx.doi.org/10.1016/j.cell.2024.01.033
4. VIMKUNYA information sheet
5. Ixchiq Information sheet
6. Bennett SR, et al. Safety and immunogenicity of PXVX0317, an aluminium hydroxide-adjuvanted chikungunya virus-like particle vaccine: a randomised, double-blind, parallel-group, phase 2 trial. *Lancet Infectious Diseases.* 2022; 22(9):1343-1355. doi: 10.1016/S1473-3099(22)00226-2.
7. https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/ fda-update-safety-ixchiq-chikungunya-vaccine-live
8. https://www.ema.europa.eu/en/news/ixchiq-temporary-restriction-vaccinating-people-65-years-older-be-lifted

Ebola Vaccine

9. https://www.who.int/news-room/fact-sheets/detail/ebola-disease [Accessed 30th September 2025]
10. https://www.ema.europa.eu/en/documents/product-information/ervebo-epar-product-information_en.pdf
11. https://bestpractice.bmj.com/topics/en-us/1210/prevention [Accessed 30th September 2025].
12. Henao-Restrepo AM, et al. (2017) Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça Suffit!) *The Lancet*, 2027; 389(100680): 505 - 518
13. Meakin S, et al. (2024) Effectiveness of rVSV-ZEBOV vaccination during the 2018-20 Ebola virus disease epidemic in the Democratic Republic of the Congo: a retrospective test-negative study. *The Lancet Infectious Diseases*. 2024; 24(12):1357 - 1365

14. Huttner A, et al. Antibody responses to recombinant vesicular stomatitis virus-Zaire Ebolavirus vaccination for Ebola virus disease across doses and continents: 5-year durability. *Clinical Microbiology & Infection*. 2023; 29(12):1587–94.
15. PREVAC Study Team. Randomised trial of vaccines for Zaire Ebola virus disease. *New England Journal of Medicine.* 2022; 387:2411-2424. doi: 10.1056/NEJMoa2200072.
16. WHO (2024). *Weekly Epidemiological Report*: No 27, 2024; 99:355–362
17. https://www.msdmanuals.com/professional/infectious-diseases/immunization/ ebola-vaccine. [Accessed 30th September 2025]
18. Choi MJ, et al. Use of Ebola vaccine: recommendations of the Advisory Committee on Immunization Practices, United States, 2020. Morbidity & Mortality Weekly Report. Recommendations & Reports. 2021; 70:1-12. https:// doi.org/10.15585/mmwr.rr7001a1
19. Ad26.ZEBOV product insert
20. MVA-BN-Filo product insert

Mpox Vaccine

21. Smallpox and mpox (orthopoxviruses) vaccine position paper. WHO. *Weekly Epidemiological Report* No 34, 2024; 99:429–456
22. https://www.who.int/news-room/fact-sheets/detail/monkeypox%20%20[Accessed%20on%2002/02/2023]
23. Vaccines and immunisation for monkeypox: Interim guidance. 16th November 2022. WHO-MPX-Immunization-2022.3-eng.pdf
24. Poland GA, et al. Prevention of monkeypox with vaccines: a rapid review. *Lancet Infectious Diseases.* 2022; 22(12):e349-e358. doi: 10.1016/S1473-3099(22)00574-6.
25. Pischel L, et al. Vaccine effectiveness of 3rd generation mpox vaccines against mpox and disease severity: A systematic review and meta-analysis. *Vaccine*. 2024; 42(25):126053. doi: 10.1016/j.vaccine.2024.06.021.

Malaria vaccine

26. World Malaria Report 2024: Addressing inequity in the global malaria response. Geneva: WHO 2024
27. Malaria vaccines: WHO position paper. *Weekly Epidemiological Record*. 2024: 9:225-248.

28. Mariano RMDS, et al. A Review of Major Patents on Potential Malaria Vaccine Targets. Pathogens 2023; 12: 247. https://doi.org/10.3390/pathogens12020247
29. Tinto H, et al. Long-term incidence of severe malaria following RTS,S/AS01 vaccination in children and infants in Africa: an open-label 3-year extension study of a phase 3 randomised control trial. *Lancet Infectious Diseases*. 2019; doi:10.1016/S1473-3099(19)30300-7.

Zoster Vaccine

30. Andrei G, et al. Advances and Perspectives in the Management of Varicella-Zoster Virus Infections. Molecules. 2021; 26(4):1132. Published online 2021 Feb 20. doi: 10.3390/molecules26041132
31. Gershon AA, et al. Pathogenesis and current approaches to control of varicella-zoster virus infections. *Clinical Microbiology Reviews*. 2013 ; 26(4):728-43. doi: 10.1128/CMR.00052-13.
32. Varicella and herpes zoster vaccines: WHO position paper. *Weekly Epidemiological Report*. No. 25, 2014; 89:265-288
33. Dooling KL, et al. Recommendations of the Advisory Committee on Immunisation Practices for Use of Herpes Zoster Vaccines. *Morbidity and Mortality Weekly Report.* 2018; 67(3):103-108.
34. Baxter R, et al. Long-term effectiveness of varicella vaccine: a 14-year, prospective cohort study. *Pediatrics* 2013; 131:1389–1396.
35. Tseng HF, et al. Effectiveness of the Adjuvanted Recombinant Zoster Vaccine in Adults ≥ 50 Years in the United States. Clinical Infectious Diseases, ciaf329, https://doi.org/10.1093/cid/ciaf329. [Accessed on 30 Sep 2025].
36. Shingrix product insert
37. https://assets.publishing.service.gov.uk/media/689cba1b1c63de6de5bb12a9/ Green-book-chapter-Shingles_12_8_24.pdf

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CHAPTER 27

IMMUNISATION IN PREGNANCY

Introduction

Pregnancy is a state of relative immunocompromise making a woman vulnerable for infections[1]. Some infections are harmful for the fetus and may result in fetal anomalies and even death and some may have serious consequences for maternal health. Immunisation plays a major role in preventing and minimising the effects of these complications during pregnancy[2].

Vaccine 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 immunisation 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 for at least 4 weeks after vaccination with live-attenuated vaccines[2]. However, some of the live attenuated vaccine manufacturers advise 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 the fetus is at risk of severe congenital anomalies with devastating life-long consequences[3,4].

Congenital rubella syndrome (CRS)

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

The National Immunisation Programme (NIP) recommends that all women in the childbearing age group (15-44 years) should be vaccinated against rubella if they have not been fully immunised (i.e. not received two doses) during childhood. MMR vaccine is a live attenuated virus vaccine and is contraindicated during pregnancy[2]. Therefore, 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 reports of neonates being affected 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 the 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].

Raricella Boster Maternal effects

The incidence of varicella pneumonia is increased to 5-14% during pregnancy[8]. Severe life-threatening pneumonia could occur during the third trimester due to the gravid uterus compromising 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

Varicella infection in the first trimester does not appear to increase the risk of spontaneous miscarriage[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]. FVS 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 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 with varicella or shingles, other than the mother, during this time. The route of infection could be transplacental, ascending vaginal or 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 negative for specific IgG)[7]. Pregnancy should be avoided for at least 4 weeks after completing the two-dose schedule and they should be advised 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]. Teratogenic effects are not seen with measles infection in pregnancy[17].

Vaccine recommendations

Women of child-bearing age, who are found to be non-immune, should be vaccinated against measles with the MMR vaccine[16]. Pregnancy should be avoided for at least 4 weeks after administration. Vaccination during pregnancy is contraindicated. However, there are no reports of neonates being affected due to inadvertent administration[6]. In this context, inadvertent administration of MMR vaccine is not considered as an indication for termination.

Vaccine recommendations for pregnant women

All live attenuated vaccines are contraindicated in pregnancy due to the theoretical risk of transmission to the fetus, although there has been no evidence of adverse effects from inadvertent administration[2]. In other countries, seasonal influenza vaccination is recommended to prevent complications associated with influenza outbreaks. Many countries advocate vaccination against pertussis with the acellular pertussis vaccine during the third trimester to reduce neonatal infection. Since 2023, respiratory syncytial virus (RSV) vaccination has been introduced to protect the newborn from severe RSV infection. Hepatitis B vaccination is being advocated to protect the newborn from perinatal infection. However, in Sri Lanka, only tetanus toxoid is routinely administered as part of antenatal care.

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 the success of the immunisation programme in Sri Lanka, both tetanus and

neonatal tetanus have reached elimination levels[19]. Nevertheless, NIP recommends Immunisation of pregnant women with tetanus toxoid.

Vaccine recommendations

Tetanus vaccine is derived from inactivated toxin (toxoid) and induces antibodies against tetanus toxin. In pregnancy, NIP recommends the following schedule for a monovalent tetanus vaccine[20].

Table 1: National Immunisation 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 written evidence of previously being vaccinated with 6 doses of tetanus toxoid containing vaccination as per national immunisation 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 when	
• 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 Immunisation 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 Immunisation 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. Immunisation during pregnancy reduces the severity of the disease in addition to its role as a primary preventive measure[23]. There is reliable data showing that vaccination during pregnancy also protects the newborn during the first few months of life[24].

Seasonal influenza vaccine may not cover all strains of the virus circulating during the season, however, since there is cross immunity against all strains, reasonable protection is conferred[25].

Vaccine recommendations

The inactivated influenza vaccine is recommended during every pregnancy, at any stage of gestation[26].

Pertussis (whooping cough)

Infants less than 3 months of age are susceptible to the more severe form of infection with pertussis. Majority of infants who succumb to pertussis are less than 6 weeks of age[27]. It has been shown that more than 90% protection against severe infection in infants less than 2 months, could be achieved by passive immunisation from mother to fetus[28]. This could only be achieved through vaccination during pregnancy which leads to high levels of antibodies available for transfer to the fetus[28]. Therefore, vaccination during pregnancy with the acellular pertussis vaccine is recommended in many countries.

Vaccine recommendations

Vaccination with the acellular pertussis vaccine is recommended between 20 weeks to 32 weeks of gestation as a single dose in each pregnancy[29]. There has been no increased risk of adverse pregnancy outcomes reported from vaccination during pregnancy[30]. Currently, pertussis vaccine is not included in the NIP for pregnancy in Sri Lanka.

Hepatitis B

Hepatitis B virus (HBV) infection in pregnancy poses serious risks, mainly vertical transmission at birth. If exposed perinatally, up to 90% of infants develop chronic HBV infection, leading to cirrhosis and/or hepatocellular carcinoma later in life[31]. Preventing maternal infection during pregnancy is therefore critical. The Hepatitis B vaccine is a recombinant vaccine and is considered safe in pregnancy. It protects the mother from acute infection and reduces the chance of fetal or perinatal exposure.

Vaccine recommendations

Vaccination of the mother during pregnancy is only indicated if she is HBsAg-negative and non-immune, not if she is already infected. Susceptible or at-risk pregnant women should receive the full vaccine series. In case of exposure, HBIG plus vaccine is indicated.

Infants born to HBsAg-positive mothers must receive both the hepatitis B vaccine and hepatitis B immunoglobulin (HBIG) within 12 hours of birth[31]. These infants should then complete the standard Sri Lanka NIP hepatitis B vaccination schedule at 2, 4, and 6 months. Post-vaccination testing with HBsAg and anti-HBs should be performed at 9-12 months of age to confirm protection and exclude chronic infection[31]. Timely newborn prophylaxis is the key strategy for preventing perinatal HBV transmission. (refer Chapter 11).

Respiratory Syncytial Virus (RSV)

RSV infection in pregnancy is usually mild in the mother but could lead to severe illness, including bronchiolitis, pneumonia and hospitalisation in the newborn. Maternal vaccination transfers

protective antibodies to the infant. The bivalent vaccine given at 32–36 weeks of pregnancy reduces severe infant RSV illness by ~82% at 3 months and ~69% at 6 months, with no major safety concerns[32].

Vaccine recommendations

CDC and FDA recommend administering a single dose of the maternal RSV vaccine between 32 and 36 weeks of gestation, given during the RSV season, to provide protection for infants against severe RSV disease during their first 6 months of life[32].

Vaccine recommendations for post pregnancy period

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

Updated COVID-19 booster guidance

Pregnancy is considered as an independent risk factor for severe infection with COVID-19[33]. WHO, CDC and almost all professional organisations 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[34]. Vaccination reduces the risk of severe infection during pregnancy by more than 80%[35]. Vaccination also reduces premature birth and severe disease of the newborn.

WHO, CDC, and ACOG emphasize the importance of receiving the most recent COVID-19 booster during pregnancy. It may be given at any stage of pregnancy, preconception, or postpartum. Current data confirm no increase in miscarriage, stillbirth, congenital anomalies, or thromboembolic events following vaccination (WHO 2023; ACOG 2025). All WHO recommended COVID-19 vaccines are suitable for Immunisation during pregnancy[36].

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[37].

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[38]. No increased risk of birth defects was detected by vaccination during first trimester[39].

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[40]. They should not stop breastfeeding after vaccination. Data regarding safety of vaccination during breastfeeding are limited, however, available evidence indicates vaccination to be safe and effective during breast feeding and may even protect the newborn from severe disease[41].

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.

References

1. Mor G, et al. The immune system in pregnancy: a unique complexity. *American Journal of Reproductive Immunology*. 2010; 63(6):425433. doi:10.1111/ j.1600-0897.2010.00836.x.
2. Keller-Stanislawski B, et al. Safety of Immunisation during pregnancy: a review of the evidence of selected inactivated and live attenuated vaccines. *Vaccine*. 2014; 32(52):7057-7064. Doi:10.1016/j.vaccine. 2014.09.052.
3. Miller E, et al. Consequences of confirmed maternal rubella at successive stages of pregnancy. *Lancet.* 1982; 2:781–784.
4. Enders G, et al. Outcome of confirmed periconceptual maternal rubella. *Lancet*. 1988; 1:1445–1447.
5. Rubella vaccines. WHO position paper. *Weekly Epidemiological Record.* 2011. No. 29, 86, 301–316.
6. da Silva e Sá GR, et al. Seroepidemiological profile of pregnant women after inad- vertent rubella vaccination in the state of Rio de Janeiro, Brazil, 2001–2002. Revista panamericana de salud pública. 2006; 19:371–378.
7. Chickenpox in pregnancy. Royal College of Obstetricians and Gynaecologists. RCOG Green-top Guideline no. 13, September 2015. Available at: http://www.rcog.org.uk/womens-health/guidelines. [Accessed May 20, 2020].
8. Schutte TJ, et al. Varicella pneumonia complicating pregnancy: a report of seven cases. *Infectious Diseases in Obstetrics and Gynecology.* 1996; 4:338–46.
9. Tan MP, et al. Chickenpox in pregnancy: revisited.Reproductive toxicology. 2006; 21:410–20.
10. Smego RA, Jr, et al. Use of acyclovir for varicella pneumonia during pregnancy. *Obstetrics & Gynecology*. 1991; 78:1112–1116.
11. Pastuszak AL, et al. Outcome after maternal varicella infection in the first 20 weeks of pregnancy. *New England Journal of Medicine*. 1994; 330:901–905.
12. Enders G, et al. Consequences of varicella and herpes zoster in pregnancy: prospective study of 1739 cases. *Lancet*. 1994; 343:1548–1551.
13. Red Book. Report of the Committee on Infectious Diseases. Kimberlin DW, et al. Eds. 31st Edition. 2018. AAP Committee on Infectious Diseases.

14. Wilson E, et al. Varicella vaccine exposure during pregnancy: Data from 10 years of the Pregnancy Registry, *The Journal of Infectious Diseases*. 2008; 197(2):S178–S184. https://doi.org/10.1086/522136.

15. Atmar RL, et al. Complications of measles during pregnancy. *Clinical Infectious Diseases*. 1992; 14:217-26. https://academic.oup.com/cid/article-abstract/14/1/217/354295.

16. McLean HQ, et al. Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013: summary recommendations of the Advisory Committee on Immunisation Practices (ACIP). Centers for Disease Control and Prevention [published erratum appears in *Morbidity & Mortality Weekly Reports Recommendations & Reports*. 2015; 64:259]. *Morbidity & Mortality Weekly Reports Recommendations & Reports.* 2013; 62(RR-4):1-34.

17. Rasmussen SA, et al. What obstetric health care providers need to know about measles and pregnancy. *Obstetrics & Gynecology*. 2015; 126:163-70.

18. Roper MH, et al. Maternal and neonatal tetanus. *Lancet*. 2007; 370:1947-1959.

19. UNICEF. Sustaining vaccination coverage: continued national commitment to primary health care with a strong focus on community engagement - Case Study Sri Lanka. December 2019.

20. Epidemiology unit. National immunisation schedule Sri Lanka. National Immunisation Programme, 2017. http:// epid.gov.lk/web/images/pdf/Immunisation/nis_final_03_05_2017.jpg.

21. Dodds L, et al. Impact of influenza exposure on rates of hospital admissions and physician visits because of respiratory illness among pregnant women. *Canadian Medical Association Journal.* 2007; 176:463.

22. Family Health Bureau, Sri Lanka. Maternal Death Surveillance and Response (MDSR) – outcomes of 2014. Available at: https://drive.google.com/file/d/1KHRrwOvoEFDC8Bh_BSHzAhE RqLuGoNKg/view.

23. Regan AK, et al. Effectiveness of seasonal trivalent influenza vaccination against hospital-attended acute respiratory infections in pregnant women: a retrospective cohort study. *Vaccine*. 2016; 34:3649–56.

24. Zaman K, et al. Effectiveness of maternal influenza Immunisation in mothers and infants [published erratum appears in *New England Journal of Medicine.* 2009; 360:648. *New England Journal of Medicine.* 2008; 359:1555–64.

25. Belongia EA, et al. Variable influenza vaccine effectiveness by subtype: a systematic review and meta-analysis of test-negative design studies. *Lancet Infectious Diseases.* 2016; 16(8):942–51. doi:10.1016/S1473-3099(16)30087-0.

26. Ding H, et al. Influenza vaccination coverage among pregnant women - United States, 2016–17 influenza season. *Morbidity & Mortality Weekly Report*. 2017; 66:1016–22.

27. Murray EL, et al. Characteristics of severe *Bordetella pertussis* infection among infants ≤90 days of age admitted to pediatric intensive care units—Southern California, September 2009-June 2011. *Journal of the Pediatric Infectious Diseases Society*. 2013; 2:1–6.

28. Amirthalingam G, et al. Effectiveness of maternal pertussis vaccination in England: an observational study. *Lancet*. 2014; 384:1521-8. https://doi.org/ 10.1016/ S0140-6736(14)60686-3.

29. Abu Raya B, et al. The effect of timing of maternal tetanus, diphtheria, and acellular pertussis (Tdap) Immunisation during pregnancy on newborn pertussis antibody levels – a prospective study. *Vaccine.* 2014; 32:5787-93 https://doi.org/10.1016/j.vaccine.2014.08.038.

30. Donegan K, et al. Safety of pertussis vaccination in pregnant women in UK: observational study. *British Medical Journal*. 2014; 349:g4219.

31. Schillie S, et al. CDC recommendations for hepatitis B screening and testing—United States, 2023. *Morbidity & Mortality Weekly Reports Recommendations & Reports.* 2023;72(1):1–25.

32. Broder KR, et al. Use of the Pfizer respiratory syncytial virus vaccine during pregnancy for the prevention of RSV-associated lower respiratory tract disease in infants: recommendations of the Advisory Committee on Immunisation Practices—United States, 2023. *Morbidity & Mortality Weekly Report.* 2023; 72(41):1101–8. doi:10.15585/mmwr.mm7241e1.

33. Allotey J, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. *British Medical Journal*. 2020; 370:m3320. doi:10.1136/bmj.m3320 pmid:32873575.

34. Covid-19 Maternal Immunisation Tracker (COMIT Berman Institute of Bioethics & Center for Immunisation Research, Johns Hopkins University.). http://www.comitglobal.org./

35. Baden LR, et al. COVE Study Group. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *New England Journal of Medicine* 2021; 384:403-16. doi:10.1056/NEJMoa2035389 pmid:33378609.

36. Questions and Answers: COVID-19 vaccines and pregnancy. World Health Organization. https://www.who.int/publications/i/item/WHO-2019-nCoV-FAQ-Pregnancy-Vaccines-2022.1.

37. Zaçe D, et al. The impact of COVID-19 vaccines on fertility-A systematic review and meta-analysis. *Vaccine*. 2022; 40(42):6023-6034. Doi:10.1016/j.vaccine. 2022.09.019

38. Badell ML, et al. Covid-19 vaccination in pregnancy. *British Medical Journal*. 2022;378 :e069741 doi:10.1136/bmj-2021-069741.

39. Ruderman RS, et al. Association of COVID-19 vaccination during early pregnancy with risk of congenital fetal anomalies. *JAMA Pediatrics*. 2022;176(7):717-719. doi:10.1001/jamapediatrics.2022.0164.

40. Drugs and Lactation Database (LactMed) [Internet]. Bethesda (MD): National Library of Medicine (US); 2006-. COVID-19 Vaccines. [Updated 2022 Sep 19] https://www.ncbi.nlm.nih.gov/books/NBK565969/.

41. Muyldermans J, et al. The Effects of COVID-19 Vaccination on Lactating Women: A Systematic Review of the Literature. *Frontiers in Immunology*. 2022; 13:852928. Published 2022 Apr 8. doi:10.3389/fimmu.2022.852928.

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CHAPTER 28

IMMUNISATION 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 are 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 immunosenescence. 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 elderly[1,4,5]

- Influenza vaccine
- Pneumococcal vaccine
- Tetanus, diphtheria and pertussis vaccine
- Varicella vaccine
- Zoster vaccine
- COVID-19 vaccine

Vaccination of older adults on vaccine-preventable diseases

Influenza

Influenza A and B viruses cause seasonal epidemics of influenza in humans. Adults aged > 65 years have the highest risk for hospitalisation, complications and death, resulting from influenza. The risk increases markedly in people over 85 years[1].

The standard-dose influenza vaccines are either 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 hospitalisation 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]. (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]. Hospitalisation 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 greater among adults with underlying diseases than in healthy older adults[7]. Further, deaths from pneumococcal bacteraemia have 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 hospitalisation and long-term antibiotic therapy[2].

Pneumococcal immunisation is recommended in the 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 that effectiveness of PPSV-23 is low among immunocompromised persons > 65 years than in immunocompetent aged 65-84 years. However, a significant serotype-specific vaccine efficacy was demonstrated against IPD with PPSV-23[1].

Impact of pneumococcal conjugate vaccine 13 (PCV13) followed by PPSV-23 in elderly was reviewed by the US Advisory Committee in Immunisation Practices which concluded that there is no evidence for an increased reduction of IPD in older adults > 65 years. An economic analysis revealed, unlike PCV13 immunisation, PPSV-23 was cost effective especially in older adults aged > 70 years[1]. (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 immunised 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 NIP, 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]. (refer Chapters 08, 22)

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 is available in Sri Lanka outside of the NIP. (refer Chapter 08 & Annex II)

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 immunisation.

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 unimmunised adults[12].

Tdap vaccine; For the prevention of tetanus, diphtheria and pertussis diseases. Adults age ≥ 65 years, previously vaccinated or not should receive one dose of the vaccine. Persons should continue to receive Tdap every 10 years[8].(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
- Laboratory evidence of immunity to varicella
- Diagnosis or verification of a history of varicella or herpes zoster by a healthcare provider.

An adult with documented evidence of a single dose of varicella vaccine in the past, should be offered a single booster dose[12].

(refer Chapter 24)

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.

The live-attenuated herpes zoster vaccine (ZVL) is effective in preventing post herpetic neuralgia with statistically significant age-related vaccine efficacy. Vaccine efficacy declines 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 NIP[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. (refer Chapter 26)

COVID-19 disease

Older adults have an increased risk of severe illness from COVID-19 infection. They are more prone for hospitalisation, intensive care management including ventilator support. The risk increases in adults > 60 years[5].

CDC recommends an additional booster dose for those aged 65 and above to reduce the risk for severe disease[16]. (refer Chapter 06)

- 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

References

1. Cunningham AL, et al. Vaccines for older adults. *British Medical Journal* 2021; 372:n188. doi: 10.1136/bmj.n188.
2. High KP. Infections in older adults. In: Bennett JE, et al, editors. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Philadelphia: Elsevier. 2020. p3704–3712.
3. Aiello A, et al. Immunosenescence and its hallmarks: how to oppose aging strategically? A review of potential options for therapeutic intervention. *Frontiers in Immunology.* 2019; 10:2247. doi: 10.3389/fimmu.2019.02247
4. Weinberg B. Vaccines for the elderly: current use and future challenges. *Immunity & Aging*. 2018; 15:3 DOI 10.1186/s12979-017-0107-2
5. Centers for Disease Control and Prevention (CDC). COVID-19 risks and vaccine information for older adults [Internet]. Atlanta (GA): CDC; [cited 2026 Mar 24]. https://www.cdc.gov/aging/covid19/covid19-older-adults.htm
6. Tanner AR, et al. Influenza vaccination: protecting the most vulnerable. *European Respiratory Review*. 2021; 30: 200258 [https://doi.org/10.1183/ 16000617.0258-2020
7. Janoff EN, et al. *Streptococcus pneumoniae*. In: Bennett JE, et al, editors. Mandell, Douglas and Bennett's principles and practice of infectious disease. 9th ed. Churchill Livingstone: Elsevier Inc; 2020; 2473-249.
8. Centers for Disease Control and Prevention. Epidemiology and Prevention of Vaccine-Preventable Diseases (The Pink Book). Hall E, et al., editors. 14th ed. Washington (DC): Public Health Foundation; 2021.
9. Communicable diseases epidemiological profile: Sri Lanka. Geneva: World Health Organization; 2010.
10. Chaudrey R, et al. Tetanus in the elderly: a forgotten illness. *Lancet*. 2001; 357:1805.
11. Kanndeil W, et al. The burden of pertussis in older adults: what is the role of vaccination? A systematic literature review. *Expert Reviews of vaccines*. 2019); 8(5):439-455 DOI:10.1080/14760584.2019.1588727

12. Kroger AT, et al. Immunisation. In: Bennett JE, et al, editors. Mandell, Douglas and Bennett's principles and practice of infectious disease. 9th ed. Churchill Livingstone: Elsevier Inc; 2020. 3771-3812.
13. Chickenpox (varicella) [Internet]. Atlanta (GA): CDC; 2021 Apr [cited 2026 Mar 24]. https://www.cdc.gov/chickenpox/hcp/index.html
14. Who needs an additional dose of COVID-19 vaccines? WHO. (updated March 2022) https://www.who.int/news-room/questions-and-answers/item/coronavirus-disease-(covid-19)-vaccines.
15. Bar-On YM, et al. Protection by a fourth dose of BNT162b2 against omicron in Israel. *New England Journal of Medicine*. 2022; 386:1712-1720. DOI:10.1056/NEJMoa2201570
16. Centers for Disease Control and Prevention. CDC recommends additional boosters for certain individuals. Content source: CDC Newsroom. https://www.cdc.gov/media/releases/2022/s0328-covid-19-boosters. html

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CHAPTER 29

IMMUNISATIONS FOR COMPETITIVE SPORTSPEOPLE

Significant numbers of Sri Lankans of all age groups, from children to senior citizens, participate 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 continents, sometimes as individuals and at other times as members 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 infections[1]. In contact sports (rugby, wrestling, gymnastics, martial arts, etc.), there is an increased risk of airborne infections[1] as well as blood-borne transmission of infections. Furthermore, there is a potential risk that some of these vaccine-preventable diseases could cause long-term problems as well. It must also be appreciated that vaccine-preventable diseases could interfere with the training schedules of athletes and/or with participation in competitions.

Intense exercise alters the functions and quantity of circulating cells of both the innate and acquired immune systems (e.g. neutrophils, lymphocytes, 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-related 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 also responsible for higher risks of infection in athletes when exposed to microorganisms[2].

The 'open window' typically lasts 3-72 hours post-exercise, depending on the intensity and duration of the activity. During this period, there is a transient decrease in circulating lymphocytes, particularly natural killer (NK) cells, and a shift towards a Th2 cytokine profile, which can impair cell-mediated immunity[3]. Therefore, it is advisable to schedule

vaccinations for periods of lower training load or periods of resting, if possible, to minimise the potential for reduced vaccine efficacy.

Administration of the National Immunisation Programme (NIP) vaccines in Sri Lanka may not adequately meet all the medical needs of sports persons[1]. An enhanced benefit from preventing even mild diseases is important from the point of view of training and participation in sports. A risk-benefit assessment has to be undertaken on an individual basis concerning immunisation and the timing of vaccinations of sportspersons. Such risk-benefit analyses of vaccination in athletes differ significantly from those of the general population, providing the rationale for specific vaccination guidelines for sportspeople[4].

In the case of sportspersons, the 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 sportspeople need to be scheduled in a way that the 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 vaccinations are quite well tolerated by athletes and the resulting antibody titres are no different to the levels in the general population[4].

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 sportspeople 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 sportspeople already covered by the programme. Regular booster vaccinations are essential to maintain immunity. Tetanus and diphtheria boosters are recommended every 10 years, and pertussis boosters are important for preventing outbreaks.

There are certain diseases for which vaccines are recommended under special circumstances and for epidemiological reasons. These are indicated for sportspeople who have to travel to certain countries in which these diseases are endemic and have not been adequately immunised. (refer Chapter 30).

The recognised diseases that fall into this group are

- Yellow fever
- Japanese encephalitis
- Poliomyelitis
- Typhoid
- Meningococcal disease
- Tick-borne encephalitis

Other vaccines 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
- Annual influenza vaccine

These two vaccines are particularly important for athletes with asthma or other chronic respiratory conditions[4].

Elderly athletes, especially those in the veteran sports categories, should consider the shingles vaccine, as they are at an increased risk of developing herpes zoster.

HPV vaccination is recommended for both male and female athletes to prevent HPV-related infections and cancers. This is especially important for athletes who may have increased exposure to HPV through close contact and risks of exposure to vulnerable situations, including spread through fomites[5].

During the era of the COVID-19 pandemic, vaccines against the SARS-CoV-2 needed special consideration. Several different vaccines and vaccination schedules were used in Sri Lanka. These were changed through necessity from time to time, taking into account the developing scenarios of the pandemic. Although the COVID-19 pandemic has evolved, staying up-to-date with current COVID-19 vaccination recommendations and booster doses remains crucial for athletes, especially those travelling internationally. Comprehensive information regarding the commonly used COVID-19 vaccines and vaccination programmes is provided in Chapter 6.

N. B.

If additional information is needed, some websites could be of assistance to the Team Physicians and other medical personnel involved in looking after sportspeople, in making decisions regarding their vaccination.

Some of the websites are listed below:

- 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
- https://www.ais.gov.au/position_statements

- https://journals.lww.com/cjsportsmed/fulltext/2022/01000/covid_vaccination_in_athletes_and_updated_interim.12.aspx doi: 10.1097/JSM.0000000000000981
- https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00082-5/fulltext https://doi.org/10.1016/S2213-2600(21)00082-5

References

1. Collins CJ, et al. Infectious disease outbreaks in competitive sports 2005-2010. *Journal of Athletic Training*. 2012; 47(5):516–518. doi:10.4085/1062-6050-47.5.02.
2. Tafuri S, et al. Vaccinations among athletes: evidence and recommendations. *Expert Review of Vaccines.* 2017; 16(9):867-9. doi: https://doi.org/10.1080/14760584.2017.1358092.
3. Gleeson M. Immune function in sport and exercise. *Journal of Applied Physiology.* 2007; 103(2):693–699. https://doi.org/10.1152/japplphysiol.00008.2007
4. Gartner BC, et al. Vaccination in Elite Athletes. *Sports Medicine*. 2014; 44(10):1361-76. doi: 10.1007/s40279-014-0217-3.
5. Ding DC, et al. Long-term persistence of human papillomavirus in environments. *Gynecologic Oncology*. 2011; 121(1):148-51. doi: 10.1016/j.ygyno.2010.11.040.

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CHAPTER 30

IMMUNISATION FOR INTERNATIONAL TRAVEL

Introduction

In an increasingly interconnected world, international travel has become commonplace for business, leisure and humanitarian purposes. However, crossing geographical borders exposes individuals to different infectious disease environments harbouring pathogens that travellers may have little or no immunity against. Immunisation stands as one of the most effective preventive health measures for international travellers, offering protection against potentially serious infectious diseases while helping to prevent their global spread.

General considerations prior to travel

Prior to travel, individuals should schedule a healthcare consultation to understand potential disease risks in their destination countries and learn about appropriate preventive measures, including immunisation.

Vaccination should be personalised based on:

- the traveller's previous vaccinations
- general health status (e.g. age, pregnancy, medication) and risk factors (e.g. allergies, chronic diseases)
- allergy to previous vaccine doses
- country/countries to be visited
- type and duration of travel
- type of activities planned during travel
- time available before departure

In general, travellers are advised to consult a travel medicine practitioner/ physician **4-8 weeks before travel** to allow sufficient time for immunisation schedules to be completed.

Travel-related vaccination is categorised into 3 groups[1]:

1. Routine vaccines to be reviewed before travel

Vaccines in this category are part of most national childhood immunisation programmes (e.g. DPT, hepatitis B vaccine, MMR). A pre-travel consultation is an excellent opportunity for healthcare providers to review the vaccination status of infants, children, adolescents, and adults and to ensure that they are up to date.

2. Vaccines recommended for certain destinations

These vaccines protect against diseases endemic to the country of origin or destination. They are intended to safeguard travellers and simultaneously prevent transmission of disease within and between countries (e.g. hepatitis A vaccine, Japanese encephalitis vaccine, typhoid vaccine, rabies vaccine).

3. Vaccines mandatory for certain countries

Some countries require proof of vaccination for travellers who plan to enter or exit the country (e.g. yellow fever vaccine, polio vaccine, meningococcal vaccine)[2].

All vaccinations should ideally be completed at least 2 weeks prior to travel. General rules regarding vaccination such as simultaneous vaccinations, co-administration of antimicrobial therapy apply (refer Chapter 3). Travellers should be provided with a written record of all vaccines administered.

It should be noted that safe and efficacious vaccines have not yet been developed against several of the most life-threatening infections. Hence, travellers should be advised on other preventive measures, such as avoiding mosquito bites, handwashing, and general precautions.

Yellow fever vaccine

Yellow fever occurs in both urban and rural settings of Africa and Central and South America. Individuals travelling to regions at risk of yellow fever virus transmission are required to be vaccinated against yellow fever:

- to protect themselves from infection
- to prevent the international spread of yellow fever.

A single dose of the live, attenuated yellow fever vaccine is highly effective and provides life-long immunity to the disease. The vaccine is recommended for all unvaccinated travellers ≥ 9 months of age in countries with evidence of persistent or periodic yellow fever virus transmission, provided there are no contraindications (refer Chapter 25).

The WHO provides an updated list of countries where there is a risk of yellow fever transmission[3]. For travel to such countries or where there is a transit of ≥ 12 hours at an airport of a yellow fever endemic country, a WHO-approved vaccine must be administered at an authorised yellow fever vaccination centre.

The only authorised centre in Sri Lanka is the **Assistant Port Health Office,** located at the premises of the Medical Research Institute, Colombo 08**.** Following vaccination, the traveller should receive an International Certificate of Vaccination and Prophylaxis (ICVP), signed and validated with the official stamp. The ICVP becomes valid 10 days after vaccination and remains valid for life.

If vaccination is contraindicated for medical reasons, the traveller should obtain a letter of medical exemption from a physician (signed and dated on the physician's letterhead) indicating the specific reasons. In such an instance, the traveller should obtain advice from the consulate or embassy of the country he/she intends to visit.

Regardless of vaccination, travellers to yellow fever endemic areas should take adequate precautions to avoid exposure to mosquito bites.

Requirement at entry to Sri Lanka: Proof of vaccination against yellow fever is required for individuals aged ≥ 9 months arriving from countries with risk of yellow fever transmission and for those having transited for ≥ 12 hours through an airport of a country with risk of yellow fever transmission[2,4]. Individuals without a valid ICVP may be quarantined or refused entry.

Meningococcal vaccine

While the risk of meningococcal disease in travellers is generally low, outbreaks may occur in places where large numbers of people congregate. Travellers to the sub-Saharan meningitis belt may be exposed to outbreaks, most commonly of serogroup A, C and W135, with much higher incidence rates occurring in the dry season (November to June)[1]. Pilgrims visiting Mecca for Hajj or Umrah are at particular risk.

The government of Saudi Arabia has made vaccination against meningococcal disease mandatory for travellers performing Hajj and Umrah pilgrimages, and who will be in close contact with the local population (e.g. employment). The current recommendation is for vaccination with a quadrivalent vaccine providing coverage against serogroups A, C, Y and W-135.

Though not mandatory, the WHO recommends meningococcal vaccination for individuals travelling to any of the 26 countries in the meningococcal belt in sub-Saharan Africa[4]. Travellers are at particular risk of infection if they plan to reside in enclosed crowded spaces such as dormitories and military barracks.

A single dose of a meningococcal vaccine should be administered at least 10 days before travel to ensure protection at departure. It is effective for 3 years. (refer Chapter 16)

Polio vaccine

The WHO provides regular updates on transmission and international spread of poliovirus, including currently affected and vulnerable countries, available from the Global Polio Eradication Initiative website[5]. Currently, only two countries remain endemic for wild poliovirus: Afghanistan and Pakistan. Until polio is eradicated globally, the risks of acquiring the disease (for travellers visiting infected regions) and of re-infection of polio-free regions (by travellers returning from infected regions) remain. Therefore, all travellers to and from countries infected by wild poliovirus or vaccine-derived poliovirus should be adequately vaccinated.

Before departure, those from polio-free countries travelling to polio-endemic regions should have completed age-appropriate polio vaccination according to their national immunisation schedule (refer Chapter 18). Those who have completed an OPV or IPV vaccine series > 12 months previously should be administered a booster dose of vaccine prior to departure. Travellers who have not received any polio vaccine in the past should complete a primary series of polio vaccination (3 doses of oral polio vaccine [OPV] and one dose of inactivated polio vaccine [IPV]) before departure. It is recommended to ensure a minimum one-month interval between each dose. Any child who has been administered at least 3 doses of polio vaccination but not completed the age-appropriate national schedule should receive an additional dose of the vaccine before travel.

Individuals of all ages residing in polio-infected countries (i.e. those with active transmission of a wild or vaccine-derived poliovirus) and long-term visitors to such countries (i.e. those who spend more than 4 weeks in the country) should have completed a full course of vaccination against polio in compliance with the national immunisation schedule. Travellers from polio-infected areas should receive a booster dose of OPV (preferred if only received IPV previously) or IPV at least 4 weeks before (and within 12 months of) travel. This is to boost mucosal immunity and reduce the risk of poliovirus shedding, which could lead to reintroduction of poliovirus into a polio-free area.

Some polio-free countries (e.g. Brunei Darussalam, India and Saudi Arabia) require resident travellers and long-term visitors from polio-infected countries to provide documentation of recent vaccination against polio to obtain an entry visa. Alternatively, they may require travellers to receive an additional dose of polio vaccine on arrival. Travellers should carry a written vaccination record or preferably the ICVP.

COVID-19 vaccine

Currently, proof of COVID-19 vaccination is not mandatory for entry to most countries. However, depending on certain circumstances such

as the occurrence of new outbreaks, countries may change their vaccination policies and entry requirements for international travellers at short notice. Therefore, travellers are encouraged to seek advice from the relevant consulate prior to departure.

Certain foreign universities and colleges may still require proof of COVID-19 vaccination from international students. Therefore, those travelling abroad for studies should check with their respective academic institutions regarding the need for producing proof of vaccination. Fully vaccinated individuals (those who were vaccinated with two doses of an accepted COVID-19 vaccine followed by a booster dose) could obtain their vaccination record through the MOH office from which they obtained the vaccine.

Hepatitis A vaccine

Hepatitis A is distributed worldwide but is most common in regions with poor food hygiene, unsafe drinking water and poor sanitation. Non-immune travellers to these settings are at significant risk of acquiring the infection.

Hepatitis A vaccination should be considered for individuals aged ≥ 1 year who are travelling to regions of intermediate or high endemicity. Those at high-risk of developing severe disease following infection, such as immunocompromised patients and those with chronic liver disease, should be strongly encouraged to get vaccinated prior to travel, regardless of the destination. Additionally, travellers at increased risk of hepatitis A, including men who have sex with men, people who require life-long treatment with blood products, and intravenous substance abusers should be vaccinated before departure[6].

While a 2-dose schedule of the inactivated vaccine is usually recommended (6-18 months apart), comparable effectiveness has been achieved with a single dose when administered to healthy individuals[1]. Protection is achieved 2-4 weeks after vaccination and given that hepatitis A has a long incubation period (2-4 weeks), the vaccine can be administered up to the day of departure and still be protective (refer Chapter 10).

Hepatitis B vaccine

The highest prevalence of hepatitis B is found in some African and eastern Asian countries with low coverage of hepatitis B vaccination[1]. High rates of infection have been demonstrated in certain risk groups such as female sex workers and injection drug users. The likelihood of non-immune travellers acquiring infection when visiting regions of intermediate to high prevalence of chronic hepatitis B (HBsAg $\geq$ 2%) depends mainly on their personal risk-taking behaviour. An additional risk may be nosocomial infection if being treated at poorly equipped healthcare facilities during travel.

Hepatitis B vaccination is universally recommended, and thus unvaccinated travellers should be offered vaccination regardless of the destination. The general recommendation for hepatitis B vaccination is a three-dose series of the vaccine administered at 0, 1 and 6 months. However, in the case of travellers, if there is insufficient time to complete the standard vaccination schedule, an accelerated three-dose schedule given at 0, 7 and 21 days may be used[1]. In such an instance, a fourth dose is recommended 12 months after the first dose (refer Chapter 11).

Influenza vaccine

While travellers are generally not considered as a risk group for influenza, certain vulnerable categories such as pregnant women, children 6-59 months of age, those with chronic medical conditions and the elderly are at high-risk for developing severe disease. Furthermore, in some countries, appropriate health care may be unavailable or hard to access for non-residents in case of severe disease. Individuals should be aware of the seasonality of influenza in the countries to which they plan to travel (in the northern hemisphere from November to April; in the southern hemisphere from April to September; in tropical and sub-tropical regions, seasonality may differ by locality)[1].

Prior to travelling to countries during their influenza season, individuals (especially those at high-risk for severe disease) should be offered vaccination according to the recommendations of their

respective national health authorities. However, given that the prevailing influenza strains in the northern and southern hemispheres may differ significantly, the annual composition of the respective influenza vaccines may be different. Thus, travellers should be aware that a vaccine obtainable in one hemisphere may offer only partial protection against influenza virus infection in the other hemisphere. Hence, travellers should also adhere to general precautions such as handwashing and avoid large crowds.

The Ministry of Health in Saudi Arabia recommends all visitors arriving for umrah or hajj or for seasonal work in hajj zones to be vaccinated against seasonal influenza[7] (refer Chapter 13).

Japanese encephalitis vaccine

For most short-term travellers to urban regions of Asia, the risk of acquiring Japanese encephalitis is very low. However, risk stratification is done according to the destination of travel, season, duration of visit and activities conducted during the stay.

Those travelling to endemic countries during transmission season and planning activities with extensive outdoor exposure (such as camping and hiking) should consider vaccination. Additionally, they should be advised on appropriate measures to avoid mosquito bites (refer Chapter 14).

Pneumococcal vaccine

Although travellers are not at an increased risk of acquiring pneumococcal disease, children aged < 2 years, adults ≥ 65 years of age and immunocompromised individuals are at risk of severe disease, particularly when travelling to regions with limited access to optimal healthcare. Thus, travellers in the above high-risk categories should be offered vaccination (refer Chapter 17).

Rabies vaccine

Timely access to anti-rabies immunisation (in case of exposure) is not guaranteed everywhere because of a short supply of recent rabies vaccines or the local availability of older-generation rabies vaccines,

which are no longer recommended by the WHO[1]. Additionally, rabies immunoglobulin may be unavailable even in major urban centres, where canine rabies is prevalent.

Prior to departure, an assessment of individual risk of exposure to rabies virus is recommended for travellers to consider the need for pre-exposure prophylaxis (PrEP). It should take into consideration the remoteness of the destination, activities planned, the prevailing rabies epidemiology and the cumulative duration of the stay in endemic settings.

PrEP should be offered to travellers planning to get involved in activities that are likely to bring them into direct contact with bats and wild carnivores. These include wildlife professionals, cavers, researchers, veterinarians and humanitarian aid workers (if not previously immunised). Those planning to visit remote areas with a significant risk of exposure to rabid domestic animals should also be offered PrEP. Additionally, they should be educated on avoiding animal bites and scratches (refer Chapter 19).

Typhoid vaccine

Travellers to endemic areas are at potential risk of acquiring typhoid fever. Areas of high endemicity include parts of sub-Saharan Africa and South and South-East Asia, especially regions with low standards of hygiene, sanitation and water supply. Furthermore, there is an increase in the emergence and spread of antibiotic resistance among *Salmonella* Typhi isolates in typhoid endemic countries[1].

Vaccination should be offered to those travelling to destinations where the risk of typhoid fever is high, especially to individuals staying in endemic areas for > 1 month and/or in locations where antibiotic-resistant strains of *S* Typhi are prevalent.

As the vaccine does not confer 100% protection, even vaccinated travellers should be advised on food and water hygiene (refer Chapter 23).

Varicella vaccine

Although international travel is not a risk factor for varicella infection, it is highly contagious and certain groups of individuals (newborns, elderly, immunocompromised) may develop very severe disease. Therefore, non-immune individuals should consider vaccination prior to travel (refer Chapter 24).

Vaccination for special groups

Infants and young children

It is important to ensure that routine vaccinations of infants and children are fully up to date according to the national immunisation programme prior to travel. Some vaccines cannot be administered before a particular age (e.g. Japanese encephalitis and yellow fever vaccines cannot be given before 6 months of age). Infants and very young children who travel before they are able to complete the full schedule of routine and required vaccines are at risk of vaccine-preventable diseases. Thus, it is important to ensure their protection against sources of infection such as contaminated food and water and mosquito bites.

Pregnant and lactating women

Pregnancy and lactation should not deter a woman from receiving vaccines that are safe and will protect both the mother and fetus during travel. Killed or inactivated vaccines are safe during pregnancy and lactation. Live vaccines (except OPV) are generally contraindicated because of the theoretical risk to the infant, although the risks and benefits of these vaccines should be evaluated on a case-by-case basis.

Elderly travellers

The proportion of people aged ≥ 60 years engaging in international travel is increasing. Ageing has a significant impact on the immunological outcome of vaccination. Cell-mediated and antibody responses to vaccine antigens are weaker compared to younger individuals, resulting in vaccine induced protection developing more slowly and waning faster. Thus, in addition to vaccination, it is

important to advise the elderly on general precautions to prevent acquiring infection during travel.

Elderly people are at greater risk for severe influenza and secondary bacterial pneumonia, and thus influenza and pneumococcal vaccines should be offered, especially when travelling during influenza season. Other vaccines that are of relevance to the elderly traveller include those against diphtheria-tetanus-pertussis, and varicella. Irrespective of previous vaccination, travellers ≥ 60 years of age should receive a dose of Tdap. Those non-immune to varicella, particularly travelling from tropical countries to temperate climates, should be offered vaccination.

Although considered very safe, a few serious adverse events have been reported after yellow fever vaccination particularly in elderly individuals. Therefore, people ≥ 60 years of age should be carefully evaluated and a riskbenefit assessment should be conducted prior to yellow fever vaccination[1].

Travellers with chronic medical conditions

Travellers with an impaired immune system due to conditions such as cancer, diabetes mellitus, uncontrolled HIV infection, or those on immunosuppressive therapy are at risk of adverse events following the administration of live vaccines. In instances where administration of live vaccines (e.g. yellow fever vaccine) is mandatory for travel, a letter of medical exemption should be issued for these individuals.

Conversely, some chronic medical conditions may necessitate travellers to get vaccinated against specific infections. Influenza can cause severe disease in vulnerable groups such as those with cardiovascular disease or chronic respiratory conditions; at-risk travellers should be offered vaccination especially when travelling during influenza season.

Similarly, individuals with functional asplenia should ensure that their Hib, meningococcal, pneumococcal and influenza vaccines are up to date prior to travel.

Travellers should also be warned that, depending on the medical condition, there may be reduced efficacy of administered vaccines. Thus, they should be advised to take additional precautions against infection during travel.

Last-minute travellers

Travelers are encouraged to access pre-travel healthcare services at least one month before departure. However, this may not always be feasible. As administered vaccines may have insufficient time to provide maximum protection prior to departure, consideration should be given to each traveller's itinerary, trip activities and risk for infection at the destination to educate on necessary preventive measures[8].

Travellers should be reassured about the safety and efficacy of multiple simultaneous vaccinations. Furthermore, use of single-dose vaccines to initiate protection (e.g. monovalent hepatitis A vaccine) and approved accelerated schedules for vaccines where multiple doses are needed (e.g. hepatitis B vaccine) could ensure vaccination is completed before departure.

Long stay travellers

Individuals planning to travel for long-term stay in a foreign destination (e.g. employment, education) should be aware of any vaccine requirements of the host country and institution. Additionally, a pre-travel consultation needs to consider disease risk in surrounding areas because long-term travellers are likely to travel locally. Accordingly, those who are planning to reside long-term in regions of India, Bangladesh, Nepal, Pakistan and China should be offered vaccination against hepatitis A, hepatitis B, typhoid fever, meningococcal disease and Japanese encephalitis. Travellers considering long stays in Europe and the United States may require MMR and varicella vaccinations.

References

1. Vaccine-preventable diseases and vaccines (2019 update). WHO. In: *International travel and health* [Internet]. https://cdn.who.int/media/docs/default-source/travel-and-health/9789241580472-eng-chapter-6.pdf. [Accessed 27.04.2025].
2. Vaccination requirements and recommendations for international travelers, and malaria situation per country: 2022 edition. WHO. (updated 3 January 2023) https://www.who.int/publications/m/item/vaccination-requirements-and-recommendations-for-international-travellers-and-malaria-situation-per-country-2022-edition [Accessed 27.04.2025].
3. Countries with risk of yellow fever transmission and countries requiring yellow fever vaccination. WHO (November 2022). https://www.who.int/publications /m/item/countries-with-risk-of-yellow-fever-transmission-and-countries-requiring-yellow-fever-vaccination-(november-2022). [Accessed 27.04.2025].
4. Vaccination during international travel. Epidemiology Unit, Ministry of Health, Sri Lanka. https://www.epid.gov.lk/vaccination-during-international-travel [Accessed 27.04.2025].
5. Global Polio Eradication Initiative. Where we work. https://polioeradication. org/about-polio/where-we-work/ [Accessed 27.04.2025].
6. Thébault A, et al. Risk factors for sporadic hepatitis A infection: a systematic review and meta-analysis. *Microbial Risk Analysis*. 2021; 17:100155.
7. Health requirements and recommendations for travelers to Saudi Arabia for hajj and umrah. WHO. https://www.who.int/ith/ITH-Haj-2019.pdf. [Accessed 29.04.2025].
8. Last-minute travelers. In: *CDC Yellow Book 2024: health information for international travel*. 2024. https://www.cdc.gov/yellow-book/hcp/preparing-international-travelers/last-minute-travelers.html. [Accessed 14.05.2025].

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CHAPTER 31

IMMUNISATION IN DISASTERS, EPIDEMICS AND OUTBREAKS

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. tsunamis, 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 the spread of 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 the causation of communicable diseases.

Changing the host factors also makes them vulnerable to communicable diseases. This includes a decrease in the immunity of the people due to poor nutrition and psychological and physical distress. This could be worsened in already immunocompromised people.

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 minimised 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). Immunisation is considered one of the specific measures to prevent disease following disasters. However, during disaster situations, mass immunisation campaigns with childhood vaccines are not indicated in the Sri Lankan setting as sustainable high National Immunisation Programme (NIP) vaccination coverage has been observed at all levels over the years.

Age-appropriate vaccination could be compromised in the victims following a disaster. This could be due to service delivery issues as well as issues related to recipients. 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 immunisation 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)/immunisation record is available, routine immunisation guidelines should be followed. If the CHDR/immunisation record is not available, evidence of vaccination should be traced through the existing documents (B portion of the CHDR), which is available with the area Public Health Midwife or history provided by the parent or guardian, and routine immunisation continued. In the absence of valid information on immunisation, 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 under medical supervision according to the national guidelines[1]. 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[2].

Other optional vaccines include hepatitis A, varicella, MMR, cholera, 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.

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.

Routine immunisation services could be disrupted during epidemics /pandemics. It is important to restart the immunisation clinics as early as possible to prevent a resurgence of vaccine-preventable diseases. When and how to restart the immunisation services need 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)[3], 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 above 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 responsible authorities.

Covid-19 vaccination

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-19 vaccines. Namely, AstraZeneca, Sinopharm, Moderna, Sputnik 5 and Pfizer.

Measles outbreak and response through vaccination

Sri Lanka maintained its measles elimination status from 2019 through 2023, supported by high routine immunisation coverage and a strong surveillance system. However, in May 2023, an import-related case led to a measles outbreak that initially affected vaccine-hesitant communities in Colombo before spreading to other districts. Although the outbreak showed signs of decline by late 2023, a resurgence occurred in early 2024, with a notable cluster in August linked to three nursing training schools.

In response, Sri Lanka implemented a special immunisation campaign, launched in January 2024 which provided an additional MMR dose to infants aged 6–9 months in high-risk districts and a catch-up program for children up to 15 years. An adult catch-up campaign in 12 districts focused on young adults aged 20-30 years. These efforts were supported by active surveillance, public awareness campaigns, and community outreach, including collaboration with religious leaders and health workers. Despite progress, the South-East Asia Regional Verification Commission (SEA-RVC) reclassified Sri Lanka as having re-established measles transmission. The country now aims to regain elimination status by 2026, with strengthened surveillance and targeted immunisation plans underway.

References:

1. Ministry of Health, Sri Lanka, General Circular No. 01-22/2010, Guidelines on immunisation against tetanus. http://epid.gov.lk/web/images/pdf/Circulars/tenanus-2012-03-23.pdf.
2. Epidemiology Unit, Ministry of Health, Sri Lanka, Immunisation handbook (3rd Edition) http://epid.gov.lk/web/images/pdf/Publication/Immunization_Guide_2012.pdf.
3. Immunisation dashboard Sri Lanka – 2024 https://immunisationdata.who.int/ dashboard/regions/south-east-asia-region/LKA.

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CHAPTER 32

IMMUNISATION 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 may 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, immunisation should be provided early in the disease process, if possible before transplantation. The immunisation status of all patients with chronic or end stage kidney, liver, heart and lung disease should be evaluated and given age-appropriate vaccines if necessary[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]. While they are generally not recommended after transplantation due to the risk of vaccine induced infection, the

MMR vaccine may be administered under certain circumstances to children[6,7] (refer Table 1). However, it is not recommended in adults[8]. Inactivated vaccines could be given up to 2 weeks before transplantation[2]. They could be given 3-6 months after transplantation, if not administered pre-transplant[1]. Vaccination should be followed by checking antibody responses 4 weeks later (Table 1).

Donor immunisation

Live donors should have been immunised according to the current immunisation 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].

Immunisation 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[9]. Pets should also be fully immunised. There is little or no risk of transmission following immunisation of pets with live vaccines[1].

Immunisation for travellers

The CDC Traveller's Health site (https://wwwnc.cdc.gov/travel/) should be consulted for up-to-date information. In general, counselling on risk reduction, need for antimicrobial prophylaxis, and recommended vaccines should be reviewed. Additional vaccines may be indicated and some vaccine series (e.g. polio virus) may require a booster dose if exposure to an endemic region is anticipated. Yellow fever vaccine is contraindicated and documentation of vaccine exemption on an International Certificate of Vaccination or Prophylaxis is accepted in most countries' ports of entry[8].

Influenza vaccine

The inactivated influenza vaccine should be administered annually[10]. While earlier studies showed immunisation before 6 months after transplantation to be poorly immunogenic[1], a study showed that vaccination at one month was safe and immunogenic[11]. Guidelines from the Kidney Disease Improving Global Outcomes (KDIGO) recommend giving the influenza vaccine one month after transplantation[1]. The Infectious Diseases Society of America (IDSA) suggests vaccination at one- month post transplantation during an epidemic[5]. When available, the high dose or adjuvanted vaccine should be administered[8].

MMR vaccine

The MMR vaccine is generally not recommended after transplantation. If the vaccine is given inadvertently or the patient is exposed to wild type measles, passive immunisation 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 seronegative adults and sero-conversion tested after one month. If the patient is still seronegative, a further dose is recommended if time permits[1]. Paediatric SOT recipients may be given the vaccine post-transplant under certain circumstances[6]. These include nonimmune liver and kidney transplant recipients who are clinically well, greater than one-year post-transplant, more than two months out from rejection episodes and on minimal immune suppression. However, adult patients should not be administered the live vaccine[8].

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 Advisory Committee on Immunisation Practices (ACIP) recommends 2 doses of the RZV for the prevention of herpes zoster and related complications in both immunodeficient and immunosuppressed adults > 19 years of age regardless of prior vaccination or natural infection. However, if vaccination prior to transplantation is not possible, transplant recipients can receive the RZV 6-12 months after transplantation[12]. 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[13]. 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[13]. 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[14]. 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[15]. 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[15]. The 7-valent pneumococcal conjugated vaccine (PCV) evoked a better response rate compared to the 23-valent polysaccharide vaccine (PPSV23). Theoretically, administering the 13-valent PCV 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 PCV is not available in Sri Lanka at present, and the 10-valent PCV could 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]. Renal transplant candidates with evidence of significant alloimmunisation may benefit from pre-transplant meningococcal vaccination because of the possibility of post-transplant eculizumab use for humoral graft rejection[8]. 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. If the SOT is performed < 4 weeks after immunisation due to the availability of an organ, IV acyclovir or ganciclovir can be considered, even without symptoms, to prevent disseminated varicella[16]. The varicella vaccine may be given to paediatric nonimmune liver and kidney transplant recipients who are clinically well, greater than one-year post-transplant, more than two months out from rejection episodes and on minimal immune suppression. However, adult patients should not be administered the live vaccine[6].

COVID-19 vaccine

Mortality rates following COVID-19 in SOT recipients is higher than in healthy individuals[17]. mRNA vaccines (mRNA-1273 (Moderna) and BNT162b2 (Pfizer) have shown better antibody responses in SOT recipients, compared to ChAdOx1 nCoV (AstraZeneca/Covishield) vaccines[17]. 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) were 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[17]. All recipients are recommended the updated covid vaccines[8].

Table 1: Recommended vaccines (paediatric and adult) adapted from[1,2,4,5,17]

Vaccine*	Type	Before transplantation	After transplantation	Monitor titre
Influenza*	Inactivated	Yes	Yes	No
Hepatitis B*	Inactivated	Yes	Yes[a]	Yes[a]
Hepatitis A[b]*	Inactivated	Yes	Yes	Yes
DTP (paediatric < 7 years)* Tdap (> 7 years and adult)*	Inactivated	Yes	Yes	For tetanus
Inactivated polio*	Inactivated	Yes	Yes	No
H influenzae type b*	Inactivated	Yes	Yes	Yes[c]
S pneumoniae conjugate (PCV)[d]	Inactivated	Yes	Yes	Yes[e]
S pneumoniae polysaccharide PPSV23)[d]	Inactivated	Yes	Yes	Yes[5]
N meningitidis[f]*	Inactivated	Yes	Yes	No
Human papillomavirus (HPV)[g]*	Inactivated	Yes	Yes	No
Rabies[h]*	Inactivated	Yes	Yes	Yes[i]
Varicella*[j]	Live	Yes	No	Yes
MMR*[j]	Live	Yes	Yes[k]	Yes
Recombinant zoster vaccine[l]	Inactivated	Yes	Yes	No
Live zoster vaccine	Live	Yes	No	No
Japanese encephalitis	Inactivated	Yes	Yes	No
COVID-19 vaccine[m]	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[9]. 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.

[d]Children > 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 < 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 eculuzimab 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[18].

[h]Recommended for exposures or potential exposures to rabies. IM schedule to be administered. Intra dermal vaccination is not recommended. Passive immunisation should be also provided for post exposure prophylaxis[8].

[i]*Checking the titre post vaccination is recommended in high-risk patients.*

[j]*Refer text*

[k]*In 2019 the American Society of Transplantation published recommendations that MMR and VZV vaccine can be given to nonimmune paediatric liver and kidney transplant recipients who are clinically well, greater than one-year post-transplant, more than two months out from rejection episodes and on minimal immune suppression[6].*

[l]*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].*

[m]*Refer text*

Haematopoietic 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[20]. 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[20,21]. The risk of post-transplant infections is dependent on the CD4 count[20]. 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[21]. Ability to produce anti-polysaccharide antibody takes even longer[21]. 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[20]. Antibody titres to vaccine-preventable diseases decline during the first decade unless revaccinated, after autologous or allogeneic HSCT[20,22,23]. 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[22]. 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[20,22].

The IDSA recommends considering patients undergoing HSCT as never vaccinated, and therefore requiring full immunisation 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 immunisation 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[23]. Inactivated vaccines and toxoids are administered 3-6 months' post-transplant, irrespective of immune status[23]. Live vaccines are delayed for 24 months, based on insufficient safety and efficacy data on earlier immunisation[20]. 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[23].

Immunisation 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 immunisation

There is emerging evidence that immunisation of donor or recipient before transplantation is beneficial[24]. However, the IDSA guidelines recommend against immunising the donor solely for the benefit of the recipient[5]. Live vaccines should be avoided within 4 weeks of stem cell harvest[5].

Vaccination schedules

Vaccination should commence 3-6 months' post transplantation, without considering immunological markers of reconstitution[25]. Recipients with mild GvHD or on low steroid therapy (< 0.5 mg/kg prednisolone or equivalent) should commence re-vaccination. For HSCT recipients who remain on high-dose steroid therapy (prednisolone > 0.5 mg/kg) or combination therapy beyond 6 months post-HSCT, or with moderate or severe GvHD, should take into account indication, intensity and expected duration of immunosuppressive therapy when deciding whether to vaccinate or defer[25]. While non-live vaccines are safe, an increase in GvHD was noted with Covid mRNA vaccines[25].

Table 2: Vaccinations recommended for autologous and allogeneic HSCT recipients adapted from[5*,23,25, 26***]**

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]	3-6 months	2	Unknown
Hepatitis B[e]	3-6 months	2	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 1 booster	Unknown

**2013 Infectious Diseases Society of America (IDSA) Clinical Practice Guideline for Vaccination of the Immunocompromised Host (2014)*

**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[26].

[c]DTaP is preferred (even though not licensed for adults) as it gives better responses[26]. 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)[26].

[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[26]. 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[26].*

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, immunisation of the patient before transplantation is recommended, along with hepatitis B immunoglobulin, due to the risk of HBV transmission[26].

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[26].

[f]*Starting at 3 months post-transplant, in an outbreak of influenza[26].*

[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[26].*

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[26].

[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[23].*

[j]*Adult recipients of autologous and allogeneic HSCT aged 18 or more should receive a 3-dose primary course of SARS-CoV-2 vaccine from 3-6 months*

following HSCT. The first two doses should be administered at the minimum licensed interval (e.g. 3 weeks for Pfizer BNT162b2 and 4 weeks for Moderna mRNA 1273 vaccines). The 3rd primary dose should be administered at a minimum interval of 8 weeks later, followed by a booster 4th dose no sooner than 3 months after the 3rd dose, both with SARS-CoV-2 mRNA vaccines.

Following this re-vaccination schedule, recommendations for additional boosters in adult HSCT recipients should follow current national recommendations, including the use of novel multi-valent vaccines[25].

Table 3: Optional vaccines (adapted from[5,26])

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[25]	Limited data regarding safety and efficacy For paediatric recipients of autologous and allogeneic HSCT who are 24 months' post procedure, have no active GvHD, have not received systemic immune suppressive therapy (IST) for 12 months, meet all other criteria for ad- ministration of live vaccines and are VZV seronegative, consider 2 doses administered 2 months apart. VZV serology should be performed for all adult recipients of autologous and allogeneic HSCT (including those who received Zoster vaccine at 24 months), for those who are VZV seronegative, have no active GvHD, have not received systemic IST for 12 months, meet all other criteria for administration of live vaccines, consider 2 doses administered 2 months apart. Anti-virals if a VZV vesicular rash appears following immunisation
Zoster[25]	Adult recipients of autologous and allogeneic HSCT aged 18 years or more should receive 2 doses of recombinant zoster vaccine at least 2 months apart, commencing at 6 months following HSCT

Human papillo-mavirus	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[18]
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[26] 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[26]
	A recent study demonstrated immunogenicity and safety in a cohort of 21 allogeneic HSCT recipients who were immunised with the yellow fever vaccine, a median of 33 months after HSCT[27]
Japanese encephalitis	No data on live vaccines[25]. Inactivated vaccine[28]

[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(DGHS/Circular/2016-127 (MRI-ARPET)[19].*

The following vaccines are contraindicated in HSCT patients.

- Bacillus Calmette– Guerin (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[25]
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, minimise 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[29]

- Live attenuated influenza vaccine
- Oral polio vaccine

References

1. Danzinger-Isakova,L, et al. On Behalf of the AST ID Community of Practice. Vaccination of Solid Organ Transplant Candidates and Recipients: Guidelines from the American Society of Transplantation Infectious Diseases *Clinical Transplantation* 2019. https://doi.org /10.1111/ctr
2. Miyairi I, et al. Review: Immunisation practices in solid organ transplant recipients. *Vaccine* 2016; 34(16):1958-64.
3. Avery RK, et al. Update on immunisations in solid organ transplant recipients: what clinicians need to know? *American Journal of Transplantation* 2008; 8 (1):9-14.
4. Donato-Santana C, et al. Immunisation of Solid Organ Transplant Candidates and Recipients: A 2018 Update. *Infectious Disease Clinics of North America* 2018; 32:517-533.
5. Rubin LG, et al. 2013 IDSA Clinical Practice Guideline for Vaccination of the Immunocompromised Host. *Clinical Infectious Diseases* 2014; 58 (3):e44-100.
6. Suresh S, et al. Live vaccines after pediatric solid organ transplant: proceedings of a consensus meeting, 2018. *Paediatric Transplantation*. 2019; 23(7):e13571.
7. Feldman AG, et al. Safety and Immunogenicity of Live Viral Vaccines in a Multicenter Cohort of Pediatric Transplant Recipients. *Journal of the American Medical Association* (JAMA). Netw Open. 2023; 6(10):e2337602. doi: 10.1001/jamanetworkopen.2023.37602.
8. Radcliffe C, et al. Vaccination strategies for solid organ transplant candidates and recipients: insights and recommendations. *Expert Reviews of Vaccines*. 2025; 24(1):313-323.
9. Dansiger-Isakov L, et al. AST Infectious Diseases Community of Practice. Vaccination in Solid Organ Transplantation. *American Journal of Transplantation.* 2013; 13:311–317.
10. Hirzel C, et al. Influenza vaccine strategies for solid organ transplant recipients. *Current Opinion in Infectious Diseases.* 2018; 31(4):309-315. doi: 10.1097/QCO.0000000000000461
11. Perez-Romero, P, et al. Influenza vaccination during the first 6 months after solid organ transplantation is efficacious and safe. *Clinical Microbiology and Infection*. 2015; 21(11):1040 e11-8.
12. Anderson T.C., et al., Use of recombinant zoster vaccine in immunocompromised adults aged 19 years: recommendations of the

Advisory Committee on Immunisation Practices—United States. *American Journal of Transplantation*. 2022; 22(3):986-990.

13. Madeleine MM, et al. HPV-related cancers after solid organ transplantation in the United States. *American Journal of Transplantation.* 2013; 13:3202-3209.
14. Chong PP, et al. A Comprehensive Review of Immunisation Practices in Solid Organ Transplant and Hematopoietic Stem Cell Transplant Recipients. *Clinical Therapeutics.* 2017; 39 (8):1581-1598.
15. Kumar D. Immunisations following solid-organ transplantation *Current Opinion in Infectious Diseases.* 2014; 27(4):329-335.
16. Bahakel H, et al. Immunisation of Solid Organ Transplant Candidates and Recipients: A 2022 Update. *Infectious Disease Clinics of North America.* 2023; 37(3):427-441.
17. Giannella M, et al. SARS-CoV-2 vaccination in solid-organ transplant recipients: What the clinician needs to know. *Transplant International*. 2021; 34(10):1776-1788.
18. GARDASIL 9. US Food and Drugs Administration. https://www.fda.gov/ vaccines-blood-biologics/vaccines/gardasil-9. Accessed 29th December 2022
19. DGHS/Circular/2016-127 (MRI-ARPET)
20. van den Brink MRM, et al. Immune reconstitution following stem cell transplantation. *Hematology.* 2015; 2015:215-219.
21. Talekar MK, et al. Immune reconstitution after hematopoietic stem cell transplantation. In: V.I. Brown (ed.), Hematopoietic Stem Cell Transplantation for the Pediatric Hematologist/Oncologist. Springer International Publishing AG. 2018.
22. Small TN, et al. Immunisation of hematopoietic stem cell transplant recipients against vaccine-preventable diseases. *Expert Reviews of Clinical Immunology.* 2011; 7(2):193-203.
23. Ljungman P, et al. Vaccination of hematopoietic cell transplant recipients. *Bone Marrow Transplantation.* 2009; 44:521-526.
24. Majeed A, et al. Revisiting Role of Vaccinations in Donors, Transplant Recipients, Immunocompromised Hosts, Travelers, and Household Contacts of Stem Cell Transplant Recipients. *Biology of Blood and Marrow Transplantation*. 2020; 26(2):e38-e50.
25. Miller P, et al. Joint consensus statement on the vaccination of adult and paediatric haematopoietic stem cell transplant recipients: Prepared on behalf of the British society of blood and marrow transplantation and

cellular therapy (BSBMTCT), the Children's cancer and Leukaemia Group (CCLG), and British Infection Association (BIA). *Journal of Infection*. 2023; 86(1):1-8.

26. Cordonnier C, et al. Vaccination of haemopoietic stem cell transplant recipients: guidelines of the 2017 European Conference on Infections in Leukaemia (ECIL 7). *Lancet Infectious Diseases.* 2019; 9(6):e200-e212. http://dx.doi.org/10. 1016/S1473-3099(18)30600-5
27. de Fontbrune FS, et al. Immunogenicity and safety of yellow fever vaccine in allogeneic hematopoietic stem cell transplant recipients after withdrawal of immunosuppressive therapy. *Journal of Infectious Diseases.* 2018; 217(3):494-497.
28. Verolet CM, et al. Live Virus Vaccines in Transplantation: Friend or Foe? *Current Infectious Disease Reports.* 2015; 17:14.
29. Kamboj M, et al. Vaccination of the Stem Cell Transplant Recipient and the Hematologic Malignancy Patient. *Infectious Disease Clinics of North America.* 2019; 33:593-609.

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CHAPTER 33

IMMUNISATION 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 infectious diseasesand certain vaccines are recommended specifically for such persons[1,2]. However, the decision to vaccinate should be taken following careful consideration of the safety of the vaccine and the likely effectiveness in that person[1].

Inborn errors of immunity (IEI)

Although there are more than 500 distinct IEI, vaccine recommendations are generally based on the type of immunodeficiency. 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. Indicators 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[1,2,4]. Refer Table 1 for recommendation for 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]

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 agammaglobulinaemia (XLA), common variable immunodeficiency (CVID)	All live vaccines	• Annual inactivated influenza • HPV[e] • RSV • Recombinant herpes zoster (RHZ)	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	• BCG • Dengue • Live influenza • OPV • Yellow fever[c]	• Hib (children < 5 years)[d] • HPV[e] • Pneumococcal[f] • RSV • RHZ	Other live virus vaccines appear to be safe. However, IVIG/SCIG may interfere with the response to measles, mumps, rubella and varicella containing vaccines.

				All inactivated vaccines are safe and likely to be effective and should be administered, although immune response might be suboptimal.
Combined immuno-deficiency and syndromes	Severe combined immunodeficiency (SCID), complete Di George syndrome (Chr22q11.2 deletion), other combined immunodeficiencies with CD3 T cell counts < 500 cells/μL, Wiskott–Aldrich syndrome, class switch recombination defects/hyper IgM syndromes, hyper IgE syndrome, ataxia telangiectasia	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.

	Less severe combined immunodeficiencies 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[f] • RSV	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
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 bacterial vaccines	• Hib (children < 5 years)[d] • Pneumococcal[f]	All inactivated vaccines in the standard schedule are safe, likely to be effective and should be administered

Complement deficiency	e.g. persistent complement component, properdin or factor B deficiency	None	• Hib (children < 5 years)[d] • Meningococcal • Pneumococcal[f]	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 meningitidis* All inactivated vaccines in 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 1* deficiency	All live-bacterial vaccines and YF vaccine; other live virus vaccines if severely lymphopaenic or with defects in IFN γ signaling or defects in IFN α, β, γ production)		All inactivated vaccines are safe, likely to be effective and should be administered Inactivated typhoid vaccine may 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 19). 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 unimmunised or received only 1 dose of Hib administered before 12 months of age, should receive 2 doses of Hib, 8 weeks apart; if ≥ 2 or are received before 12 months of age, should receive 1 dose of Hib 8 weeks after the last dose; if a primary series is completed and received a booster dose at 12 months of age or older, no additional Hib doses are recommended. For over 5 years: 1 dose of Hib regardless of previous vaccination at diagnosis.*

[e]*3 dose schedule recommended regardless of age.*

[f]*PPSV23 is started 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.

Refer Table 2a for recommendations of adults with functional asplenia and Table 2b for recommendations in children with asplenia.

Table 2a: Vaccination for adults with asplenia[1,3,4]

Vaccine	Primary series	Revaccination (booster)
Pneumococcal conjugate vaccine (PCV) and 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

Table 2b: Vaccination for children with asplenia[1,3,4]

Vaccine	Primary series	Revaccination (booster)
Pneumococcal conjugate vaccine (PCV) and PPSV23	All children should receive an age-appropriate series of pneumococcal vaccines *Children <2 years* • Unvaccinated children 2 months-1 year – 2 doses 8 weeks apart and a booster at 1 year. Single dose of PPSV23 at ≥ 2 years of age • Unvaccinated children 1-2 years – 2 doses 8 weeks apart and a booster at least 6 months after the last dose. Single dose of PPSV23 at ≥ 2 years of age at least 8 weeks after the last PCV	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

	Children ≥ 2 years – • Previously unvaccinated - single dose of PCV followed by PPSV23 > 8 weeks later • Previously vaccinated with PCV- single dose of PPSV23 > 8 weeks after the last PCV	
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
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 and then every 5 years Booster dose every 5 years

Meningococcal serotype B*	Primary series according to manufacturer's advice	≤ 6 years of age - single booster dose 3 years after completing the primary schedule ≥ 7 years of age - single booster dose 5 years after completing the primary schedule
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

*This vaccine is currently not available in Sri Lanka

Persons on corticosteroid therapy

Persons with inflammatory or autoimmune diseases may require long-term corticosteroids. During vaccination of such individuals, immunosuppressive effect of the corticosteroid should be taken into consideration. Ideally, non-live vaccines should be administered at least 2 weeks before and live vaccines should be administered at least 4 weeks before initiating therapy[3].

Vaccine recommendations are based on potency, route of administration and duration of corticosteroid therapy[3]. (refer Table 3)

Table 3: Vaccination of persons on corticosteroid therapy[3,5]

Immuno-suppression	Dose and duration of prednisolone[a]	Vaccine recommendation[b]
High	**Adults/ children > 10 kg BW** ≥ 20 mg/day for ≥ 14 days **Children ≤ 10 kg BW** ≥ 2 mg/kg/day for ≥14 days	**Live vaccines** • 4 weeks before starting treatment, or • ≥ 4 weeks after treatment ends **Non-live vaccines** • 2 weeks before starting treatment, or Immediately after treatment ends[c]
Moderate	**Adults** ≥ 20 mg/day for < 14 days **Children ≥ 10 kg BW** ≥ 20 mg/day for < 14 days or < 20 mg/day for ≥ 14 days **Children <10 kg BW** ≥ 2 mg/kg/day <14 days or < 2 mg/kg/day for ≥14 days	**Live vaccines** • 4 weeks before starting treatment, or • Immediately after treatment ends **Non-live vaccines** • Any time before, during or after treatment
Mild	**Adults** < 20 mg/day, any duration **Children > 10 kg BW** < 20 mg/day for < 14 days or < 10 mg/kg for < 28 days **Children <10 kg BW** < 2 mg/kg/day < 14 days or < 1 mg/kg/day > 28days	**All vaccines** Any time before, during or after treatment
No	• Local administration, any dose (eye/inhaled/IM/intra-articular) • Oral administration, any dose budesonide/fluticasone • Single dose of dexamethasone • Physiological maintenance doses[c] (replacement therapy)	**All vaccines** Any time before, during or after treatment

[a]*or prednisolone-equivalent dose of other glucocorticoids (1mg prednisolone is equivalent to hydrocortisone 4 mg, methylprednisolone and triamcinolone 0.8mg, dexamethasone and betamethasone 0.15 mg.*

[b]*if patients require prompt therapy for chronic inflammatory conditions, this therapy should not be delayed because of past administration of vaccines.*

[c]*Physiological maintenance doses include a daily dose of 15–25 mg hydrocortisone or equivalent or fludrocortisone (0.05–0.2 mg/day) in adrenocortical insufficiency.*

Note: Children with immunosuppressive diseases (e.g. systemic lupus erythematosus) or those on additional immunosuppressive therapy should not receive live-virus vaccines during therapy, even when the dose of systemic corticosteroid is low or moderate[3].

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 are 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[6]. In adults, immunosuppressive doses are described for methotrexate, azathioprine and 6–mercaptopurine (methotrexate ≥ 0.4 mg/kg/week, azathioprine ≥ 3.0 mg/kg/day and 6-mercaptopurine ≥ 1.5 mg/kg/day)[7]. Live vaccines are contraindicated during immunosuppressive therapy and should be administered at least 4 weeks prior to initiating therapy[3,6,7,8].

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[3,9]. Generally, live vaccines should not be given at least 3 months after discontinuation of immunosuppressive doses of DMARDS. Live vaccines may be given 4 weeks after completing treatment with leflunomide or mTOR inhibitors such as tacrolimus[9]. This interval may extend if combination immunosuppressive therapy is used[2].

Response to inactivated vaccines may also be impaired during immunosuppression. Therefore, immunisation 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[6].

Vaccination in patients with autoimmune inflammatory rheumatic diseases (AIIRD) should preferably be administered during quiescent disease. (refer Table 4).

Table 4: Recommendations for vaccination of patients with AIIRD[6,7,9]

Vaccine	Recommendations
Influenza	Non-live seasonal influenza vaccine Two doses 4 weeks apart in the 1st year and then one dose annually[a,b]
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 naïve	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 strongly considered in VZV naïve patients on methotrexate. This could be considered in patients treated with TNFi, anti-IL1, anti-IL6 and low-dose glucocorticoids (refer Chapter 24)
Herpes zoster	Consider in those aged ≥ 50 years with AIIRD Recombinant 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 12)

[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 PPSV23 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[6,7].

Some of the commonly used biologics and the intervals for administration of live-attenuated virus vaccines are shown in Table 5.

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[a]	4 weeks
IL1 inhibitors	anakinra rilonacept canakinumab	1 dosing interval[a]	4 weeks 4 weeks 4 weeks
T-lymphocyte co-stimulation blockade	abatacep	1 dosing interval[a]	4 weeks
Type I interferon receptor antagonist	anifrolumab	1 dosing interval[a]	4 weeks
B-lymphocyte depletion	rituximab	6 months	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 withheld 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 vaccines*[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 immunosuppressive 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 immunisation with tetanus immunoglobulin should be carried out[8]. Patients who need to be immunised against rabies should receive both RIG as well as the ARV using the IM schedule.

Since IgG crosses the placenta during the third trimester, rituximab, anti-TNF biologics except certolizumab pegol, are detectable until 6 months after birth in newborns of 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 and OPV at least until 6 months of age. Whenever available, measurement of child's serum levels of the relevant biologic could guide the decision for or against administering a live vaccine[7]. Non live vaccines should be administered at the recommended intervals keeping in mind that the response may be suboptimal[2].

Immunocompetent household members should be encouraged to receive vaccines according to standard schedule with the exception of the oral polio vaccine[7].

Refer Table 4 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[8].

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[4]. 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[10].

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[11]. Among patients with solid tumours, patients with lung cancer have a high case fatality rate following influenza[11]. 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 41% of patients undergoing treatment for acute leukaemia were not protected against tetanus. In contrast, treatment with radioimmunotherapy for non-Hodgkin lymphoma in children did not influence their specific immunity to tetanus[11].

Severe infections due to *H influenzae* is rare. However, patients with Hodgkin lymphoma and multiple myeloma may benefit from vaccination[11]. Although the mortality due to chickenpox has decreased due to the wider use of acyclovir for prophylaxis and treatment, immunisation with varicella vaccine is indicated in seronegative

individuals. However, interrupting maintenance chemotherapy in order to vaccinate is not indicated[11]. The mortality rate remains high in cancer patients who are infected with measles[11].

Timing of immunisation

All live vaccines are contraindicated in cancer patients receiving immunosuppressive therapy and/or who have poorly controlled malignant disease. Live vaccines should be given $\geq$ 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)[10]. MMR or varicella containing vaccines should be deferred accordingly in patients receiving blood products or immunoglobulin (refer Chapter 36).

The response to inactivated vaccines may be impaired during chemotherapy. Therefore, immunisation 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[11]. 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, in order to avoid precipitating an acute febrile episode[10].

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 [10,11]. 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[2,10,11]. Schedules after chemotherapy may vary by person, depending on their age, vaccination history, the type of cancer, other immunosuppressive treatments received and other comorbidities and should be done with consultation of the treating oncologist.

Refer Table 6 for recommendations for vaccination of persons with malignancies.

Table 6: Vaccination of persons with malignancies[12]

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 15) 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*

Treatment with chimeric antigen receptor (CAR) T-cell therapy

T lymphocytes with genetically engineered receptors (CAR T-cells) have been developed as anti-cancer medication. CAR T-cells targeting B lymphocytes have been used for malignancies involving B lymphocytes, including acute lymphoblastic leukaemia and B cell lymphoma. The targets include CD 19 (pan B cell marker) and BCMA (a marker involved with B cell development). B lymphocytes (normal and malignant), as well as CD19+ plasma cells (but not CD19- plasma cells) are destroyed if the target is CD19. BCMA CAR T cells, used in myeloma, eliminate plasma cells expressing BCMA[11].

Patients can develop hypogammaglobulinaemia after therapy. Bacterial infections are more frequent before 30 days post treatment with CAR T-cells targeting CD 19/20, whereas infections with respiratory viruses are more common > 30 days[11].

Immunization strategies in CAR T cell therapy[11,12]

Pretreatment

As immune responses diminish immediately after CAR T cell therapy, the only recommendations are for immunization with

the influenza and SARS CoV-2 vaccines, at least 2 weeks before therapy.

Post treatment for adults

Non-live vaccines should be administered ≥ 3 months after therapy, if the CAR T cell treatment is the final therapy, and the patient is in remission. The vaccines include hepatitis A and B (if lacking sero-protection), tetanus, diphtheria and pertussis. Influenza and SARS-CoV-2 immunizations can also commence ≥ 3 months. Live vaccines should be deferred till one year, and the patient should not be immunocompromised.

Data for paediatric cases are not available at present.

Table 7: Vaccination recommendations for adult CAR T recipients, [11,12]

Vaccines	**Consensus guidelines (EBMT/JACIE/EHA, ASH-ASTCT)**
Killed and inactivated vaccines: PCV10 (3 doses) PPSV23 (1 dose)* DTaP (3 doses) HBV (3 doses) HAV (2 doses) COVID-19 (3+ doses) IIV (2 doses) ACYW-135 (2 doses) Hib (3 doses)	≥ 3months after CAR-T therapy AND Demonstrated immune reconstitution AND No ongoing immunosuppression

Live vaccines MMR (2 doses) VZV (2 doses)	≥12 months after CAR-T therapy AND Demonstrated immune reconstitution** AND No ongoing immunosuppression AND No IVIg in prior 8 months

*Minimum 8 weeks after 3rd PVC

** CD4+ >0.2 × 10^9/L, CD19 or CD20+ B cells >0.2 × 10^9/L

EBMT/JACIE/EHA-European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE) and the European Haematology Association (EHA). ASH-ASTCT- American Society of Hematology-American Society of Transplantation and Cellular Therapy

References

1. Altered Immunocompetence. CDC vaccines and immunisations. Updated August, 2023. https://www.cdc.gov/vaccines/hcp/imz-best-practices/altered-immunocompetence.html [Accessed 23.08.2025].
2. Immunisation of immunocompromised persons: Canadian Immunisation Guide. Updated May 2025. https://www.canada.ca/en/public-health/services/ publications/healthy-living/canadian-immunisation-guide-part-3-vaccination-specific-populations/page-8-immunisation-immunocompromised-persons.html. [Accessed 23.08.2025].
3. Kimberlin DW, et al. (ed.) Immunisation and Other Considerations in Immunocompromised Children. Red Book: 2024-2027 Report of the Committee on Infectious Diseases. 33rd ed. American academy of Paediatrics.
4. Vaccination for people who are immunocompromised. Australian Immunisation Handbook, Australian Government Department of Health and Aged Care, Canberra, 2022. https://immunisationhandbook.health.gov.au/contents/ vaccination-for-special-risk-groups/vaccination-for-people-who-are-immunocompromised [Accessed 23.08.2025].
5. Recommended timing of live vaccine administration for people receiving corticosteroids. Australian Immunisation Handbook, Australian Government Department of Health and Aged Care, Canberra, 2022. https://immunisation handbook.health.gov.au/resources/tables/table-

recommended-timing-of-live-vaccine-administration-for-people-receiving-corticosteroids [Accessed 23.08.2025].

6. Jansen MHA, et al. EULAR/PRES recommendations for vaccination of paediatric patients with autoimmune inflammatory rheumatic diseases: update 2021. *Annals of the Rheumatic Diseases*. 2023; 82(1):35-47. doi:10.1136/annrheumdis-2022-222574.
7. Furer V, et al. 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. *Annals of the Rheumatic Diseases.* 2020; 79(1):39-52. doi:10.1136/annrheumdis-2019-215882.
8. Guideline for Vaccinations in Patients with Rheumatic and Musculoskeletal Diseases Guideline Summary. American College of Rheumatology (ACR). 2022. doi: 10.1002/art.42386. Epub.
9. Secondary (acquired) immunodeficiency due to medical conditions. Australian Immunisation Handbook, Australian Government Department of Health, Canberra, 2018, immunisationhandbook.health.gov.au. https://immunisation handbook.health.gov.au/contents/vaccination-for-special-risk-groups/vaccination-for-people-who-are-immunocompromised/secondary-acquired-immunodeficiency-due-to-medical-conditions.
10. Ljungman P. Vaccination of Immunocompromised Hosts. In: Orenstein WA, et al. (eds) Plotkin's Vaccines. 8th ed. Philadelphia, PA: Elsevier. 2021; 1432-1449.
11. Shahid Z, et al. Best Practice Considerations by the American Society of Transplant and Cellular Therapy: Infection prevention and management after Chimeric antigen receptor T cell therapy for hematological malignancies. *Transplantation and Cellular Therapy*. 2024; 30(10):955-969. doi: 10.1016/j.jtct.2024.07.018.
12. Reynolds G, et al. Vaccine schedule recommendations and updates for patients with hematologic malignancy post-hematopoietic cell transplant or CAR T-cell therapy. *Transplant Infectious Diseases*. 2023;251(Suppl 1):e14109. doi: 10.1111/tid.14109.

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CHAPTER 34

IMMUNISATION OF HIV INFECTED PERSONS

Immunisation 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 experience more severe diseases compared to uninfected persons. The antibody response is frequently impaired in PLHIV, since the virus attacks CD4 T cells, which are important in antibody formation. As HIV infection alters immune function, vaccination of PLHIV may not confer the same degree of protection gained by immunocompetent persons. However, many of these vaccines offer protection but the immunity may remain lower and decline more rapidly compared to HIV-negative individuals. To overcome this, some vaccines could be administered with a modified schedule such as more frequent doses and a higher antigen content to improve 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, vaccines should be given before the immune status of the patient is suppressed. Persons with severe immunodeficiency* 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 or after immune reconstitution occurs with ART.

In general, all inactivated vaccines could be administered safely to persons with altered immunocompetence[3]. Live vaccines may pose a risk and should not be given in persons with severe immunosuppression*[1]. However, 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.

* Severe immunosuppression

> 5 years of age - CD4 counts < 200 cells/μL

≤ 5 years of age - CD4 percentage < 15%

General principles of immunisation in HIV-infected children

HIV infected children also have an increased risk of infections and may have more severe illness. Therefore, they should be protected from vaccine-preventable diseases and completing immunisation is important. Vaccines may be less effective in HIV-infected children due to altered immune status with HIV. Therefore, consideration should be given to the most appropriate time for immunisation. It is important to immunise the HIV-infected children prior to the impairment of their immune system or after immune reconstitution occurs with ART.

Table 1: Immunisation schedule for HIV infected children**

Age	Standard schedule	Child with HIV	Remarks
0-4 weeks	BCG	BCG vaccination should be delayed until; ART has been started and the infant is confirmed to be immunologically stable (CD4 > 25%)[4] or confirmed HIV negative	If the mother is HIV positive with a detectable viral load, postpone BCG till HIV is excluded in the infant Neonates born to women of unknown HIV status should be vaccinated as the benefits of BCG vaccination outweigh the risks[4]
On completion of			

2 months	Pentavalent (DTP-HepB-Hib) & OPV - 1st dose	Pentavalent (DTP-Hep B-Hib) + inactivated polio vaccine (IPV) full dose IM***-1st dose Pneumococcal conjugate vaccine (PCV) - 1st dose	OPV and fIPV are not recommended in infants with HIV infection
4 months	Pentavalent & OPV - 2nd dose fractional IPV (fIPV) - 1st dose	Pentavalent) + IPV full dose IM***- 2nd dose PCV - 2nd dose	OPV and fIPV are not recommended in infants with HIV infection
6 months	Pentavalent & OPV -3rd dose	Pentavalent + IPV full dose IM*** - 3rd dose PCV - 3rd dose	OPV is not recommended in infants with HIV infection
9 months	MMR - 1st dose fIPV - 2nd dose	MMR	Should be postponed in severe immunosuppression*
12 months	Live JE	Inactivated JE vaccine, if available Hep A - 1st dose (2nd dose 6-12 months later)	Live JE is not recommended for HIV infected children Children with severe immunosuppression* may have a suboptimal response to Hep A vaccine
13-15 months		Varicella - 2 doses 3 months apart[3] PCV - booster dose	Patients with severe immunosuppression* should not receive the vaccine

18 months	DTP OPV - 4th dose	DTP + IPV full dose IM ***	OPV is not recommended for children with HIV infection
3 years	MMR - 2nd dose	MMR - 2nd dose	Should be postponed in severe immunosuppression*
5 years	DT OPV - 5th dose	DT+IPV full dose IM*** Pneumococcal polysaccharide vaccine[3]	OPV is not recommended for children with HIV infection
10-15 years	HPV - 2 doses (females)	HPV- 0, 6 months) 3 doses (both females and males) (0, 1-2, 6 months)	
10-15 years	aTd	aTd	

** *Adapted from the National Immunisation Schedule*

*** *IPV dose and route - 0.5mL intramuscular*

COVID-19 vaccination for children with HIV infection[5]

Children aged 16-17 years

Children aged 16-17 years with HIV infection should receive two doses of the COVID-19 vaccine at an interval of at least eight weeks apart. Those who have severe immunosuppression* 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 12-15 years with HIV infection should receive two doses of Pfizer BioNTech vaccine at an interval of at least eight weeks. Children aged ≥ 12 years with severe immunosuppression* 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 5-11 years with HIV should receive two doses of the paediatric dose (10 μg) 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 immunisation in HIV infected adults

Live vaccines

- Persons with severe immunosuppression* should not be given live vaccines. Where indicated, vaccination may be considered when immune restoration occurs with ART[1].
- In persons with a moderate immunodeficiency[1], it is important to weigh the risk and benefits before vaccination.
- Co-administration of multiple live vaccines in HIV-infected individuals is not recommended due to issues related to safety, immunogenicity and efficacy. An interval of four weeks between vaccinations is recommended[1].

****Moderate immunodeficiency - CD4 count of 200-300 cells/μL

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. When 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 PLHIV should be prioritized for early vaccination regardless of their CD4 count	All COVID vaccine doses recommended for people without HIV are recommended for persons with a current CD4 count	A booster dose can be taken 4 to 6 months after the completion of the primary vaccination series >200 cells/ µL. For persons with CD4 count of <200 cells/µL, an additional vaccine dose should be administered as part of the extended primary 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	2-3 doses	Every 10 years if at risk	3 doses at 0, 1 and 6 months if the CD4 cell count is < 350 cells/µL and 2 doses at 0 and 6 months if the CD4 cell count is > 350 cells/µL
Hepatitis B	All non-immune	4 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 3 further vaccine doses and retesting	Could be given regardless of the CD4 cell count. Screen HBsAb levels according to initial response
Human papilloma virus	Age and gender related	3 doses of quadrivalent vaccine up to 45 years of age in MSM and up to 40 years in females 0, 1-2 and 6 months apart	None	Could be given regardless of the CD4 cell count

Inactivated polio	To all non-immune	5 doses (at 0, 1, 2 months, 5 years and 10 years)	Every 10 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	2 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 (conjuga ted)	At risk	2 doses 1 month apart	Every 5 years if at risk	Could be given regardless of the CD4 cell count
MMR	To all non-immune	2 doses at least 1 month apart	None	Could be given when the CD4 cell count is > 200 cells/μL
Mpox vaccine	Anyone who is at risk	JYNNEOS vaccine, two doses, given 28 days apart	None	

Pneumoc occal (polysac charide) PPSV23 andpneumo coccal (conjugate) - PCV13/10	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 immunog lobulin + 5 doses of the vaccine IM at 0, 3, 7, 14 and 30 days	None	Could be given regardless of the CD4 cell count Intradermal ARV not recommended for; 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
Tetanus-diphtheria (aTd)	To all non-immune	5 doses at 0, 1, 2 months, 5 years and 10 years	Every 10 years	Could be given regardless of the CD4 count
Tetanus toxoid	To all non-immune	5 doses at 0, 1, 2 months, 5 years and 10 years	Every 10 years	Could be given regardless of the CD4 count
Typhoid Vi capsular polysaccharide	At risk	Single dose	Every 10 years	Could be given regardless of the CD4 count
Varicella	All non-immune	2 doses 3 months apart	None	Could be given regardless of the CD4 count

Yellow fever	At-risk	Single dose	Every 10 years if at risk	Age > 60 years, CD4 cell count is < 200 cells/μL and pregnant women should not receive the vaccine

*Yeast based vaccine 40 μg/dose or 2 doses of 20 μg/dose vaccine

Recommendations for pre-exposure vaccination in HIV-infected adults[1]

COVID-19 vaccine

Despite the differences in the efficacy of the vaccines, there is insufficient data to recommend one vaccine type over another for PLHIV[9]. All PLHIV should receive the recommended doses of vaccines for COVID-19 regardless of their treatment status, nadir or current CD4 cell count, and current viral load. Persons with moderate**** or severe immunosuppression* and may receive one additional dose at least 8 weeks after the last vaccine dose.

In persons 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.

***H influenzae* type b vaccine (Hib)**

PLHIV with the following conditions who are at risk of having an infection, should receive one dose of a Hib-containing vaccine regardless of previous immunisation, 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 PLHIV who are at risk of hepatitis A. All PLHIV serologically negative for hepatitis A should be offered monovalent hepatitis A vaccine.

HAV IgG should be performed at least 1 month after the last dose of vaccination to identify non-responders[6]. Non-responders should be revaccinated.

Hepatitis B vaccine

HIV infection affects the response to the hepatitis B vaccine and the HBs Ab seroconversion strongly correlates with CD4 cell count and viral load. Therefore, to improve the vaccine response it is recommended to revaccinate non-responders once the CD4 count is > 350 cells/μL, suppression of viral load with ART, use higher doses and more frequent vaccine doses. Duration of vaccine-induced protection is unknown in PLHIV. 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 HBs Ab levels 4-8 weeks after the last dose of vaccination.

Ultra-rapid vaccination course (three standard-dose administrations given over 3 weeks) could be considered only in selected patients with CD4 cell counts > 500 cells/μL where there is an imperative need to ensure rapid completion of vaccination and/or where compliance with a full course is doubtful. High-dose vaccination in an ultra-rapid schedule should be avoided due to the lack of safety data[1].

HBsAb level > 100 IU/L is regarded as ideal, whereas a level < 10 IU/L is classified as non-responsive. Individuals with HBsAb levels ≥ 10 but < 100 IU/L should receive one booster dose[1]. Individuals who have HBsAb levels < 10 IU/L after the primary vaccine course should receive three further vaccine doses at monthly intervals. It is preferred 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 to guide subsequent booster doses.

Post Exposure prophylaxis

refer Chapter 11 on hepatitis B vaccine

Human papillomavirus vaccine

HIV-infected individuals are at higher risk of human papillomavirus (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.

All eligible HIV-positive adults who have received fewer than three vaccine doses before the age of 18 years should complete a three-dose vaccination course with quadrivalent HPV.

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.

It is recommended that 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 is suggested 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].

It is suggested to consider HPV vaccination for HIV-positive patients who develop high-grade HPV disease with the aim of potentially reducing the risk of recurrences.

In ART naïve patients with CD4 cell count < 200 cells/μL, vaccination may be postponed until the patient is established on ART. Three doses of the quadrivalent vaccine need to be administered at 0, 1-2 and 6 months to HIV-infected individuals[1]. If the schedule is interrupted, the vaccine series should be completed rather than restarted. 9vHPV can replace quadrivalent vaccine for both men and women once available[1].

Inactivated polio vaccine

Inactivated polio vaccine could produce neutralising antibodies in HIV positive adults and children and in patients with CD4 count < 300 cells/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 and reducing complications in PLHIV.

It is recommended to offer an annual inactivated influenza vaccine to all PLHIV, especially for pregnant women.

Japanese encephalitis vaccine

There is insufficient evidence on the safety, immunogenicity, and clinical efficacy of JE vaccination in HIV-positive adults.

Live JE vaccine is not recommended in HIV-infected patients. 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].

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

There is no evidence to suggest that mumps and rubella are more severe in the HIV setting. However, measles can be life-threatening in people with severe immunosuppression*[1]. There may be no rash, and complications such as pneumonitis and encephalitis may present several months after the initial infection. A history of measles immunisation is not a reliable predictor of measles IgG seropositive status and seropositivity does not guarantee protection.

The MMR vaccine is contraindicated in PLHIV with severe immunosuppression* while it is in generally safe in PLHIV with less profound immunosuppression.

HIV-positive adults should be screened for measles IgG regardless of a history of childhood vaccination. Measles seronegative patients with CD4 cell counts > 200 cells/μL who are clinically stable are offered two doses of the MMR vaccine at an interval of at least 1 month. 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[1].

After a significant exposure to measles, HIV-positive adults be screened for measles IgG within 3 days of exposure and regardless of a history of previous vaccination (although prophylaxis should not be delayed while waiting for the results). A risk assessment be undertaken about the need for and mode of post-exposure prophylaxis, as follows:

- Measles seronegative, CD4 cell count > 200 cells/μL, preferably with stable viral load suppression on ART: MMR vaccine within 3 days of contact or HNIG within 6 days of contact.
- Measles seronegative, CD4 counts < 200 cells/μL: HNIG within 6 days of contact or IVIG up to 18 days after contact

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 > 200 cells/μL and they are not pregnant.

Mpox vaccine

Persons who are at risk of being exposed to mpox or expects they might be exposed should receive the JYNNEOS vaccine. This involves two doses, given 28 days apart. The preferred method is a 0.5 mL subcutaneous injection, but a 0.1 mL intradermal (ID) injection is an acceptable alternative. Live-replicating vaccines should not be given to individuals with HIV, as they are contraindicated[1].

Pneumococcal vaccine

Studies conducted on the clinical efficacy of the pneumococcal polysaccharide vaccine (PPSV23) in HIV infected persons have shown inconsistent findings. 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 pneumococcal vaccine to all PLHIV without a history of pneumococcal vaccination or with unknown vaccination history.

Rabies vaccine

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.

Varicella zoster vaccine

PLHIV 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.

Post exposure prophylaxis

Varicella-zoster immune globulin (VZIG) is recommended for HIV infected individuals following a significant exposure to VZV; close contact with a patient who has active VZV infection.

Persons with severe immunosuppression are susceptible for VZV infection, and should receive VZIG as soon as possible, preferably within 96 hours, but up to 10 days after exposure. Due to the high cost of VZIG, it is reasonable to check VZV serology before administering VZIG 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 PLHIV has not been studied and is not recommended[10].

Yellow fever vaccine

PLHIV aged < 60 years and CD4 cell count > 200 cells/μL who are planning to travel to countries with 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].

References

1. BHIVA guidelines on the use of vaccines in HIV-positive adults. British HIV Association. 2015. [cited 2019 Jul 28]. http://www.bhiva.org/documents/Guidelines/Vaccination/2015-Vaccination-Guidelines
2. Calles NR, et al. Immunisation for children with HIV/AIDS. [cited 2019 Jul 28]. http://bipai.org/Curriculums/HIV-Curriculum/Immunisations-for-Children-with-HIV/AIDS.aspx
3. Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children. AIDSinfo. [cited 2019 Aug 13]. http://aidsinfo.nih.gov/guidelines

4. BCG vaccines: WHO position paper, February 2018. *Weekly Epidemiological Record*. 2018; 93(8):73–96.
5. Immunisation against infectious disease. Salisbury D, et al. Eds. Department of Health. United Kingdom. 2021 [cited 2021 Aug 21]. https://assets.publishing.s ervice.gov.uk/government/uploads/system/uploads/attachment_data/file/1034373/Greenbook-cover-Nov21.pdf
6. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Centers for Disease Control and Prevention; National Institutes of Health; HIV Medicine Association of the Infectious Diseases Society of America; 2017. [cited 2019 Apr 4]. https://aidsinfo.nih.gov/ contentfiles/lvguidelines/adult_oi.pdf
7. BHIVA guidelines on immunisation for adults with HIV SARS-CoV-2 (COVID-19). British HIV Association. 2021. [cited 2022 Jul 20]. https://www.who.int/ news-room/questions-and-answers/item/coronavirus-disease-(covid-19)-covid-19-vaccines-and-people-living-with-hiv
8. Kroon FP, et al. Antibody response after influenza vaccination in HIV-infected individuals: a consecutive 3-year study. *Vaccine*. 2000;18(26):3040–9. https://doi.org/10.1016/S0264-410X(00)00079-7
9. Pneumococcal vaccine timing for adults. Centers for Disease Control and Prevention. [cited 2019 Jun 10]. https://www.cdc.gov/vaccines/vpd/pneumo/ downloads/pneumo-vaccine-timing.pdf
10. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: Varicella-zoster virus. National Institutes of Health; Centers for Disease Control and Prevention; HIV Medicine Association of the Infectious Diseases Society of America. [cited 2023 Jan 24]. https://clinicalinfo. hiv.gov/en/guidelines/hiv-clinical -guidelines-adult-and-adolescent-opportunistic-infections/varicella-zoster

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CHAPTER 35

IMMUNISATION IN OTHER SPECIAL CLINICAL CIRCUMSTANCES

Preterm and low birth weight infants

Preterm infants and infants of low birth weight (< 2500 g) 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 immunisations 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 immunisation is at present available only for hepatitis A and B, all patients requiring repeated transfusions should be immunised 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 immunoglobulim	IV	3 mL/kg	150	6
Hepatitis B immunoglobulim as hepatitis B prophylaxis	IM	100 IU or 400 IU	10	3
NHIG for treatment of idiopathic thrombocytopenic purpura	IV	NA	400	8
NHIG for treatment of idiopathic thrombocytopenic purpura	IV	NA	1000	10
NHIG 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 various doses	IV	NA	300-400	9
Rh (D) immunoglobulin (anti-D)	IM	NA	NA	0
Tetanus immunoglobulin as tetanus prophylaxis	IM	250 IU (given within 24 hours of injury)	10	3
Tetanus immunoglobulin 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, immunisations 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 Immunisation 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 lung disease, 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 PCV* 1 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

*PCV10 or PCV13

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)
- RSV - recommended for adults > 75 years or adults aged 60-74 years with heart disease to protect against lower respiratory disease that can result in hospitalization and death. Chronic cardiovascular disease includes heart failure, coronary artery disease, congenital heart disease and excludes isolated

hypertension[8]. Current guidance recommends a single dose, rather than annual vaccination[8]

- Covid-19 - yearly boosters with current vaccine

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).

In addition, RSV vaccine is recommended (in those over 60 years) for patients with chronic obstructive pulmonary disease, emphysema, asthma, interstitial lung disease, and cystic fibrosis[8].

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 *Haemophilus 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 immunised 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 immunisation 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 immunisation is commenced early in the disease process[12].

Children should receive all routine immunisations 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[9,12]. For children < 16 years, double the routine dose should be administered[13]. 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)[14]. In CKD, an anti-HBs titre of above 100 mIU/mL is regarded as protective[12]. 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[12]. Patients on haemodialysis should be tested annually, and a booster given if the titre falls < 10 mIU/mL[14].

- 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 32)

- Hepatitis A, pneumococcal, inactivated influenza, Tdap vaccines should be administered.
- Hepatitis B immunisation

  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)[14]. In general, an anti-HBs titre of above 100 mIU/mL is regarded as protective[12]. 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[12]. Patients on haemodialysis should be tested annually, and a booster given if the titre falls < 10 mIU/mL[11,14].
- 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.
- RSV vaccine is recommended in those > 75 years, as well as in patients with end stage renal disease or dependence on haemodialysis or other renal replacement therapy aged 60-74 years[8].

Children with nephrotic syndrome[12]

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 33). 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-immunised children should be vaccinated with live vaccines as soon as possible, especially varicella zoster virus[15]. Following close contact with varicella infection, non-immune children on immunosuppressive agents should be given varicella-zoster immunoglobulin if available. Immunise healthy household contacts with live vaccines to minimise 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 immunised

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).
- RSV vaccine is recommended to those > 75 years, and in patients 60-74 years with cirrhosis[8].

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; immunisation 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).
- RSV vaccine is recommended to those > 75 years, and in patients 60-74 years with diabetes complicated by chronic kidney disease, neuropathy, retinopathy, or other end–organ damage or requiring treatment with insulin or sodium–glucose cotransporter 2 (SGLT2) inhibitor[8].
- 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 immunised even if they have had zoster or have an unknown chickenpox history.

Table 3[21]. Recommended Child and Adolescent Immunisation Schedule by Medical Indication

Vaccine						
	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. influenza*e type b (Hib)						
Pneumococcal conjugate						
Inactivated poliovirus						
Influenza (inactivated)						
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

Recommended for persons with an additional risk factor for which the vaccine would be indicated

Children with a personal or family history of seizures

Infants and children with a history of seizures should be given routine immunisation 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 immunisation 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 immunisation[2].

Healthcare personnel

Healthcare personnel should protect themselves, their families and patients by ensuring that they have received all appropriate immunisations. All those without evidence of immunity should receive vaccines that were not given in the primary immunisation 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 immunisations according to the routine schedules, may not be immune. To ensure age-appropriate immunisation, all children should have a routine appointment at 11-12 years of age for administration of appropriate vaccines.

Tdap or aTd and HPV vaccines should be administered at 11-12 years of age.

During adolescent visits, immunisation status should be reviewed and deficiencies rectified. It is imperative that adolescents and young adults intending to travel abroad should have their immunisation status reviewed according to their travel plans at least 2-6 months prior to departure, to allow time to administer required vaccines[2].

References:

1. Ginige, S, editor. Immunisation Handbook. 3rd Edition. Epidemiology Unit, Ministry of Health, Sri Lanka; 2012. p 265.
2. Kimberlin DW, et al. eds. Red Book 2021-2024. Report of the Committee on Infectious Diseases. 32nd Edition. American Academy of Paediatrics. 2021.
3. Australian Technical Advisory Group on Immunisation (ATAGI). Australian Immunisation Handbook, Australian Government Department of Health and Aged Care, Canberra, 2022. immunisation handbook.health.gov.au. [Accessed on 15th October 2022].
4. Grohskopf LA, et al. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunisation Practices - United States, 2022–23 Influenza Season. *Morbidity and Mortality Weekly Report:* Recommendations and Reports 2022; 71(No. RR-1):1–28.
5. Pneumococcal Vaccination: Summary of who and when to vaccinate. Immunisation schedules. Centres for Disease Control. 2026. https://www. cdc.gov/vaccines/vpd/pneumo/hcp/who-when-to-vaccinate.html [Accessed 4th February 2023].
6. Ministry of Health General Circular No:01-26/2012
7. Fountoulaki K, et al. Beneficial effects of vaccination on cardiovascular events: Myocardial infarction, stroke, heart failure. *Cardiology* 2018; 141:98–106.
8. Healthcare Professionals: Immunisation Schedules. Centres for Disease Control. 2025. https://w https://www.cdc.gov/vaccines/hcp/imz-schedules/index..html. [Accessed 6th February, 2026].ww.cdc.gov/vaccines/hcp/imz-schedules/index..html. [Accessed 6th February, 2026].
9. Immunisation of persons with chronic diseases: Canadian Immunisation Guide. https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunisation-guide-part-3-vaccination-specific-populations/page-7-immunisation-persons-with-chronic-diseases.html#p3c6a5.[Accessed on 4th February 2023].

10. Cochlear Implants and Vaccination Recommendations. Centres for Disease Control. 2026. https://www.cdc.gov/vaccines/vpd/mening/public/dis-cochlear-faq-gen.html.[Accessed on 6th February 2026].
11. Ma BM, et al. Vaccination in patients with chronic kidney disease-Review of current recommendations and recent advances. *Nephrology*. (Carlton). 2021; 26(1):5-11
12. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. *Kidney International*. 2021; 100(4S):S1-S276
13. Hepatitis B vaccine: Canadian Immunisation Guide. Government of Canada. 2022. https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunisation-guide-part-4-active-vaccines/page-7-hepatitis-b-vaccine.html#higher-vaccine [Accessed 6th February, 2026]
14. Immunisation against infectious disease. UK Health Security Agency. January 2021. https://www.gov.uk/government/publications/immunisation-against-infectious-disease-the-green-book-front-cover-and-contents-page.[Accessed 15th October 2022]
15. Alukal JJ, et al. Vaccination in Chronic Liver Disease: An Update. *Journal of Clinical and Experimental Hepatology*. 2022; 12(3):937-94
16. Valour F, et al. Vaccination in adult liver transplantation candidates and recipients. *Clinics and Research in Hepatology and Gastroenterology*. 2020; 44(2):126-134. doi: 10.1016/j.clinre.2019.08.007
17. Immunisation schedules. Centres for Disease Control. 2023. https://www.cdc. gov/vaccines/schedules/hcp/imz/adult.html.
18. Schillie S, et al. Prevention of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunisation Practices. *Morbidity and Mortality Weekly Report*. 2018; 67(1): 1-3
19. Saadatian-Elahi M, et al. Diabetes as a risk factor for herpes zoster in adults: A systematic literature review. *Diabetes Research and Clinical Practice*. 2020; 159:107983. doi: 10.1016/j.diabres.2019.107983.
20. Dooling KL, et al. Recommendations of the Advisory Committee on Immunisation Practices for Use of Herpes Zoster Vaccines. *Morbidity and Mortality Weekly Report*. 2018; 67 (3): 103.

21. Child and Adolescent Immunisation Schedule by Medical Indication. Centres for Disease Control. 2025. https://www.cdc.gov/vaccines/hcp/imz-schedules/child-adolescent-medical-indication.html. [Accessed 18th March, 2026]

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CHAPTER 36

PASSIVE IMMUNISATION

Introduction

Passive immunisation 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[1]. Transferred antibodies will protect a term infant from certain diseases within the first few months after birth.

Passive immunisation 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 - When there is a high risk of exposure or following exposure to a specific infectious agent, where severe consequences are anticipated or when time does not permit adequate protection by active immunisation 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[2].

Types of products

a) 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 immunisation 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**.

Indications

- ***Hepatitis A prophylaxis***[2,4]

HNIG could be used as both pre-exposure and post-exposure prophylaxis. HNIG alone is used for individuals in whom the vaccine is contraindicated (e.g. life-threatening allergic reaction to a previous dose of hepatitis A vaccine, or allergy to any vaccine component).

For fully susceptible persons older than 60 years, immunocompromised patients of all ages, patients with chronic liver disease or other chronic medical conditions, HNIG may be administered as pre- or post-exposure prophylaxis in addition to the hepatitis A vaccine[5]. Criteria for "fully susceptible" is defined as no history or evidence of hepatitis A vaccination and no reliable history of hepatitis A infection or laboratory-confirmed hepatitis A (previous anti-HAV IgG positive, or HAV RNA positive)[5].

Although effectiveness is greater when administered soon after exposure, HNIG could be given up to 2 weeks. Fully susceptible persons with chronic liver disease or pre-existing chronic hepatitis B or C infection are at risk of severe disease and may be offered HNIG up to

28 days post exposure[5]. The dose should be decided according to the manufacturers instruction and once given, protection lasts 4-6 months[6].

This product is not available in Sri Lanka at present.

(refer Chapter 10)

- ***Measles prophylaxis***[3,7]

HNIG could be used following exposure to measles in infants less than 6 months of age and in mild to moderately immunocompromised children with HIV who lack immunity to measles virus. However, in most HNIG preparations an accepted minimum level of measles antibody is not required. Therefore, the present preparations are possibly less effective compared to earlier preparations[7]. In addition, 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[7].

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[2].

- ***Rubella prophylaxis***[3]

Usefulness of HNIG in prevention of rubella is uncertain.

b) Hyperimmune globulins/specific immunoglobulins

Products could be either homologous or heterologous[1].

Homologous hyperimmune globulins - These are 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[8].

(Refer Chapter 11)

- ***Rabies immunoglobulin*** – (refer Chapter 19)
- ***Tetanus immunoglobulin (TIG)***

TIG should be considered in individuals, who have incomplete vaccination or unknown vaccine status, presenting with[3],

- 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 receive TIG, regardless of their history of tetanus immunisations. TIG is administered intramuscularly at a dose of 250 IU. The dose may be increased to 500 IU if the injury occurred more than 24 hours ago, there is high risk of heavy contamination or is due to a burn[9]. 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].

- ***Varicella zoster immunoglobulin (VZIG)***

  Indications for VZIG following a significant exposure[10],

  - Newborn of a mother who developed chickenpox (not zoster) within 7 days before or within 7 days after delivery
  - 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

- Children with congenital or acquired immunodeficiency (e.g. leukaemia, lymphoma and other malignant neoplasms affecting the bone marrow or lymphatic system, receiving a high-level immunosuppressives, infected with HIV, haematopoietic stem cell transplant recipients) may receive either oral antivirals or VZIG as prophylaxis

  Individuals receiving regular IVIG do not require VZIG if the last dose was given within 3 weeks

VZIG should be given as early as possible within 10 days, according to the manufacturer's instructions. If VZIG is unavailable by 96 hours immediate use of IVIG is advised[11].

Any person who receives VZIG and does not develop the infection, should receive varicella vaccine subsequently, provided there are no contraindications for live vaccines. Immunisation should be delayed until 5 months after VZIG[1].

Heterologous hyperimmune globulin – These are 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)
- ***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 internalised 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[11].

- ***Diphtheria antitoxin[12]***

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. Although hypersensitivity reactions could occur, the once universally

recommended skin prick testing prior to infusion is no longer recommended. A single dose of diphtheria antitoxin with the dose based on disease severity and time since onset is recommended by the WHO. Antitoxin, probably is of no value in cutaneous disease.

c) 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. The 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 varies between products and lots of the same product[2].

Indications

Replacement therapy

All IVIG products are licensed to prevent serious bacterial infections in primary or secondary humoral immunodeficiency and combined immunodeficiencies.

Measles post-exposure prophylaxis[7]

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 $\geq$ 30 kg body weight).

Patients who have received a HSCT within the past 12 months and patients with severe inborn errors of immunity need 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 since diagnosis of the immunosuppressive condition/ after end of treatment with

immunosuppressive therapy or IgG negative in a rapid test carried out within 72 hours of exposureor IgG test within 72 hours is not possible[7].

- Patients on or after completing immunosuppressive chemotherapy for acute lymphoblastic leukaemia (ALL)
- Patients with lymphoproliferative disorders
- Patients who have received solid organ transplants
- Patients more than 12 months after receiving a haematopoietic stem cell transplant (HSCT)
- Patients receiving or within 6 months of completing treatment with biologics (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 an IgG test, 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[7]. Where a second exposure occurs more than 3 weeks after a first dose of immunoglobulin, a further dose of immunoglobulin needs 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 6 months between IVIG and MMR vaccine.

Tetanus

IVIG could be given at a dose of 200-450 mg/kg for treatment of tetanus when hyperimmune globulin is not available[3]. 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 there is limited data to support this. 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 or 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 200 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[10]. However, IVIG is not routinely tested for varicella antibodies and the effectiveness in post-exposure prophylaxis is uncertain[3].

d) 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 makes it inadequate for prophylactic or therapeutic use in acute infections[1].

e) 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. Advantages of these preparations are high specific activity, standardised potency, unlimited availability and minimal biohazard potential compared to immunoglobulin. However, these have monovalent specificity and single isotype compared to polyvalent specificity and multiple isotypes with different effector functions in polyclonal preparations. Therefore, there is a potential for selection of escape mutants[3].

Monoclonal antibody products are available for the prevention of respiratory syncytial virus (RSV) infection. (refer Chapter 20).

Several other monoclonal antibodies for treatment of infection with Zaire ebolavirus (ansuvimab, mab114, atoltivimab, maftivimab, odesivimab), for reduction of recurrences of *Clostridium difficile* infection (bezlotoxumab) and treatment of inhalation anthrax (obiltoxaximab, raxibacumab) are licensed for use in the USA.

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 headache.

Precautions[3]

- Immunoglobulins should be administered cautiously to individuals with a 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 thrombocytopaenia and coagulation disorders.

References

1. Wodi AP, et al. Principles of vaccination. In: Centers for Disease Control and Prevention. *Epidemiology and prevention of vaccine-preventable diseases*. 14th ed. Washington (DC): Public Health Foundation; 2021.
2. Kimberlin DW, et al, editors. *Red Book: report of the Committee on Infectious Diseases*. 33rd ed. Itasca (IL): American Academy of Pediatrics; 2024.
3. Slifka MK, et al, editors. *Plotkin's vaccines*. 8th ed. Philadelphia (PA): Elsevier; 2021.
4. Nelson NP, et al. Prevention of hepatitis A virus infection in the United States: recommendations of the Advisory Committee on Immunisation Practices, 2020. *Morbidity and Mortality Weekly Review*, *Recommen dations and Reports*. 2020; 69(1):1.

5. Public health control and management of hepatitis A: updated guidance; UK Health Security Agency. 2024. https://assets.publishing.service.gov.uk/media/65ccdbbd1d93950012946677/Hepatitis-A-guidance-13-february-2024.pdf [Accessed 19.03.2025].
6. Ramsay M, editor. Hepatitis A. In: *Immunisation against infectious disease (Green Book)*. UK Health Security Agency; 2021. Chapter 17.
7. National measles guidelines; UK Health Security Agency. 2024. https://www.gov.uk/government/publications/national-measles-guidelines [Accessed%2019.03.2025].
8. Schillie S, et al. Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunisation Practices. *Morbidity and Mortality Weekly Review*. 2018; 67(1):1–31.
9. Liang JL, et al. Prevention of pertussis, tetanus, and diphtheria with vaccines in the United States: Recommendations of the Advisory Committee on Immunisation Practices (ACIP). *Morbidity and Mortality Weekly Review*. 2018; 67(2):1–44.
10. Breuer J, et al. Guidelines on post-exposure prophylaxis (PEP) for varicella or shingles. UK Health Security Agency; 2025. https://www.gov.uk/government/publications/post-exposure-prophylaxis-for-chickenpox-and-shingles/guidelines-on-post-exposure-prophylaxis - pep-for-varicella-or-shingles-january-2023[Accessed 19.03. 2025].
11. Rao AK, et al. Clinical guidelines for diagnosis and treatment of botulism, 2021. *Morbidity and Mortality Weekly Report*. 2021; 70(RR-2):1–30.
12. Clinical management of diphtheria. Geneva: WHO; 2024. https://iris.who. int/bitstream/handle/10665/375887/WHO-DIPH-Clinical-2024.1-eng

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CHAPTER 37

ADVERSE EVENTS FOLLOWING IMMUNISATION (AEFI)

Immunisation is considered as one of the most cost-effective public health interventions for protecting the individual and the public from vaccine preventable diseases (VPDs). Immunisation has saved millions of lives globally. Modern vaccines are both safe and effective.

Vaccines are biological products administered to individuals to induce immunity and provide protection against specific diseases. These products are formulated together with excipients, such as adjuvants, to enhance their effectiveness. As with all medicinal products, vaccines may occasionally cause adverse events following immunisation (AEFI). The majority of these events are minor and self-limiting, while serious reactions are rare. Nevertheless, robust systems should be in place to monitor AEFI, identify potential risks, and implement timely regulatory actions on the products where necessary, thereby ensuring vaccine safety and maintaining public confidence in immunisation programmes[1].

The majority of serious adverse events reported following immunisation are coincidental and not related to the vaccine itself. In some instances, however, they may result directly from the vaccine or from errors in its storage, handling, or administration[1].

Irrespective of the cause, when AEFIs occur, they can undermine public confidence and lead to vaccine hesitancy, with parents refusing further immunisation for their children. This in turn increases their susceptibility to VPDs, many of which are disabling and potentially life-threatening.

Surveillance of AEFI, through the systematic collection, analysis, and use of data on events following immunisation, provides essential information to guide timely action, sustain public trust, and ensure the smooth functioning of the National Immunisation Programme. Vaccine pharmacovigilance, including AEFI surveillance, should

therefore be an integral component of all immunisation programmes. It facilitates appropriate case management, prevents inappropriate responses, and ensures that genuine safety signals are identified and acted upon.

To strengthen vaccine acceptance and improve the quality of immunisation services, AEFI surveillance must be fully integrated into both public and private sector immunisation services in the country[1].

Definition of AEFI

An AEFI is any untoward medical occurrence which follows immunisation 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, abnormal laboratory finding, symptom or disease.

Reported adverse events could either be true adverse events, resulting from the vaccine or the immunisation process, or coincidental events that are not due to the vaccine or immunisation process, but are temporally associated with immunisation[2].

The five categories of AEFI as defined by the Council for International Organisations of Medical Sciences (CIOMS) and WHO based on the causes are described in Table 1.

Table 1: Cause specific categorisation of adverse events following immunisation (CIOMS/WHO, 2012)[2]

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.

Immunisation error-related reaction	An AEFI that is caused by inappropriate* vaccine handling, prescribing or administration and thus by its nature is preventable
Immunisation anxiety-related reaction/ Immunisation stress related response (ISRR) [3]	An AEFI arising from anxiety about the immunisation.
Coincidental event	An AEFI that is caused by something other than the vaccine product, immunisation error or immunisation anxiety.

***** *"Inappropriate" refers to usage (handling, prescribing and administration) other than what is licensed and recommended in a given jurisdiction based on scientific evidence or expert recommendations.*

Vaccine reactions

Based specifically on 1) cause and on 2) seriousness and frequency, vaccine reactions may be grouped into two broad categories:

1. Cause-specific vaccine reactions:
    a. vaccine product-related reactions
    b. vaccine quality defect-related reaction
2. Vaccine reactions by seriousness and frequency:
    a. common or minor reactions
    b. rare or serious reactions

Vaccine product–related reactions are usually rare and may result from immune-mediated mechanisms (e.g. anaphylaxis) or replication of live vaccine organisms (e.g. vaccine-associated poliomyelitis after OPV). Certain high-risk individuals may be more susceptible, although such reactions do not occur in most vaccine recipients.

Vaccine quality defect–related reactions arise from problems during vaccine manufacturing or defects in the administration device. Examples include incomplete inactivation of wild poliovirus or contamination during production. The introduction of Good

Manufacturing Practices (GMP) and strengthened national regulatory authorities has made these reactions extremely rare.

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 (Table 2).

Table 2: Frequency of occurrence of reported adverse reactions[1]

Frequency category	Frequency in rate	Frequency in %
Very common	≥1/10	≥10%
Common (Frequent)	≥1/100 and < 1/10	≥1% and <10%
Uncommon (Infrequent)	≥1/1,000 and < 1/100	≥0.1% and <1%
Rare	≥1/10,000 and <1/1,000	≥0.01 and <0.1%
Very rare	<1/10,000	< 0.01

Common minor reactions

These are caused when the recipient's immune system reacts to antigens or components of the vaccine (e.g. aluminium adjuvant, stabilisers or preservatives). Minor AEFI could be local or systemic. Local reactions include pain, swelling and redness at the injection site. Systemic reactions include fever, malaise and irritability. Their frequency varies by the type of antigen. Local reactions are reported very commonly (> 10%) with whole-cell DTP. Fever is a very common (> 10%) systemic reaction reported for most antigens. For live attenuated vaccines such as measles/MMR and OPV, the systemic reactions can occur from vaccine virus infection. Measles vaccine can cause fever, rash and/or conjunctivitis but this is very mild compared to "wild" measles. However, it can be serious, and even fatal, for severely immunocompromised individuals. Systemic reactions from OPV are uncommon and affect less than 1% of vaccinees with diarrhoea, headache and/or muscle pain.

A safe and good quality vaccine reduces these reactions to a minimum while producing the best possible immunity. The occurrence of minor reactions is expected and observed with all vaccines. However, if the

observed vaccine reaction rate is significantly higher than the expected vaccine reaction rate for any vaccine, an investigation is needed to explain this[3].

Severe and serious vaccine reactions

An AEFI is considered serious if it:

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

Some examples are seizures, thrombocytopaenia, hypotonic hyporesponsive episodes (HHE), inconsolable crying and anaphylaxis. Most of the rare and more serious vaccine reactions do not lead to long-term problems.

In contrast, "severe" is used to describe the intensity of a specific event (as in mild, moderate or severe). The event itself, however, may be of relatively minor medical significance. Severe AEFI could be disabling but is rarely life-threatening. For example, fever is a common and relatively minor medical event but, according to its severity, it may be graded as mild, moderate or severe.

Prevention and treatment of vaccine reactions

Vaccines are very rarely contraindicated. However, it is important to check for contraindications to avoid serious reactions.

Advice should be given to parents on managing the common minor reactions, in addition to instructions on seeking proper medical care if there are more serious symptoms. Such action will help to reassure parents about immunisation and prepare them for common reactions. Early medical care by a qualified clinician for serious reactions will minimise any unwanted outcome and ensure early recovery.

Vaccine anaphylaxis is very rare. However, it is recommended that preparedness to provide emergency treatment for anaphylaxis is necessary in all clinic settings. All immunisation providers need to be trained and develop competence in recognising and managing anaphylaxis.

Immunisation error related reactions

These are adverse events that result from inappropriate practices during handling, storage, prescribing, reconstitution, preparation, and/or administration of a vaccine. These may include:

- inappropriate transport, storage or handling of the vaccine
- use of a product after the expiry date
- failure to adhere to a contraindication
- failure to adhere to vaccine indications or prescription (dose, route, site, age)
- use of an incorrect diluent or administration of a product other than the intended vaccine
- incorrect sterile technique or inappropriate procedure with a multidose vial

Immunisation error-related reactions are preventable. The identification and correction of these errors in a timely manner are, therefore, of great importance.

To avoid/minimise immunisation errors, the following should be noted:

- the cold chain should be maintained properly at all levels
- vaccines must be reconstituted only with the diluents supplied by the manufacturer
- reconstituted vaccine should be used within six hours after reconstitution; it must be discarded at the end of each immunisation session and should never be retained
- no other medicines or substances should be stored in the refrigerator where vaccines are stored

- health care workers must be adequately trained on immunisation and closely supervised to ensure that proper procedures are followed
- careful epidemiological investigation of an AEFI should be conducted to identify the cause and to correct immunisation practices
- adequate attention must be given to contraindications and prior to immunisation

Immunisation anxiety (Immunisation stress related responses - ISRR)

This category describes a range of signs and symptoms that may occur before, during, or after vaccine administration as a response to stress or anxiety. Common manifestations include fainting, palpitations, and hyperventilation, while less common reactions may include syncopal hypoxic convulsions. These events are not caused by the vaccine itself, but are related to the process of injection.

Coincidental events

Coincidental events are health events that occur after immunisation but are not caused by the vaccine, arising from a chance temporal association. Such events are inevitable, given the large number of vaccine doses administered, and may still need investigation since the public, parents, or media may incorrectly attribute them to vaccination. Proper investigation helps dispel misconceptions, reassure the community, and maintain confidence in the immunisation programme.

Vaccine adverse reactions previously unknown or partially known are called “signals”. All signals need a comprehensive scientific evaluation to establish causality.

AEFI surveillance

AEFI may be detected in both government and private medical institutions when patients seek treatment. The main service points likely to encounter AEFI cases include outpatient departments, paediatric wards, and surgical wards.

All identified AEFI should be documented by the treating clinician in the relevant cage of the Child Health Development Record (CHDR) and the notifiable AEFI should be reported to the Medical Officer of Health (MOH) of the patient's area of residence, with copies sent to the Regional Epidemiologist and the Epidemiology Unit. Notification of AEFI is the responsibility of the treating clinician[4].

The list of notifiable AEFI is provided in Annex IV, and the standard notification form to be used by both government and private institutions/clinicians is included in Annex IV.

For the purpose of surveillance, the AEFI (irrespective of the cause) occurring within 30 days of administration of a vaccine should be notified. If necessary, any AEFI with an onset beyond 30 days of vaccination may also be notified[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 (011-2695112), fax (011-2696583), or by email (chepid@sltnet.lk). All deaths suspected to be linked with immunisation require a post-mortem investigation performed by a Consultant Judicial Medical Officer[5].

Anaphylaxis reactions following immunisation 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 V).

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 immunisation. 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 the MOH and the Regional Epidemiologist of patients' residential area and to the Epidemiology Unit by the health care provider and local agent of the

relevant vaccine. Any death following administration of such a vaccine should be reported to both NMRA and the Epidemiology Unit, within 24 hours[4].

References

1. Global manual on surveillance of adverse events following immunisation. Geneva: World Health Organization; 2019. https://apps.who.int/iris/handle/%2010665/206144
2. Definitions and applications of terms for vaccine pharmacovigilance. Geneva: CIOMS/WHO; 2012. https://cioms.ch/publications/product/definitions-and-applications-of-terms-for-vaccine-pharmacovigilance/
3. Causality assessment of an adverse event following immunisation (AEFI): user manual for the revised WHO classification. 2nd ed. Geneva: World Health Organization; 2019.
4. National guidelines on immunisation safety surveillance. 2nd ed. Sri Lanka: Epidemiology Unit, Sri Lanka. 2016. https://www.epid.gov.lk/storage/%20post/pdfs/en_647d8a63b4aef_aefi_covid_19.pdf
5. Guidelines on paediatric autopsies on death following immunisation. General Circular No. 01-25/2012. 2012. Director General of Health Services, Ministry of Health.

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CHAPTER 38

MANAGEMENT OF ANAPHYLAXIS FOLLOWING IMMUNISATION

Introduction

Anaphylaxis is a serious systemic hypersensitivity reaction that is usually rapid in onset and may cause death. Severe anaphylaxis is characterised by potentially life-threatening compromise in airway, breathing and/or circulation, and may occur without typical skin features or circulatory shock being present[1]. The incidence of anaphylaxis following immunisation is rare, estimated to be 1-10 cases per million doses[2]. The onset is generally within an hour after immunisation but may be delayed for up to 12 hours[2]. It is usually due to allergy to excipients. These include egg (yellow fever vaccine), gelatin (usually MMR, varicella, live JE and yellow fever vaccines)[3] and bovine serum albumin (BSA) (MMR, varicella, live JE, rabies vaccines)[4]. Patients with allergy to cow's milk or red meats may be allergic to vaccines containing gelatin or BSA[3,4]. In addition, allergy to red meat due to galactose-α-1, 3-galactose (alpha-gal), has been implicated in allergy to MMR and varicella[5]. Initial reports of increased anaphylactic reactions to the mRNA vaccines were probably due to immunisation stress–related responses (ISRR)[6]. Complement activation related pseudo allergy (CARPA)[6] and other complement mediated reactions, and allergy to polyethylene glycol have been implicated as well, but there is no convincing evidence[7].

Vaccines stimulate an immune response to cause protection. Hence, the majority of adverse events after vaccination are due to this immune response and are not allergic. Although anaphylaxis following immunisation is rare, fainting (vasovagal episode) before, during or within minutes of vaccination is relatively common and maybe be mistakenly diagnosed as anaphylaxis. The features useful in differentiating a fainting attack from anaphylaxis are given in Table 1.

Table 1. Differences between a fainting attack and anaphylaxis[8]

Adapted from Resuscitation Council UK with permission

Clinical Feature	Fainting attack	Anaphylaxis
Onset	Over seconds	Over minutes to hours
Resolution	Usually rapid on lying flat, without additional treatment	Over minutes to hours
Airway		
- Airway swelling	Absent	May be present
- Hoarseness	Absent	May be present
- Stridor	Absent	May be present
Breathing		
- Respiration	Shallow, not laboured	Increased respiratory rate and/or work of breathing
Wheeze/persistent cough	Absent	May be present
Circulation-		
- Heart rate	Usually slow, rarely normal	Tachycardia common (but alone does not indicate anaphylaxis)
- Pulse	Central pulse usually palpable	Low-volume central pulse
- Blood pressure	Usually transiently low	Persistent hypotension
Disability- Consciousness	Dizziness, transient loss of consciousness Improved by lying flat	Dizziness, loss of consciousness persistent despite lying flat
Exposure (Skin)	Often pale/clammy	Flushed, itchy, urticaria/hives, angioedema

Clinical diagnostic criteria for anaphylaxis[1,8]

Anaphylaxis is highly likely when any one of the following two criteria are fulfilled:

Criterion 1

Acute onset of an illness (minutes to several hours) with simultaneous involvement of the skin, mucosal tissue, or both (e.g. generalised hives, pruritus or flushing, swollen lips-tongue-uvula), and at least one of the following:

a) Respiratory compromise (e.g. dyspnoea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxaemia).

b) Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g. hypotonia [collapse], syncope, incontinence).

c) Severe gastrointestinal symptoms (e.g. severe crampy abdominal pain, repetitive vomiting), especially after exposure to non-food allergens.

Criterion 2

Acute onset of hypotension 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 typical skin involvement.

Persistent anaphylaxis is highly likely when the following criterion is fulfilled[9]:

- Presence of symptoms and/or examination findings that fulfil anaphylaxis criteria that persist for at least 4 hours.

Refractory anaphylaxis is highly likely when both of the following 2 criteria are fulfilled[9]:

1. Presence of anaphylaxis after appropriate adrenaline (epinephrine) dosing and symptom-directed medical management (e.g. intravenous fluid bolus for hypotension).
2. The reaction has been treated with 3 or more appropriate doses of adrenaline (or initiation of an intravenous adrenaline infusion).

Biphasic anaphylaxis is highly likely when all the 4 criteria are fulfilled[9]:

1. New or recurrent symptoms and/or examination findings that fulfil anaphylaxis criteria
2. Initial symptoms and examination findings have completely resolved before the onset of new or recurrent symptoms or examination findings.
3. Absence of allergen or trigger re-exposure.

New or recurrent symptoms or examination findings occur within 1 to 48 hours from complete resolution of the initial symptoms or examination findings.

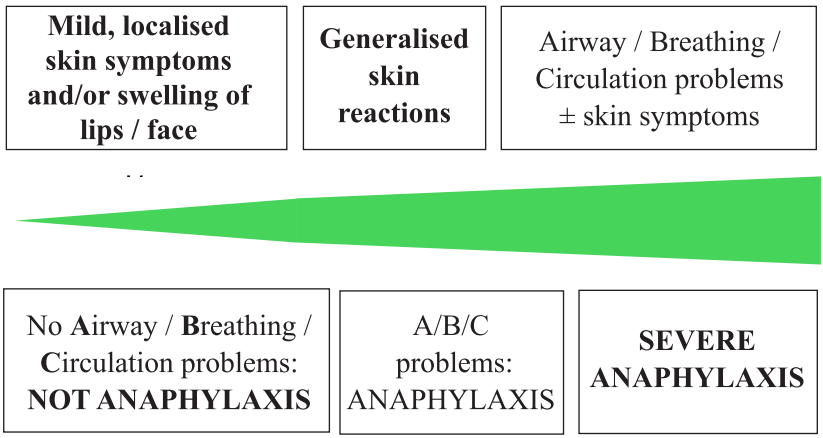


Figure 1: Signs and symptoms of allergic reactions and spectrum of severity of allergy symptoms (Reproduced with permission from Resuscitation Council UK)[8]

Anaphylaxis is a clinical diagnosis and the key to diagnosis involves early pattern recognition: ***Sudden onset of the characteristic symptoms and signs within minutes to hours after exposure to a vaccine.***

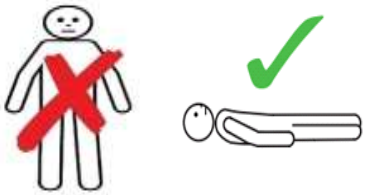
Table 1: Airway, breathing and circulation problems

Airway problems	Breathing problems	Circulation problems
• Airway swelling e.g. throat and tongue swelling (pharyngeal / laryngeal oedema) causing difficulty in breathing and/or swallowing. Patients may complain of "throat is closing up" • Hoarse voice • Stridor (high-pitched inspiratory noise caused by upper airway obstruction)	• Shortness of breath – increased respiratory rate • Wheeze (bronchospasm) and/ or persistent cough • Patient becoming tired with the effort of breathing • Confusion due to hypoxia • Cyanosis (a late sign) • Respiratory arrest	• Signs of shock: pale, clammy • Significant tachycardia • Arrhythmia • Hypotension – feeling faint (dizziness), collapse • Decreased conscious level or loss of consciousness • Cardiac arrest

Reproduced with permission from the Resuscitation Council UK[8]

In infants and early childhood, anaphylaxis could be difficult to recognise as they are unable to 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].

Positioning of Patient



- Patients with anaphylaxis should not be placed in the upright position or suddenly stand or walk or suddenly sit up. Fatality can occur within minutes if a patient stands, walks or sits suddenly or is placed in the upright position. Laying the patient flat (see image above) will improve venous blood return to the heart.
- Patients must NOT walk or stand, even if they appear to have recovered. A wheelchair, stretcher or trolley bed should be used to transfer the patient:
    - To the ambulance and from the ambulance to the treatment room bed.
    - From the treatment room bed, to and from the toilet.
- **If unconscious or vomiting**, lay the patient on their side in the recovery position



- **The left lateral (recovery) position is recommended for patients who are pregnant** (see image above). This reduces the risk of compression of the inferior vena cava by the pregnant uterus and improves venous return to the heart



- **Patients with mostly respiratory symptoms may prefer to sit with their legs outstretched in front of them** (see image above), which may help support breathing and improve ventilation. They should not sit on a chair as this may trigger hypotension. Monitor closely and immediately lay the patient flat if there is any alteration in conscious state or drop in blood pressure.

- The correct way to hold an infant or young child is flat (see image above), not over the shoulder.





- Do not allow the patient to stand or walk until they are haemodynamically stable, which is usually a minimum of 1 hour after 1 dose of adrenaline and 4 hours if more than 1 dose of adrenaline was administered[12].

Adrenaline administration and dosages

INTRAMUSCULAR ADRENALINE* (1:1,000) *without delay is ***the most important lifesaving therapeutic agent in the treatment of anaphylaxis and is the route of choice for most healthcare providers***.

Adrenaline acts to reduce airway mucosal oedema, induce bronchodilation, induce vasoconstriction and increase strength of cardiac contraction. **The best site for IM injection is the anterolateral aspect of the middle third of the thigh** (outer mid-thigh)**.** The needle used for injection must be sufficiently long to ensure that the adrenaline is injected into muscle: use a 21G or 23G needle. ***In the initial treatment, adrenaline should not be given via the intravenous (IV) route because of the risk of potentially lethal arrhythmias even if IV access is possible.***

If airway/breathing/circulation (ABC) problems persist, a second dose of IM adrenaline should be given after 5 minutes. Alternate right and left thigh for repeat doses of adrenaline (to maximise absorption of adrenaline). Intravenous (IV) fluids are an important adjunct in the presence of shock or poor response to an initial dose of adrenaline. If ABC problems persist despite three (3) appropriate doses of IM adrenaline, then the patient should be treated as for "Refractory Anaphylaxis" by experienced specialists in an appropriate setting.

IV boluses of adrenaline are NOT recommended due to risk of cardiac ischaemia or arrhythmia UNLESS the patient is in cardiac arrest.

In Sri Lanka, adrenaline is mostly under-used or inappropriately administered as multiple bolus doses via the intravenous route which contributes to pulmonary oedema and death. Administration of a single dose of IM adrenaline is usually well tolerated and poses minimal risk in the context of an individual having an allergic reaction. **Table 2 provides details of adrenaline IM dosing according to age and weight [1,8,11,13,14]. There is large inter-individual variability in the response to adrenaline.**

Action after administration of adrenaline

Observation of patient for at least 4 hours after last dose of adrenaline

Relapse, persistent and/or biphasic reactions may occur, and overnight observation is strongly recommended for patients if they have one or more of these features:

- Severe or persistent anaphylaxis (e.g. required repeated adrenaline doses or IV fluid resuscitation
- A history of severe or persistent anaphylaxis
- Concomitant illness (e.g. severe asthma, history of arrhythmia, systemic mastocytosis)
- Lives alone or is remote from medical care or presents for medical care late in the evening

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 on a β-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

Table 2[1,8,11,13,14]: ADRENALINE (1: 1,000 ampoules contain 1mg adrenaline per 1mL) in the INITIAL management of acute anaphylaxis

<table>
<tr><th>Site & route of administration</th><th>Frequency of administration</th><th>Dose (ADULT)</th><th>Dose (CHILD under 12-years of age)</th></tr>
<tr>
<td>Adrenaline 1:1000, IM to the midpoint of the anterolateral aspect of the middle third of the thigh immediately

Use a 21 or 23 G 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</td>
<td>Repeat at 5-minute intervals for a maximum of 3 doses in the field setting. If features of anaphylaxis persist despite 3 doses of IM adrenaline, the patient should be treated for refractory anaphylaxis with expert support.
Note: Persisting or worsening cough associated with pink frothy sputum (sign of pulmonary oedema) is an important sign of hyper-adrenalism</td>
<td>0.3-0.5 mL
(0.3-0.5 mg)

small adults
(30–50 kg) -
0.3 mL (0.3 mg)

weight >50 kg -
0.5 mL (0.5 mg)

Maximum 0.5 mL
(0.5 mg)/dose

Pregnant women- dose is the same as for non-pregnant women.</td>
<td>0.01 mL/kg (up to maximum of 0.3 mL (0.3 mg)/dose

Guide based on weight
<table>
<tr><th>Weight (kg)</th><th>Volume (mL) 1:1000 adrenaline</th></tr>
<tr><td>< 7.5</td><td>0.1 mL</td></tr>
<tr><td>10</td><td>0.1 mL</td></tr>
<tr><td>15</td><td>0.15 mL</td></tr>
<tr><td>20</td><td>0.2 mL</td></tr>
<tr><td>30</td><td>0.3 mL</td></tr>
<tr><td>40</td><td>0.4 mL</td></tr>
<tr><td>>50</td><td>0.5 mL</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td></td>
<td>Should not be withheld due to a fear of causing reduced placental perfusion.
The left lateral position is recommended.</td>
<td>If weight is not available (adapted from[8])
<table>
<tr><th>Age</th><th>Volume (mL)
1:1000 adrenaline</th></tr>
<tr><td><6 months</td><td>0.1 mL</td></tr>
<tr><td>6 months-6 years</td><td>0.15 mL</td></tr>
<tr><td>6-12 years</td><td>0.3 mL</td></tr>
</table>
Infants with anaphylaxis may retain pallor despite 2 to 3 doses of adrenaline, and this can resolve without further doses.
More than 2 to 3 doses of adrenaline in infants may cause hypertension and tachycardia, which is often misinterpreted as an ongoing cardiovascular compromise or anaphylaxis.
Blood pressure provides a guide for effectiveness of treatment, to check if additional doses of adrenaline are required.
The correct way to hold an infant is flat as shown in the diagram above</td>
</tr>
<tr>
<td colspan="4">DO NOT inject adrenaline directly into an IM immunisation site as it dilates blood vessels and speeds absorption of the vaccine[19].</td>
</tr>
</table>

Store adrenaline at less than 25^{0}C and protect from light.

Supportive management at immunisation centres after administration of appropriate dose of adrenaline IM before and during transfer of patient to hospital

- Check pulse, blood pressure, ECG, pulse oximetry, conscious state.
- Give high flow oxygen if available and airway support if needed.

  Give oxygen if available. If person is unresponsive and not breathing normally give CPR. 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/minute to

  - all patients with respiratory distress
  - those receiving repeated doses of adrenaline or
  - presence of concomitant asthma, other chronic respiratory disease or cardiovascular disease

Fluids

Obtain IV access in adults and tachycardic and/or hypotensive children. The first sign of cardiovascular compromise in children is ongoing tachycardia. Hypotension can occur later, when it can then be difficult to get IV access, resulting in a significantly prolonged recovery process. If hypotensive, give IV normal saline (0.9% sodium chloride/Hartmann) as a rapid IV fluid bolus (10 mL/kg in a child or 500–1000 mL in an adult) and monitor the response[8].

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 recognised. 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.

Glucocorticoids (e.g. hydrocortisone)

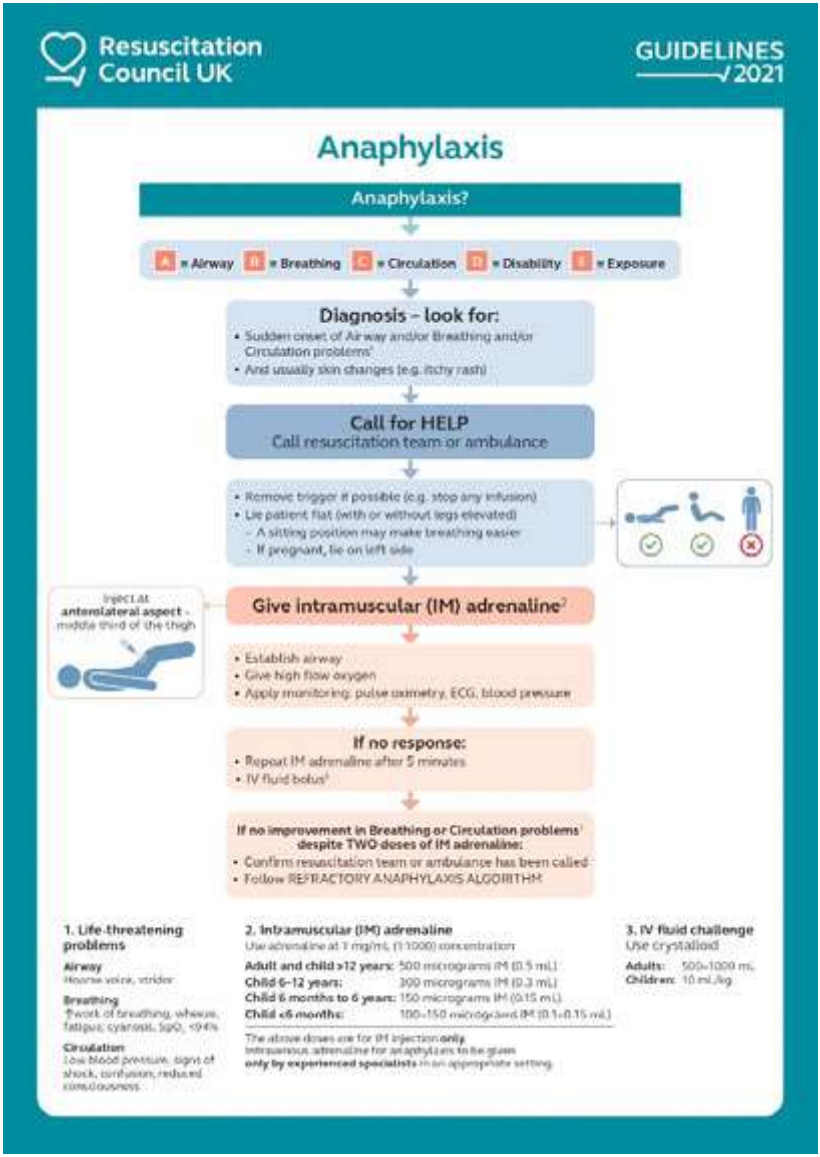
Most updated guidelines[8] strongly advise against the routine use of corticosteroids to treat anaphylaxis, owing to lack of evidence that glucocorticoids help shorten persistent symptoms or prevent biphasic reactions. Data also suggest that the routine use of steroids is associated with an increase in morbidity. Glucocorticoids may have a benefit in specific scenarios: first, anaphylaxis occurring in the context of poorly controlled asthma; and second, in cases of refractory anaphylaxis (defined as persistence of ABC features despite two appropriate doses of adrenaline)[8].

Antihistamines

Antihistamines do not relieve life threatening respiratory or cardiovascular symptoms of anaphylaxis and are no longer considered medications of choice in the treatment of anaphylaxis due to lack of supporting evidence from randomised controlled trials. The initial use of antihistamines is associated with occurrence of biphasic reactions, possibly due to delayed administration of adrenaline.

Antihistamines maybe helpful for treating the cutaneous features of the allergic reaction such as urticaria and angioedema but must not be used to treat ABC problems or delay the use of adrenaline. In such a situation, non-sedating antihistamines (e.g. cetirizine) are preferred, as first-generation antihistamines (such as chlorphenamine) can cause sedation which may mimic some signs of anaphylaxis and, if given rapidly by intravenous bolus, can precipitate hypotension. Injectable promethazine should not be used in anaphylaxis as it can worsen hypotension and cause muscle necrosis.

Algorithm for the treatment of anaphylaxis adapted from Resuscitation Council UK[8]



* The use of this algorithm was authorised by RCUK

Table 3[11]: 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. • Overly rapid intravenous infusion • Repeated intravenous bolus doses 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

Serum tryptase

The specific test to confirm a diagnosis of anaphylaxis 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 concentrations in the blood may not increase significantly until 15 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 sample is very important.

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.

1. First sample from ideally within 30 minutes-2 hours[9]) after the start of symptoms. A sample taken later may still demonstrate raised tryptase levels[13].
2. Second sample preferably at 24 hours or in convalescence (for example in a follow up allergy clinic). This provides baseline tryptase levels.

A level of serum tryptase half to two hours after the start of the reaction more than (1.2 × baseline tryptase) +2 ng/mL supports a diagnosis of anaphylaxis[13]. A non-significant rise does not exclude anaphylaxis[9]. An elevated baseline serum tryptase level is associated with mast cell disorders or hereditary alpha tryptasaemia.

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.
- Serum may be stored at 2-8 ^{0}C for up to 48 hours. For longer delays store at -20 ^{0}C and transport to testing laboratory in ice.
- In case of death, serum tryptase may be assessed if the patient had died within 30 minutes–6 hours after the onset of anaphylaxis. The post-mortem should have been carried out within 24 hours of death. The sample should be taken from the femoral artery and processed as mentioned above.
- Haemolysed samples are not suitable for testing.

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.

Requirements for acute management of anaphylaxis (emergency trolley)

These should be always available at immunisation centres and wards.

- Adrenaline 1:1000 vials (regularly check expiry date)
- 1 mL syringes
- All ages: 25G needles, 25 mm length
- Preterm/very small infants: 25G needles, 16 mm length
- Very large adults: 21G needle, 38 mm length
- Oxygen, airway equipment, including rebreather oxygen masks, nebuliser masks and suction
- Manual blood pressure cuff
- IV access equipment (including large bore cannulae)
- At least 3 litres of normal saline/Hartmann solution

Post anaphylaxis management

Patients with vaccine associated anaphylaxis should be referred to a specialist for further management.

References

1. Cardona V, et al. World Allergy Organisation Anaphylaxis Guidance 2020. *World Allergy Organization Journal.* 2020; 13:100472.
2. Ruggeberg JU, et al and the Brighton Collaboration Anaphylaxis Working Group. Anaphylaxis: Case definition and guidelines for data collection, analysis, and presentation of immunisation safety data. *Vaccine.* 2007; 25:5675–5684.
3. Dreskin ST, et al. International Consensus (ICON): allergic reactions to vaccines. *World Allergy Organization Journal*. 2016; 9:32.
4. de Silva R, et al. Sensitisation to bovine serum albumin as a possible cause of allergic reactions to vaccines. *Vaccine*. 2017; 35(11):1494-1500.
5. Dasanayake D, et al. Alpha-gal allergy in a South Asian country. *BMC Immunology*. 2025; 26(1):37.
6. Csuth Á, et al. COVID-19 mRNA vaccine allergy. *Journal of Allergy and Clinical Immunology*. 2024; S0091-6749(24)01163-1.

7. Kelso JM. The adverse reactions to vaccines practice parameter 10 years on-what have we learned? *Annals of Allergy Asthma and Immunology*. 2022: S1081-1206(22)00049-7.
8. Resuscitation Council UK 2021 Resuscitation Guidelines. Available at: https://www.resus.org.uk/library/2021-resuscitation-guidelines.
9. Golden DBK, et al. Anaphylaxis: A 2023 practice parameter update. *Annals of Allergy Asthma and Immunology*. 2024; 132(2):124-176.
10. Acute Anaphylaxis Clinical Care Standard 2021, developed by Australian Commission on Safety and Quality in Health Care, in consultation with the Australasian Society of Clinical Immunology and Allergy (ASCIA), Allergy & Anaphylaxis Australia (A&AA), and the National Allergy Strategy (NAS).
11. Simons FER, et al. World Allergy Organisation Guidelines for the Assessment and Management of Anaphylaxis. *World Allergy Organization Journal*. 2011; 4:13–37.
12. Pumphrey RS. Fatal posture in anaphylactic shock. *Journal of Allergy and Clinical Immunology*. 2003; 112(2):451–2.
13. Muraro A, et al. EAACI guidelines: Anaphylaxis (2021 update). *Allergy.* 2022; 77(2):357-377
14. Shaker MS, et al. Anaphylaxis – a 2020 Practice Parameter Update, Systematic Review and GRADE Analysis. *Journal of Allergy and Clinical Immunology*. 2020: doi: 10.1016/j.jaci.2020.01.017.

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CHAPTER 39

STORAGE AND TRANSPORT OF VACCINES

The successful control of vaccine-preventable diseases depends in part on the correct storage and handling of vaccines. Exposure of vaccines to temperatures outside the recommended ranges can significantly reduce their potency and effectiveness. Moreover, some vaccines are also sensitive to light and can become ineffective if not protected properly.

Storage and handling errors can result in substantial financial losses due to wasted vaccine doses and the associated costs of revaccination. Such errors may also erode public confidence, especially when patients are required to receive repeat doses. It is preferable not to administer a vaccine than to give one that has been improperly stored.

Every facility that stores vaccines must have comprehensive, written protocols for both routine and emergency vaccine storage and handling. These protocols should be readily accessible to all staff members and must be reviewed and updated at least annually.

Vaccines are biological products that are sensitive to both heat and freezing. Exposure to temperatures outside the recommended range can reduce their potency, rendering them less effective or even ineffective. Therefore, maintaining the correct temperature from the point of manufacture until the moment of administration is critical. The system used for keeping and distributing vaccines in the recommended temperature 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-Guerin (BCG) Human papillomavirus (HPV) Japanese encephalitis (Killed) Tetanus, DT, aTd, Tdap	Hepatitis B Hib (freeze-dried) Meningococcal Pneumococcal

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 recommended cold chain conditions reduces vaccine efficacy and may result in vaccine failure. It can also increase the risk of adverse reactions following immunisation, particularly with vaccines that have been inadvertently frozen. Depending on the nature of the product, vaccines can be damaged by either heat exposure or freezing. With the current distribution system in Sri Lanka, vaccines should neither be transported nor stored in a frozen state at the facility level. However, at the national level, where long-term storage (more than six months) is required, it is recommended that OPV and MMR vaccines be stored in -20°C freezer rooms.

Exposure to heat over time can be monitored using Vaccine Vial Monitors (VVMs), which change colour to indicate cumulative heat exposure. These indicators help guide decisions on whether vaccines remain suitable for use. However, during the storage and transportation of freeze-sensitive vaccines such as DTP, TT, DT, aTd, hepatitis B, HPV, and Hib, the risk of freezing is greater than the risk of heat exposure.

This chapter provides general guidelines on the storage and transport of vaccines. However, manufacturers' product information and package

inserts should be referred to for specific and detailed information about the 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 and MMR. 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 for more than one to two hours[1]**.**

Ice-lined refrigerators (ILRs) are specially designed for the storage of vaccines in immunisation programs. Unlike domestic refrigerators, ILRs provide superior temperature stability and are equipped to maintain vaccine potency during power outages. Their thick insulation and ice lining enable them to keep internal temperatures within the recommended +2 ^{0}C to +8 ^{0}C range for extended periods even during power failures.

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 ^{0}C, with a desired average temperature of 5 ^{0}C.

Storage and transport of RNA vaccines:

BioNTech/Pfizer COVID-19 vaccine requires storage at −80 ^{0}C with a shelf life up to 12 months, whereas the Moderna COVID-19 vaccine

requires storage at −20 ^{0}C with the same shelf life. Special packaging with dry ice (-78.5 ^{0}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 ^{0}C.

Storage of vaccines in a refrigerator: (Fig. 1)

- The temperature of the refrigerator should be allowed to stabilise 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 ^{0}C
- Every vaccine-containing refrigerator should have a calibrated thermometer and an electronic temperature monitoring device for routine monitoring of 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 immunisation session. Discard all these items immediately
- All vaccine storage refrigerators should have generator backup. Ideally, the generator should automatically start during power interruption
- In case of a power failure, do not open the refrigerator. Take immediate steps to restore power interruption
- Ice-lined refrigerators could maintain the required temperature for up to 24 hours if the 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]

In general, most vaccine vials should be discarded within six hours of opening or at the end of an immunisation session, whichever comes first. However, the World Health Organization (WHO) has established four specific criteria under the Multi-Dose Vial Policy (MDVP). If **all**

four criteria are fully met, remaining doses of opened vials of qualifying vaccines may be safely used for up to **28 days** after opening, without compromising vaccine safety or efficacy.

a) The expiry date has not passed; **and**

b) The vaccine is **approved** for use for up to 28 days after opening the vial, **and**

c) Vials have been stored under appropriate cold chain conditions; **and**

d) The VVM on the vial, if attached, has not reached the discard point.

Keep open 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 immunisation session, whichever comes earlier. The open vial policy is not applicable for freeze-dried vaccines.

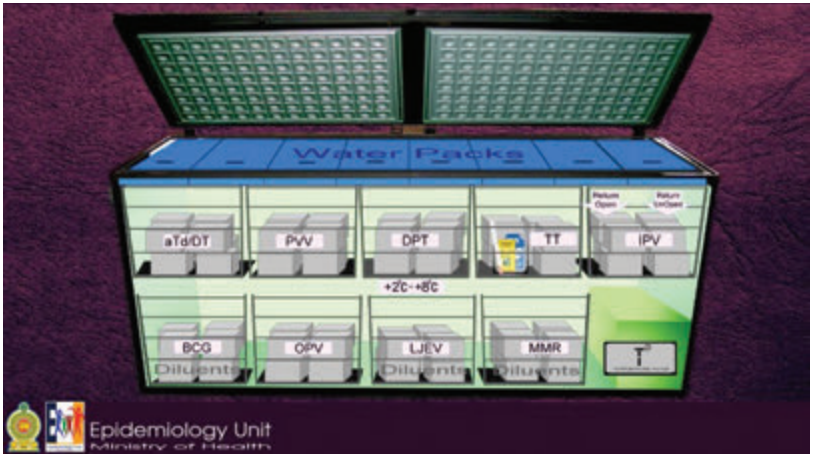


Figure 1: Storage of vaccines in a refrigerator[1]

Diluent[5]

A vaccine diluent is a liquid used to reconstitute a lyophilized (freeze-dried) vaccine before administration. Diluents are sensitive to heat or freezing, and may require transportation and storage within the cold chain. Diluents differ in composition, and each vaccine presentation is matched with a specific diluent designated by the manufacturer. It is critical to use only the assigned diluent for a given vaccine. Never substitute a vaccine diluent with water for injection or any other liquid.

Unless otherwise specified by the manufacturer, diluents should be stored at +2 °C to +8 °C for long-term preservation. When a diluent is packaged with a vaccine, it must always be stored together with the corresponding vaccine at +2 ^{0}C to +8 ^{0}C.

Diluent not packaged with the vaccine can be stored at room temperature ONLY if the manufacturer's instructions allow it. In this case, the manufacturer's instructions regarding cooling prior to reconstitution should be followed. Diluents should NEVER be frozen.

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 the

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 the electronic temperature monitoring device need to be monitored regularly. If the temperature of the refrigerator is below 2 ^{0}C or above 8 ^{0}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.

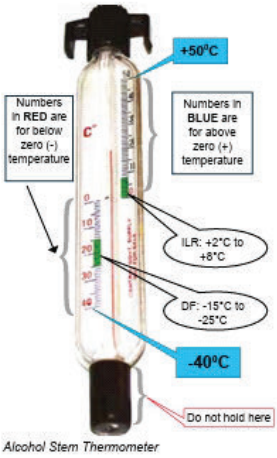


Figure 2: Stem thermometer



Figure 3: Electronic temperature monitoring device

Electronic temperature monitoring devices **(**Figure 3)

The electronic data loggers are also being introduced to monitor the temperature of vaccine storage facilities. The device continuously displays the temperature of the Ice Lined Refrigerator (ILR) on a digital LCD screen. It also indicates whether any alarm situations have occurred within the past 30 days. For each alarm event, it records and displays the duration of the temperature excursion. This information can be accessed using the "Read" button, which allows users to review

the temperature history from the current day up to the previous 30 days. If no temperature excursions have occurred during this period, the device displays an "OK" indicator. Designed for continuous operation, the device usually has a shelf life of two years from the date of activation and cannot be turned off once activated. It ensures uninterrupted, round-the-clock temperature monitoring without the need for user intervention. Specifically engineered for ILRs and walk-in coolers, the device supports environments that must maintain temperatures between +2 ^{0}C and +8 ^{0}C.

An electronic temperature monitoring device should be placed in an appropriate position where they can be read easily and is 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.

Cold chain monitoring systems

Vaccine vial monitors (VVM)

VVM is a label fixed to the vaccine vial's outer surface containing heat-sensitive material. VVM will measure increases in 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 & 4b).

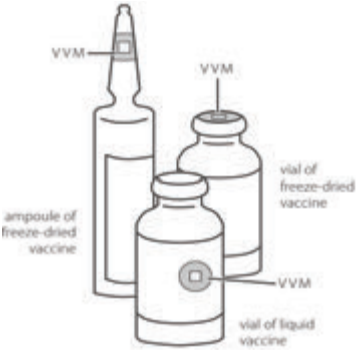


Figure 4a: Location of VVMs

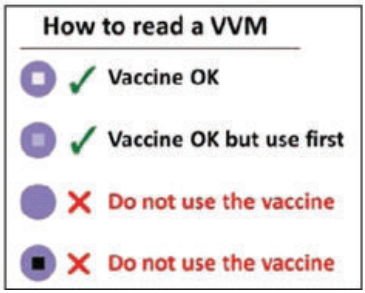


Figure 4b: Interpretation of the VVM[1]

Shake Test

The shake test is carried out when there is an indication or suspicion of exposure of liquid vaccines 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 (e.g. hepatitis B) suspected as having being exposed to freezing temperatures likely to have damaged them.

The Shake Test procedure[1]: (Figure 5)

Shake test - Test vial

Take a vaccine vial you suspect that may have been frozen – This is "TEST" vial.

Shake test - Control vial

1. Take a vaccine vial of the same antigen, same manufacturer, and same batch number as the suspect vaccine vial you want to test.
2. Freeze solid this vial at -20 ^{0}C overnight in the DF, and this is the 'CONTROL' vial and label accordingly to avoid its usage.

3. Let it thaw. Do NOT heat it.
4. Hold the Control and the Test vials together between thumb and forefinger, and vigorously shake the vials for 10-15 seconds
5. Place both vials to rest on a flat surface, side-by-side and observe them for 30 minutes.
6. Compare for rate of sedimentation.
7. If the sedimentation rate in the 'Test vial" is slower than in the "Frozen vial", the vaccine has not been damaged, it has passed the shake test. Use the vaccine batch – it is not damaged.
8. If the sedimentation rate is similar in both vials or if sedimentation is faster in the "Test" vial than in the "Frozen" vial, the vaccine is damaged, it failed in shake test. Do NOT use. Notify your supervisor.

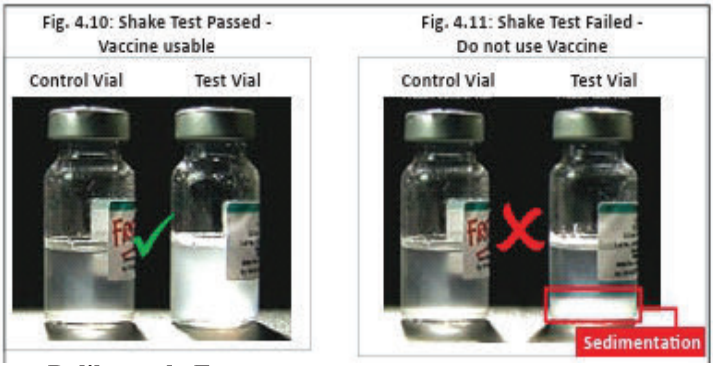


Figure 5: Interpretation of the shake test to determine damage due to freezing of vaccines[2]

Transport of vaccines to outreach health centers

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, HPV 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.

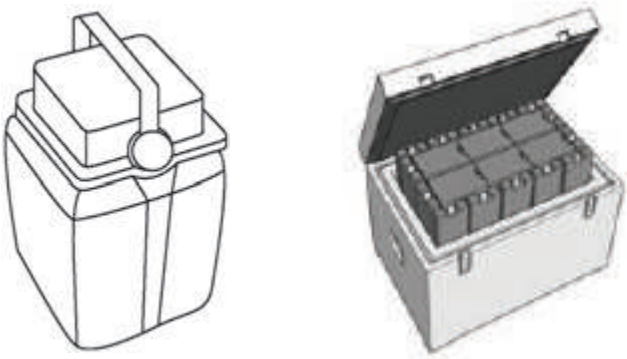


Figure 6: Vaccine carrier

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 immunisation 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.



Fig 7: 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 7). 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 are 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].

References

1. World health organization. Immunisation in practice: module 2: the vaccine cold chain. Geneva: World Health Organization; 2015.
2. Centers for Disease Control and Prevention. Vaccine storage and handling. In: Atkinson W, Wolfe S, Hamborsky J, McIntyre L, editors. Epidemiology and prevention of vaccine-preventable diseases. 14th ed. Washington (DC): Public Health Foundation; 2021. Chapter 5.
3. World health organization. WHO policy statement: multi-dose vial policy (MDVP). Geneva: World alth Organization; 2014. Report No.: WHO/IVB/14.07.
4. World health organization. Guidance note: vaccine diluents. Geneva: World Health Organization; 2015.

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CHAPTER 40

VACCINE HESITANCY

Introduction

Vaccination is one of the most successful and cost-effective public health interventions in history, preventing an estimated 4-5 million deaths annually worldwide[1]. Sri Lanka's National Immunisation Programme (NIP) introduced in 1978, has been recognised internationally as one of the most successful programmes in South Asia, achieving elimination of polio, rubella, and neonatal tetanus and substantial control of measles[2,3,4]. High coverage rates, exceeding 95% for most childhood vaccines, have been sustained for decades through strong political commitment, efficient service delivery, and community trust.

However, even in high-performing programmes, the challenge of **vaccine hesitancy** has emerged as a pressing issue. WHO defines vaccine hesitancy as the "delay in acceptance or refusal of vaccination despite availability of vaccination services"[5], vaccine hesitancy is context-specific, varying across time, place, and vaccines. It is driven by complex and interrelated factors including confidence, complacency, and convenience.

Globally, vaccine hesitancy was identified by the WHO as one of the top ten threats to global health in 2019[6]. The COVID-19 pandemic highlighted the scale and speed at which misinformation and distrust can spread, threatening immunisation programmes worldwide[7]. In Sri Lanka, while overall coverage has remained high, outbreaks of measles (2019, 2023), hesitancy around COVID-19 vaccination, and slow uptake of influenza vaccines demonstrate that complacency is an issue.

This chapter reviews the key drivers of vaccine hesitancy, presents the WHO Vaccine Hesitancy Determinants Matrix, and outlines strategies at individual, community, and policy levels, to address this growing challenge in the Sri Lankan context.

Understanding vaccine hesitancy

Vaccine hesitancy exists on a spectrum: from unquestioning acceptance, through delay and selective refusal, to complete rejection of all vaccines[8]. This continuum is shown in Figure 1 which is adapted from the WHO Report of the SAGE Working Group on Vaccine Hesitancy, Geneva: WHO; 2014[8]. Importantly, the majority of hesitant individuals fall in the middle, expressing uncertainty rather than outright opposition. This group is amenable to engagement and reassurance from healthcare professionals, underscoring the importance of effective doctor–patient communication.

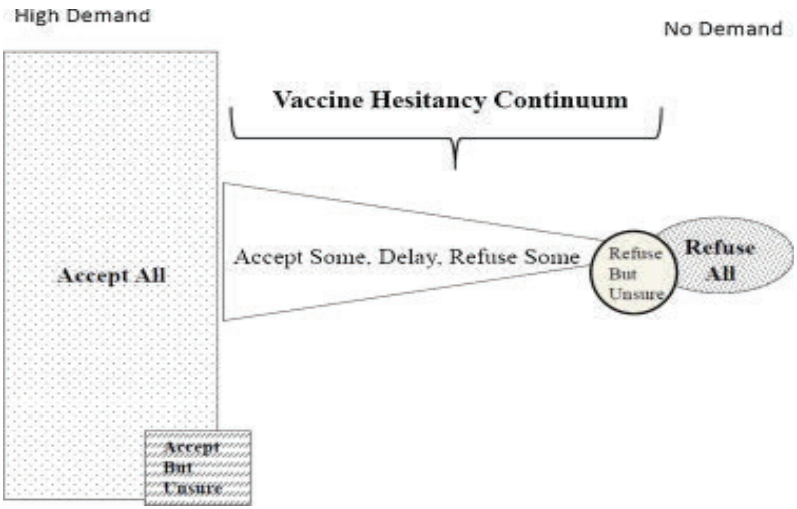


Figure 1: The continuum of vaccine hesitancy between full acceptance and outright refusal of all vaccines

The WHO's SAGE identified three overarching determinants, namely confidence, complacency and convenience (Three 'C's)[2]:

- **Confidence**: Trust in the safety and effectiveness of vaccines, the healthcare system, and policy-makers.
- **Complacency**: Low perceived risk of vaccine-preventable diseases, leading to undervaluing of vaccination.
- **Convenience**: Barriers to access, including availability, affordability, and quality of services.

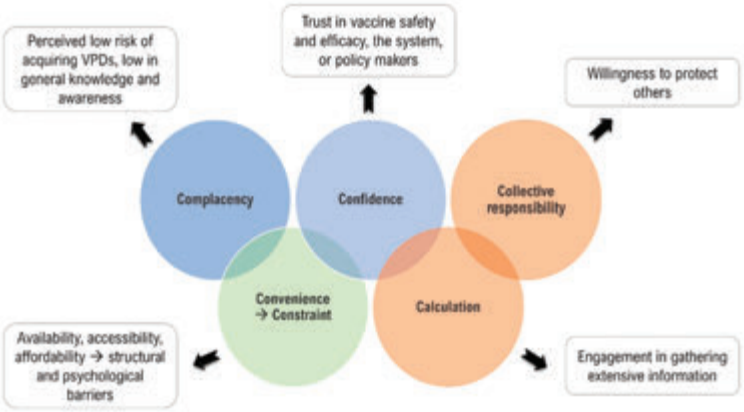


Figure 2: Vaccine hesitancy model: the 3Cs to 5Cs

Based on empirical and theoretical research, this 3Cs model has been revised in 2018 and become the 5Cs model, replacing convenience with constraint and adding calculation and collective responsibility[9]. Therefore, the determinants of vaccine hesitancy are 5-fold, as given below in Figure 2[9].

These concepts pertinent to determinants provide a simple framework but do not capture the full complexity of the issue. For this reason, the SAGE Working Group proposed the **Vaccine Hesitancy Determinants Matrix**[5].

Vaccine hesitancy vs. anti-vaccination attitudes

It is essential to distinguish **vaccine hesitancy** from outright **anti-vaccination movements**, as the terms are often used interchangeably in media and public discourse but carry different meanings in clinical and public health practice.

- **Vaccine hesitancy**: A **spectrum of attitudes** ranging from mild uncertainty to selective acceptance or delay of vaccines[10,11]. Most hesitant individuals are not opposing vaccination in principle; rather, they seek reassurance, additional information, or time before deciding. For example, parents who delay the MMR vaccine until a child is older due to safety concerns still fall under "hesitancy" rather than rejection.

- **Vaccine refusal**: The **complete rejection of one or more vaccines** despite availability. This may be driven by misinformation, mistrust, cultural beliefs, or previous negative experiences[10, 11]. Refusal can be selective (e.g. rejecting HPV while accepting childhood vaccines) or blanket refusal of all vaccines.
- **Anti-vaccination ("Anti-vaxx") Groups**: These represent a more **ideologically entrenched stance**, often rejecting vaccination entirely while actively promoting misinformation or conspiracy theories. Unlike hesitant individuals, who can often be reassured through empathetic dialogue, anti-vaccine activists may frame vaccination as an infringement on freedom or a threat to bodily autonomy. During the COVID-19 pandemic, for example, organised online groups propagated narratives about "microchips in vaccines" or "DNA alteration," reinforcing entrenched resistance[12].

For clinicians, the distinction matters:

- **Vaccine-hesitant patients** usually benefit from respectful listening, clear communication, and reassurance.
- **Anti-vaccine activists**, while fewer in number, can have disproportionate influence on communities, often requiring a broader public health and community-level communication approach rather than persuasion in one-on-one encounters.

Table 1: Vaccine Hesitancy Determinants Matrix

Category	Examples of determinants
Contextual influences	***Historic, sociocultural, environmental, institutional, economic or political factors*** • religion/culture/gender norms • politics/policies • media environment (including social media) • geographic barriers • influential leaders and anti-vaccine movements

Individual and social group influences	Personal perceptions and social/peer environment • knowledge and awareness of vaccines/diseases • risk–benefit perceptions • experience with vaccination (e.g. adverse events) • trust in health system and professionals • peer, family, and community influence
Vaccine and vaccination specific issues	***Directly related to vaccines or delivery services*** • risk/benefit balance of specific vaccines • vaccine safety and efficacy concerns • introduction of new vaccines • mode of administration (e.g. injection vs oral) reliability of vaccine supply • quality of vaccination services (staff, waiting times, attitudes)

Adapted from: WHO SAGE on Immunisation. Report of the SAGE Working Group on Vaccine Hesitancy. Geneva: WHO; 2014[5].

Key drivers of vaccine hesitancy

Vaccine hesitancy is a worldwide issue, though its underlying drivers vary by region, socio-political setting, and vaccine type. Some of the major drivers include the following[5,10].

- misinformation and the "Infodemic"
- concerns about safety and adverse events
- erosion of trust in institutions
- complacency in high-income settings
- access and convenience barriers in LMICs
- cultural and religious beliefs
- introduction of new vaccines

Role of healthcare professionals

Healthcare professionals, particularly doctors, are consistently identified as the most trusted sources of vaccine information[7,10]. Their

influence extends beyond direct patient interactions, as they serve as role models within their communities. Effective strategies include: **active listening, empathy, clarity, cultural sensitivity, and transparency**. Every encounter with a healthcare professional should be used as an opportunity to promote appropriate vaccinations.

Strategies to address vaccine hesitancy

Various strategies need to be applied at individual, community, system, policy and National levels[9,10,13].

Individual-level strategies

- motivational interviewing techniques
- tailored communication addressing parental concerns
- evidence-based but empathetic dialogue

Community-level strategies

- partnering with religious/community leaders
- school-based education on HPV, aTd and influenza
- using social influencers for counter-messaging

System-level strategies

- training healthcare workers in vaccine risk communication
- strengthening surveillance of AEFI and communicating findings openly
- ensuring equitable vaccine access in estates and rural areas

Policy and national-level strategies

- National campaigns with transparent messaging
- regulating misinformation on social media

sustaining investment in NIP even during crises

Case examples

- **Philippines (Dengvaxia)**: demonstrates long-term impact of trust breakdown[14].
- **India (Polio eradication)**: religious leaders pivotal in overcoming hesitancy[15].

- **Sri Lanka (HPV vaccine introduction, 2017)**: Introduction to NIP was done with school-based programmes[16]. Initial parental concern addressed by school-based sessions with teachers and health staff.

Vaccine hesitancy is a complex, context-dependent challenge that threatens to undermine the hard-won gains of immunisation programmes. For Sri Lanka, where public trust in health services has historically been high, the challenge lies in safeguarding this trust in an era of economic uncertainty and widespread misinformation. Healthcare professionals, as trusted messengers, play a critical role in addressing hesitancy through empathetic, transparent, and evidence-based communication. Strengthening community engagement, ensuring equitable access, and proactively countering misinformation will be vital to sustaining Sri Lanka's exemplary immunisation achievements.

References

1. Immunisation coverage. Geneva: WHO. 2021.
2. Ministry of Health Sri Lanka. *Annual Health Bulletin*. Colombo: Ministry of Health; 2022.
3. Maternal and Neonatal Tetanus Elimination (MNTE) status report. 2023. Epidemiology Unit, Ministry of Health, Sri Lanka.
4. Strengthening Immunity among High-Risk Occupational groups. The Special Measles-Rubella (MR) Immunisation Campaign for Police, Tri-Forces and Civil Security Personnel. Epidemiology Unit, Ministry of Health, Sri Lanka. *Weekly Epidemiological Report*. 2025; 52(36).
5. Report of the SAGE Working Group on Vaccine Hesitancy. Geneva: WHO. 2014.
6. Ten threats to global health in 2019. Geneva: WHO; 2019.
7. Larson HJ, et al. Volatility of vaccine confidence. *Science*. 2021; 371(6536):1289.
8. MacDonald NE. SAGE Working Group on Vaccine Hesitancy. Vaccine hesitancy: Definition, scope and determinants. *Vaccine*. 2015; 33(34):4161-4.
9. Nuwarda RF, et al. Vaccine Hesitancy: Contemporary Issues and Historical Background. *Vaccines* (Basel). 2022; 10(10):1595. doi: 10.3390/vaccines 10101595. PMID: 36298459

10. Dubé E, et al. Vaccine hesitancy: an overview. *Human Vaccine Immunotherapy*. 2013; 9(8):1763-73.
11. Johnson NF, et al. The online competition between pro- and anti-vaccination views. *Nature*. 2020; 582(7811):230–3.
12. Wilson SL, et al. Social media and vaccine hesitancy. *British Medical Journal Global Health*. 2020; 5(10):e004206.
13. Larson HJ, et al. The state of vaccine confidence 2016: global insights through a 67-country survey. e*BioMedicine*. 2016; 12:295-301.
14. Fatima K, et al. Dengvaxia controversy: impact on vaccine hesitancy. *Journal of Global Health*. 2018; 8(2):020312.
15. Banerjee P, et al. Vaccine acceptance in rural India: Engaging faith leaders as vaccine ambassadors. *Front Public Health*. 2022; 10:979424. doi: 10.3389/fpubh.2022.979424.
16. Debellut F, et al. Human papillomavirus (HPV) vaccination program in Sri Lanka: Ongoing costs and operational context of a routinised program. *Vaccine*. 2024; 17:100456. doi: 10.1016/j.jvacx.2024.100456.

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CHAPTER 41

FREQUENTLY ASKED QUESTIONS

1. **In the National Immunisation 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 (varicella), 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.

2. **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 should 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[1].

3. **Does natural immunity produce better protection than vaccine induced immunity?**

   There is no clear answer. Certain diseases such as chickenpox produce natural immunity, but 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[2].

4. **Is an interval of 4 weeks mandatory between immunisation 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[3].

5. **Could one interchange different brands of vaccines?**

   There is little clinical data to support switching from one brand of vaccine to another brand for many vaccines, but there is no contraindication to do so. In the absence of the same brand, it is recommended to use an available brand rather than avoiding vaccination[4].

6. **Why are vaccines given in the anterolateral mid-thigh and not the gluteal region?**

   This is to prevent damage to the sciatic nerve. Moreover, vaccines deposited in the fat of the gluteal region do not induce the appropriate immune response due to irregular absorption of the vaccine[5].

7. **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.

8. **Students going for overseas studies are recommended a number of vaccines within a short period. Is it safe to give several vaccines at short intervals?**

   It is advisable to plan an overseas stay well in advance, enabling adequate time intervals for vaccinations. Most vaccines could be given as accelerated schedules. Please refer to the accelerated schedules under each chapter.

Non-live vaccines could be given simultaneously. Also, a live vaccine and a non-live vaccine could be given at the same time, to different sites. Two or more live vaccines could be administered concurrently at different sites, if the person intends to travel within a short period of time.

9. Should vaccination be delayed in small-for-dates babies?

Small-for-dates babies should receive the BCG vaccine when they are fit to be discharged from the hospital. They should receive their routine vaccinations at the recommended age[6].

10. What precautions should be taken when vaccinating preterm babies?

It is important that preterm infants have their immunisations according to the NIP. Their age should be calculated from the date of birth[7]. 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, under the care of a paediatrician[8].

11. Could a child receive a non-NIP vaccine at the same time of other scheduled NIP vaccines?

Yes.

12. Is it possible to give 2 vaccines to the same limb?

It should be avoided as much as possible. In the event that the same limb has to be used for both vaccines, it is recommended there is a minimum 2.5 cm gap between the two injection sites[9].

13. Which live vaccines are recommended for household members and close contacts of an immunocompromised person?

Live vaccines cannot be given to immunocompromised people. Immunisation of household members and close contacts with MMR, varicella and rotavirus vaccines will protect the immunocompromised people from household transmission of these infections. However, OPV is contraindicated for the

immunocompromised people as well as their close contacts as the vaccine virus could be transmitted and cause vaccine associated paralytic polio (VAPP) in the immunocompromised[10].

14. 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[11]. However, the NIP of Sri Lanka recommends that a child between 6 months to 5 years of age should be revaccinated without a Mantoux test/tuberculin skin test (TST)[12].

15. 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. DT can also be given, as DTaP is available only in the private sector (refer Chapter 8).

16. 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 immunisation is not life-long. Epidemiological evidence suggests that routine immunisation of adolescents and adults could significantly result in lowering the incidence and severity of the disease. Pertussis vaccination for adults (Tdap) may be given at intervals of ten years[13].

17. What follow up action should be taken if a 12-year-old child was given a tetanus toxoid instead of aTd/Tdap?

A dose of aTd/Tdap is recommended after 6 months.

18. 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 long term protection up to 20 years[14].

19. 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. Vaccination for adults with diabetes over the age of 60 years should be decided by the clinician[15].

20. Is it necessary for me to take the hepatitis B vaccine if I do not belong into any risk group?

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, it is advisable to get an effective vaccine rather than being unprotected[15]. It also prevents primary hepatocellular carcinoma.

21. 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.

22. 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 titre measured after 1 month. If the antibody titre is < 10 mIU/mL a second full series should be given[16].

23. Is it beneficial to give the HPV vaccine to women who are already sexually active?

Ideally, HPV immunisation 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 45 years, by the manufacturer[17].

24. Does the HPV vaccine protect against all types of cervical cancers?

No. There are two types of vaccines available in Sri Lanka: quadrivalent (oncogenic serotypes 16 & 18 and non-oncogenic 6 & 11) and bivalent (oncogenic serotypes 16 & 18). Serotypes16 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[18]. The nine valent HPV vaccine is currently not available in Sri Lanka.

25. How long does the HPV vaccine protection lasts after three doses?

Current studies have shown that the HPV vaccine results in a high antibody level not requiring booster doses for at least 14 years. Studies will continue and more data regarding the effectiveness of the vaccine will be available in the future[19].

26. 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[17].

27. 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[20].

28. If HPV vaccination is administered unintentionally during pregnancy, would that be harmful to the fetus?

HPV vaccines are not currently recommended for pregnant women since 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 the HPV vaccine and later learns that she is pregnant, there is no reason to be alarmed[17].

29. Do I have to take the 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 the WHO, based on recent virus surveillance studies, epidemiological trends and post-vaccination studies, to decide which type of influenza virus strains should be included in the flu vaccine. Therefore, the current 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.

30. 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.

31. 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% of vaccinated children will remain vulnerable to these diseases. However, after the 2nd dose, only 1% will remain susceptible[21].

32. What is the minimum interval between two doses of MMR vaccines for adults?

4 weeks[22].

33. 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.

34. 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, the Mantoux test should be postponed for 4 weeks after vaccination[23].

35. 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, immunocompromised children, splenectomised individuals, 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.

36. Should I recommend the pneumococcal conjugate vaccine (PCV) to children below 5 years?

There is sufficient global and regional data justifying the use of PCV vaccination in this age group. 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. The WHO has recommended PCV to children below 5 years of all countries in their position paper[24,25,26].

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.

37. It has been observed that there are 3 types of PCV schedules that are commonly implemented in the private sector in Sri Lanka in infancy.

1. 2^{nd}, 4^{th} and 6 months (total of 3 doses)
2. 2^{nd}, 4^{th} and 12 months (total of 3 doses)
3. 4^{th} and 6^{th} months (total of 2 doses)

Which of above schedule/s could be recommended to achieve optimum immunity?

Out of the above (2) is more appropriate. (refer Chapter 17)

38. How many types of pneumococcal vaccines are currently available in Sri Lanka? Are they interchangeable?

Pneumococcal conjugate 10 valent vaccine (PCV 10)

Pneumococcal polysaccharide 23 valent vaccine (PPSV 23)

They are not interchangeable as they contain different serotypes of pneumococcus.

39. There had been children admitted to hospitals for the treatment of pneumonia even after taking PCV. Does it mean that PCV was ineffective?

No. The currently available PCV 10 in Sri Lanka protects against 10 common serotypes causing the disease. As there are over 100 serotypes of pneumococcus, the possibility of developing pneumonia caused by other uncommon serotypes would remain unchanged. In addition, PCV would not protect children from pneumonia caused by other bacteria, viruses and fungi.

40. Would it be possible that a person who has previously contracted pneumococcal disease be protected from future episodes of pneumonia?

No. As there are over 100 serotypes of pneumococcus, prior infection of one serotype of pneumococcus may not confer immunity to other serotypes. Also, pneumonia can be caused by other bacteria, viruses and fungi.

41. Is there any relationship between influenza and pneumococcal infection?

Influenza is caused by a virus and patients with influenza can get secondary bacterial pneumonia due to pneumococcus. This is an important cause of morbidity and mortality for those infected with influenza. It has been identified that *S pneumonia*e is responsible for up to 10% of deaths[27]. Therefore, pneumococcal vaccination becomes lifesaving in some individuals during flu epidemics.

42. 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.

43. Can pneumococcal vaccines be received together with seasonal influenza vaccine?

Yes. Pneumococcal vaccines can be given together with seasonal influenza vaccine, but they should be administered with a different syringe and at a different injection site.

44. Why is it recommended to give inactivated polio vaccine (IPV) together with bivalent oral polio vaccine (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 protection to the individual and the community[28].

45. 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[29].

46. "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 people in the household and the community.

47. 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 the varicella vaccine, about 99% of people with two doses are completely protected from chickenpox infection and almost 100% from severe disease[30]. On the other hand, if a vaccinated person does get chickenpox, it is usually a mild form with <50 skin lesions[31].

48. How do you manage a child younger than 1 year of age who has been 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 he develops chickenpox. Immunosuppressed children and neonates should receive VZIG[32].

49. 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[33].

50. When a mother has chickenpox at the time of delivery, can the neonate be protected by chickenpox vaccination?

No. The vaccine is recommended only 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 ideally receive VZIG, regardless of whether the mother had received VZIG. If VZIG is not available IV acyclovir is recommended[32].

51. Could the chickenpox vaccination reduce 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[34].

52. What is the place of varicella vaccination in the post exposure clinical management of close contacts?

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 varicella 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 due to the long incubation period. Furthermore, varicella vaccination would be effective in prevention of chickenpox if administered within 3-5 days of exposure[35].

53. Is it safe to recommend varicella vaccine to an expectant mother who has been already exposed?

No. It is not recommended during pregnancy. If she has no natural immunity to varicella or has not been vaccinated, post-exposure prophylaxis with varicella zoster immune globulin (VZIG) is indicated. Pregnant women can also be given oral acyclovir as post-exposure prophylaxis. (800 mg 4 times daily, from days 7 to 14 after exposure)[36].

Oral acyclovir should be prescribed for pregnant women with chickenpox if they present within 24 hours of the onset of the rash and if they are 20+0 weeks of gestation or beyond. Use of acyclovir before 20+0 weeks should also be considered. Acyclovir is not licensed for use in pregnancy but can be prescribed in the best interest of the woman, on the basis of available evidence, in consultation with her[37].

54. 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 immunisation. 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 more than 20 years[38].

55. How long should a female avoid pregnancy, after receiving rubella and varicella containing vaccines?

The minimum interval should be one month for varicella vaccine and rubella containing vaccines, because of the theoretical risk to the developing fetus. However, pregnancy within this period is not an indication for termination as no teratogenic effects have been identified[39].

56. Are there any specially recommended vaccinations for diabetic patients?

The American Diabetic Association (ADA), WHO and CDC recommend influenza, hepatitis B and pneumococcal vaccines for all patients with diabetes[40,41].

References:

1. Recommendations for interrupted or delayed routine immunisation*: Summary of WHO position papers*. Updated September 2020.
2. Biggs AT, et al. Vaccination and natural immunity: advantages and risks as a matter of public health policy. *Lancet Regional Health - Americas*. 2022; 8:100242. doi:10.1016/j.lana.2022.100242
3. Timing of vaccine administration*:* Canadian immunisation guide for health professionals. Public Health Agency of Canada. https://www.canada.ca/%20en/public-health/services/publications /healthy-living%20canadian-immunisation-guide-part-1-key-immuni sation-information/page-10-timing-vaccine-administration.html
4. Principles of vaccine interchangeability: Canadian immunisation guide for health professionals. Public Health Agency of Canada. https://www.canada.ca/en/%20public-health/services/publications/healthy-living/canadian-immunisation-guide-part-1-key-immunisation-information/page-7-principles-vaccine-interchangeability.html
5. Immunisation Practices. Advisory Committee. General recommendations on immunization. *Morbidity and Mortality Weekly Report*. 1983; 32(1):1–8,13–7.
6. D'Angio CT. Active immunisation of premature and low birth-weight infants: a review of immunogenicity, efficacy, and tolerability. *Pediatric Drugs*. 2007; 9:17–32. doi:10.2165/00148581-200709010-00003
7. Doherty M, et al. Vaccination of special populations: protecting the vulnerable. *Vaccine*. 2016; 34(52):6681–6690.
8. Australian Government Department of Health. *Australian immunisation handbook: vaccination for preterm infants*. https://immunisationhandbook. health.gov.au/contents/vaccination-for-special-risk-groups/vaccination-for-preterm-infants
9. Vaccine administration practices: Canadian immunisation guide for health professionals. Public Health Agency of Canada. https://www.canada.ca/en/%20public-health/services/publications/ healthy-living/canadian-immunisation-guide-part-1-key-immunisation-information/page-8-vaccine-administration-practices.html
10. Sassine J, et al. Infection prevention in the immunocompromised traveler due to conditions other than transplantation: a review. *Therapeutic Advances in Infectious Disease*. 2025; 12. doi:10.1177/2049936125 1313827
11. BCG vaccine: WHO position paper. *Vaccine*. 2018; 36(24):3408–3410.

12. Ginige S, editor. *Immunisation Handbook*. 3rd ed. Colombo: Epidemiology Unit, Ministry of Health, Sri Lanka; 2012.
13. Kardos P, et al. Understanding the impact of adult pertussis and current approaches to vaccination: a narrative review and expert panel recommendations. *Human Vaccines & Immunotherapy*. 2024; 20(1):2324547. doi:10.1080/21645515. 2024.2324547
14. Centers for Disease Control and Prevention. *Hepatitis A vaccine administration*. https://www.cdc.gov/hepatitis-a/hcp/vaccine-administration/index.html
15. Universal hepatitis B vaccination in adults aged 19-59 years: updated recommendations of the Advisory Committee on Immunisation Practices—United States, 2022. *Morbidity and Mortality Weekly Report*. 2022; 71(13):477–483.
16. Schillie S, et al. Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunisation Practices. *Morbidity & Mortality Weekly Reports, Recommendations & Reports*. 2018; 67(RR-1):1–31.
17. GlaxoSmithKline. Cervarix product monograph. 2010.
18. Pils S, et al. From the monovalent to the nine-valent HPV vaccine. *Clinical Microbiology and Infection*. 2015; 21(9):827–833. doi: 10.1016/j.cmi. 2015.05.001.
19. Kjaer SK, et al. Final analysis of a 14-year long-term follow-up study of the effectiveness and immunogenicity of the quadrivalent human papillomavirus vaccine in women from four Nordic countries. *E Clinical Medicine*. 2020; 23:100401. https:// doi:10.1016/j.eclinm.2020.100401. [Accessed on 9th October 2025]
20. Naleway AL, et al. Primary ovarian insufficiency and adolescent vaccination. *Pediatrics*. 2018; 142(3):e20180943. https://www.sciencedirect.com/%20science/article/pii/S2589537020301450
21. Seagle EE, et al. Measles, mumps, and rubella antibody patterns of persistence and rate of decline following the second dose of the MMR vaccine. *Vaccine*. 2018; 36(6):818-826. https://doi.org/10.1016/j.vaccine.2017.12.075
22. Immunisation Advisory Centre. Quick answers to frequent MMR questions. https://www.immune.org.nz/factsheets/quick-answers-to-frequent-mmr-questions
23. Tuberculin skin testing information for health care providers. Centers for Disease Control and Prevention. 2020.

24. Pneumococcal conjugate vaccines in infants and children under 5 years: WHO position paper. *Weekly Epidemiological Record*. 2019; 94:85–104.
25. Kularatna S, et al. Burden of invasive pneumococcal disease in Sri Lanka. *Vaccine*. 2015; 33(27):3122–3128. doi: 10.1016/j.vaccine.2015.04.093.
26. Demczuk WH, et al. Serotype distribution of invasive *Streptococcus pneumoniae* in older adults in Canada. *Vaccine*. 2018; 36(31):4701–4707. doi: 10.1016/j.vaccine.2018.06.018.
27. Song JY, et al. Impact of preceding flu-like illness on pneumococcal pneumonia. *PLoS One*. 2014; 9(4):e93477.doi: 10.1371/journal.pone.0093477.
28. Gamage D, et al. Boosting mucosal immunity after fractional-dose IPV. *Journal of Infectious Diseases*. 2018; 218(12):1876–1882.
29. Varicella (chickenpox). Immunisation Advisory Centre. New Zealand. https://www.immune.org.nz/diseases/varicella-chickenpox
30. Varicella (chickenpox) vaccine: Canadian immunisation guide. Public Health Agency of Canada. https://www.canada.ca/en/public-health/services%20/publications/healthy-living/canadian-immunisation-guide-part-4-active-vaccines/page-24-varicella-chickenpox
31. Liese JG, et al. Effectiveness of varicella vaccination in children in Germany. *Pediatric Infectious Disease Journal*. 2013; 32(9):998-1004. doi: 10.1097/INF.0b013e31829ae263
32. Blumental S, Lepage P. Management of varicella in neonates and infants. *BMJ Paediatrics Open*. 2019; 3(1):e000433. doi: 10.1136/bmjpo-2019-000433.
33. Clinical overview of chickenpox. Centers for Disease Control and Prevention. https://www.cdc.gov/chickenpox/hcp/clinical-overview/index.html
34. Harder T, et al. Chickenpox vaccination and risk of herpes zoster. *Clinical Infectious Diseases*. 2019; 69(8). https://doi.org/10.1093/cid/ciy1099
35. Uahwatanasakul W, et al. Frequently asked questions about varicella vaccine. *Australian Prescriber*. 2005; 28:2–5. https://doi.org/10.18773/austprescr. 2005.001
36. Post-exposure prophylaxis for varicella or shingles. UK Health Security Agency. 2025. https://www.gov.uk/government/publications/post-exposure-prophylaxis-for-chickenpox-and-shingles
37. Chickenpox in pregnancy. Green-top Guideline No. 13. Royal College of Obstetricians and Gynaecologists. 2015.

38. Asano Y. Varicella vaccine: the Japanese experience. *Journal of Infectious Dis*. 1996; 174(Suppl):S310–S313. http://www.jstor.org/stable/30126269. [Accessed 7 Feb. 2023].
39. Epidemiology and prevention of vaccine-preventable diseases. 14th ed. Washington (DC): Public Health Foundation; Centers for Disease Control and Prevention. 2021.
40. Hepatitis B vaccines: WHO position paper. *Weekly Epidemiological Records*. 2017; 92:369–392.
41. Vaccination recommendations for adults with diabetes. https://www.cdc.gov/ vaccines/adults/rec-vac/health-conditions/ diabetes.html

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Annex I
NATIONAL IMMUNISATION PROGRAMME OF SRI LANKA 2026

VACCINE	Birth	Month 2	Month 4	Month 6	Month 9	Month 12	Month 18	3 years	School entry	10 – 15 years	Pregnancy	COMMENTS
BCG (OPV)	●											•Within 24 hours of birth, before leaving hospital. •Children between 6 months - 5 years of age, with no evident BCG scar.
bPolio		●	●	●			●		●			
fIPV			●		●							
DTP-Hep B-Hib (Pentavalent)		●	●	●								
DTP							●					
MMR					●			●				Any child <15y who has not received 2 doses of MCV should receive 1 or 2 doses of MCV to complete vaccination One dose of the MMR vaccine should be given to all non-pregnant females between 15-44y of age who have not been vaccinated with rubella containing vaccine earlier

JE (live)						◒						
DT									◒			
aTd										◒		
HPV										◒ ◒		Females only (grade six at school, 2 doses at least 6 months apart)
Tetanus											◒	*If no documented evidence of previously being vaccinated with TTCV-* • 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 *If documented evidence of 6 doses of TTCV and a gap of >10 years after the last dose* *one booster dose of tetanus toxoid during first pregnancy * *TT is not indicated if the last dose is within 10 years*

bPolio (bivalent polio), fIPV (fractional IPV), aTd (adult tetanus & diphtheria), TTCV (tetanus toxoid containing vaccine, MCV (measles containing vaccine)

Annex II

VACCINES OUTSIDE OF THE NATIONAL IMMUNISATION PROGRAMME OF SRI LANKA 2026

VACCINE	AGE									COMMENTS
	Birth	Month 2	Month 4	Month 6	Month 12	Month 18	2nd year	School entry	Over 10 years	
DTaP-Hep B- IPV-Hib (Hexavalent)		■	■	■		■				
Pneumococcal conjugate		■	■		■					2 months, 4 months and 12 months or 4 months, 6 months and 12 months (2+1 schedule) is recommended
Rotavirus (Monovalent)		■	■							Should be completed by 24 weeks of age
Rotavirus (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										Adults - 3 doses at 0, 1 & 6 months
HPV										**Bivalent:** ◦ 9-14 years – 2 doses at 0 & 6 months ◦ 15-45 years – 3 doses at 0, 1 & 6 months **Quadrivalent:** ◦ 9-14 years – 2 doses at 0 & 6 months ◦ 15-45 years – 3 doses at 0, 2 & 6 months
Influenza										Given annually after 6 months of age ● 6 months-3 years – half the adult dose 3 year and older – 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 or later

SPECIAL CIRCUMSTANCES

Disease	Reference
Cholera	Refer Chapter 5
Meningococcal	Refer Chapter 16
Pneumococcal polysaccharide	Refer Chapter 17
Rabies	Refer Chapter 19
Yellow fever	Refer Chapter 25

Annex III

RECOMMENDATIONS FOR ROUTE AND SITE OF IMMUNISATION

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 — acellular 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

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	Injection site abscess ☐	BCG Lymphadenitis ☐
Requiring Investigation	Severe local reaction ☐	
CNS Adverse Events	Vaccine associated paralytic poliomyelitis ☐	GBS ☐
Requiring Investigation	Encephalopathy ☐ Encephalitis ☐	Meningitis ☐
	Seizures Febrile ☐ Seizures Afebrile ☐	
Other Adverse Events	Anaphylaxis ☐ Persistent screaming ☐	Cellulitis / Osteomyelitis ☐
Requiring Investigation	Hypotonic Hyporesponsive Episode ☐	Toxic Shock Syndrome ☐
Adverse Events Not	Allergic reaction ☐	Arthralgia ☐
Requiring Investigation	High fever (>39°C / 102°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 patient's residence)

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. Guillen_Barre syndrome (within 30 days after immunizations) c. Encephalopathy (within 72 hours after vaccination) d. Encephalitis (within 1- 30 days after vaccination) e. Meningitis (within 1-30 days after immunization) f. Seizures
4. Other adverse events requiring investigation
a. Anaphylaxis b. Persistent screaming c. Hypotonic hyporesponsive Episode d. Osteitis/osteomylitis (within 8-16 months of vaccination) e. Toxic shock syndrome (within few hours of immunization) d. Hypotonic hypo responsive episodes
5. Other adverse events not requiring investigation
a. Allergic reaction (other than anaphylaxis) b. Arthralgia c. High fever (>39°C) d. Nodule at the injection site
5. Other severe and unusual events

Annex V

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 4 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.

Book review by Professor Pujitha Wickramasinghe, Senior Professor in Paediatrics, University of Colombo

SLMA Guidelines and Information on Vaccines

Eighth edition 2023, 469 pages

As we all know immunization has become an integral part of our life. Sri Lanka has a success story to tell the world on immunization and control of vaccine preventable diseases. Advances in science introduced new vaccines and vaccine schedules were improved to optimize delivery and achieve the best return on investment. Undoubtedly the series of SLMA publications on vaccines provided an updated information and empowered the medical fraternity of Sri Lanka, with 7 editions spanning little over two decades. Earlier the main interest groups of vaccines were the clinicians who looked after children, pregnant women, microbiologists, and immunologist. However, the COVID-19 pandemic brought a paradigm shift in vaccine development, demand, distribution, and deployment all over the world. The newest publication in the SLMA series on vaccines, 'SLMA GUIDELINES AND INFORMATION ON VACCINES', 8th edition, is compiled by 30 able experts in the field, and meticulously edited by 5 eminent personal lead by Dr Lucian Jayasuriya.

The content of the book spreads over 40 chapters with the inclusion of three new chapters, namely on COVID-19, Emerging Illness, and Vaccine Hesitancy. The chapters are arranged in a logical sequence helping the reader to get well oriented and understand the concepts and facts. A uniform format shared across the chapters that discuss about individual vaccines helps the reader to browse through easily. Meticulously page setting and use of simple language has made it reader friendly.

The first chapter gives a beautiful overview on vaccine evolution in the world which is useful to the historians and interested school children and under-graduate students. It gives the reader a different perspective of the book.

Chapter two gives a comprehensive but brief outline of the function of the immune system which is helpful to recapitulate the basics of immune function, and its relevance to the development and action of immunity. It provides a good working knowledge, and the comprehensive listing of the references provide good opportunity to gather more advanced up to date information to the reader.

Basic knowledge required and some common practical issues faced in day-to-day immunization are discussed in the third and thirty eighth chapters, which is quite useful specially for the beginners in the field. I wish that the publication included the impact of antimicrobial therapy on BCG vaccination as well as provided a cross reference to the effects of prednisolone on vaccination. Chapters on how to manage anaphylaxis and reporting adverse events during immunization, although rare, are very important for both patient safety and sustenance of the immunization programme.

Chapters 4 to 25 provide information on specific vaccines, and the information provided does not confine to the respective vaccine but also a concise summary about the microbiology, disease entity and possible clinical outcomes of the illness as well as latency/effect on fetus/ etc. The content is expanded by including two new chapters.

One is on COVID-19 and the other is on emerging diseases namely Ebola, Zoster, M pox and Malaria.

The publication has taken a life course approach to vaccination inclusive of all ages and stages of life. The pandemic brought a new dimension to vaccination in Sri Lanka. Faced with an aging population as well as increasing incidence of non-communicable diseases, vaccinations beyond childhood and pregnancy has gained importance and interest. Vaccination would be a major way in preventing morbidity in these groups of population as well as bringing monetary savings to the health sector. Advances in medical field has improved survival rates in children with immunodeficient states. Further immune compromised states occur due to transplantation, use of immune modulators in diseases treatment or specific disease states. All of them require special protection, and this publication provides the caring physicians the required information in an easy referencing manner.

Vaccinating during different situations are important. Sports is an important part of the life of a youth. Sports have become so competitive, not only at national or international level but also at school level. Further it has bread into a profession where an athlete cannot afford to miss out training or an event due to a vaccine preventable disease. This book has created awareness and empowered the caring physician on this. Editors have addressed vaccination during disasters thus ensuring continuity of vaccination as well as preventing outbreaks of illnesses, which is sometimes missed amidst the chaos.

A timely inclusion is the chapter on vaccine hesitancy. After four decades of successful implementation and augmentation of the vaccine programme in Sri Lanka, over last few years subtle hesitancy has developed among certain groups of the population scattered all over the country. Inclusion of this chapter in this edition is a timely step taken, which empowers local medical fraternity on this emerging issue before it is too late, which is undoubtedly contributing to the spread of measles in the country at this moment of time.

As someone who had used this book almost from its first publication pleased to see the heights it has grown to date. Although it is slightly bulkier, with closer to five hundred pages, the A5 format has made it easy to handle. Its highly recommended to be placed on the desk of a practicing clinician as a handbook on vaccination. In an era where most of the material are available on palm held devices, I hope the editors and the publisher would take this to the next level, a web based interactive publication. That would make it more user friendly, easily accessible, and a solution to its bulkiness and exorbitant printing cost.

Once again while congratulating Dr Lucian Jayasuriya lead team of experts, for making a comprehensive easy to read publication, I wish all success in updating and upgrading the publication with time

Wickramasinghe VP. *Ceylon Medical Journal* 2023; 68(2): 89 – 90.

DOI: https://doi.org/10.4038/cmj.v68i2.9781

Typeset & printed by
Techno Graphics
No.77, De Soyza Road, Moratuwa
Phone: +94 77 6000600
Email: technographics678@gmail.com

SLMA Guidelines and Information on Vaccines Nineth Edition 2026

ISBN 978-624-5972-15-9, 498 pages

Published by the Sri Lanka Medical Association
No. 6, Wijerama Mawatha, Colombo 7

The printing of this book was sponsored by
Serum Institute - Citihealth, Sri Lanka
as a contribution to medical education

ISBN 978-624-5972-15-9
9 786245 972159