



SLMA GUIDELINES AND INFORMATION ON VACCINES

SIXTH EDITION

**SRI LANKA MEDICAL ASSOCIATION
COLOMBO
2017**



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&
INFORMATION ON
VACCINES**

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Third Edition 2008

SLMA Guidelines on Vaccines and Information on Vaccines

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First Print 2008 - 5000 copies

Second Print 2009 – 3,500 copies

Fourth Edition 2011

SLMA Guidelines and Information on Vaccines

Editors

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First Print 2011 – 4000 copies

Second Print 2012 – 5000 copies

Third Print 2013-3000 copies

Fifth Edition 2014

SLMA Guidelines and Information on Vaccines

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First Print – 2000 copies 2014

Second Print – 5000 copies 2015

Third Print – 2000 copies 2016

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PREFACE

It is my pleasure and privilege to write this preface for the 6th edition of 'Guidelines and Information on Vaccines'. I express my sincere appreciation to SLMA's Expert Committee on Communicable Diseases for this valuable output. Their sustained commitment to update our profession with a user-friendly compilation of time appropriate information on current immunization needs of our citizens is highly commendable.

This practical guide has enjoyed a very high rating by local practitioners over sixteen successive years, indeed a very remarkable achievement for an entirely volunteer group of medical professionals. I thank Past President Dr. Lucian Jayasuriya for his unstinting commitment and coordination in ensuring this project to have such a successful continuity. I have observed with humility the diligent announcements and regular reminders of the numerous meetings of the highly capable editorial team. My heartfelt gratitude is extended to each and every author for his or her valuable time, excellent contribution and for maintaining the high standards.

Sri Lanka has enjoyed the unique achievement of maintaining a continuum of a near universal coverage, at grass root level, of its national immunization programme. It is noteworthy that the national policy on immunization (NPI) aims at prioritizing vaccine preventable diseases. The past six decades have witnessed the successful implementation of the NPI, particularly in the fields of maternal and child health. More recently, the rapidly changing population dynamics, advances in immunology and temporal trends in the epidemiology of communicable diseases have led to the need for the development of newer vaccines. Hence the busy practitioner requires a parallel update on the long list of vaccines with their scientific basis and cost effectiveness.

The Sri Lanka Medical Association is proud to have given the required leadership for this distinct need in developing and updating a comprehensive handbook on vaccines for the Sri Lankan medical profession. The inclusion of SLMA as the lead professional body with

many members of its Expert Committee on Communicable Diseases contributing to the National Advisory Committee on Communicable Diseases of the Ministry of Health has enabled a healthy approach to the development of nationally relevant updates by consensus.

With regard to the content, layout and inclusion of novel aspects of immunization and their potential for side effects in this edition, I have no hesitation in endorsing these updates. The SLMA is indeed proud of to launch the 6th Edition in 2017. I am truly grateful to Prof Anura Weerasingle for his commitment, over nearly two decades, as Joint Editor of the first five editions. I warmly welcome the new joint editor Dr. Geethani Galagoda and look towards your contributions in the coming decades. Notable changes made to this edition include the deletion of a separate chapter for the measles vaccine, since this is included in MMR, a separate chapter on dengue vaccine by Dr. Hasitha Tissera and the immunization of transplantation recipients by Dr. Rajiva de Silva. It is noteworthy that all chapters have been completely revised by a new team of experts.

Looking forward to the ready response of members of our profession, including postgraduate trainees and medical undergraduates, I expect the best practices of immunization to be instituted in the whole of Sri Lanka and ensure the optimal protection of the Health of our people.

Prof. Chandrika Wijeratne

President

Sri Lanka Medical Association

INTRODUCTION

A new chapter in the history of medicine began when on 14th May 1796, Edward Jenner inoculated James Phipps, an eight-year-old boy, to prevent smallpox using pus from cowpox blisters on the hands of a milkmaid.

This led to the production of an effective vaccine which contributed to the eradication of smallpox from the world nearly two centuries later. This was certified by a commission of eminent scientists on 9th December 1979 and endorsed, by the World Health Assembly on 8th May 1980.

Beginning from the latter part of the twentieth century, many new developments have taken place in the sphere of vaccine production.

The new vaccines represent a major advance in the science of discovery as well as in production technologies. This period witnessed the production of several conjugate vaccines, *Haemophilus influenzae* type b (Hib), pneumococcal and meningococcal vaccines. The other major development has been in the successful production of combined vaccines which reduces the number of injections without compromising on the efficacy of individual vaccines. The next step forward was utilisation of a new technology, e.g. genetic recombination for production of hepatitis B, influenza, rotavirus and human papillomavirus (HPV) vaccines.

Vaccines have been useful in preventing malignancies. The hepatitis B virus vaccine prevents chronic liver disease which could result in liver cancer. The HPV vaccine is targeted to prevent cervical cancer, which is caused by persistent HPV infection.

This wave of new vaccines also correlated with new pricing policies, such as tiered pricing to make vaccines more affordable for developing countries. Along with these changes, the formation of the Global Alliance for Vaccines and Immunization (GAVI) and the availability of new streams of funding led to an emphasis on global vaccination efforts.

With regard to childhood immunization programmes, the World Health Organization (WHO) established the Expanded Programme on Immunization (EPI) in 1974. Through the 1980s, WHO and the United Nations International Emergency Childrens Fund (UNICEF) worked together to achieve universal childhood immunization of the six EPI vaccines (BCG, OPV, diphtheria, tetanus, pertussis, and measles) and as a result the current global immunization coverage of these is over 80%.

In the present era of emerging antimicrobial resistance (AMR), vaccines will have an important role to play. Scientists are exploring the value of vaccines in the avoidance of AMR. As the first step towards this, WHO will launch an exercise towards the prioritization of vaccines focusing on their role against AMR and will lead the development of a roadmap laying out a global strategy for this purpose.

Vaccination against smallpox was introduced in Sri Lanka under the Vaccination Ordinance as early as 1886. Subsequently BCG was introduced in 1949 and DPT in 1961. This was closely followed by OPV in 1962. Sri Lanka had already introduced these vaccines before the WHO launched the EPI, and measles vaccination was included into the National Immunization Programme (NIP) in 1984.

Sri Lanka's immunization programme is widely recognized as one of the strongest performers in the region and is among the best in the world. It has effectively controlled or eliminated all traditional childhood vaccine preventable diseases through outstanding levels of sustained infant immunization coverage. Throughout the last decade, immunization coverage of infants in Sri Lanka against the six diseases has exceeded 99% as per WHO fact sheet of 2013. Hep B vaccine administered simultaneously with the DPT vaccine was added to the NIP in 2003, with the support of (GAVI). Subsequently with the introduction of the *Haemophilus influenzae* type b (Hib) vaccine in 2008, the pentavalent vaccine (DTwPHep B — Hib) replaced the DTP and hepatitis B vaccines requiring only a single injection to administer all five vaccines. The introduction of the live Japanese encephalitis (JE) vaccine in 2011 has reduced the number of doses required for effective prevention of JE. The MMR vaccine has been introduced to

the childhood immunization programme in 2011 and has replaced the measles and measles-rubella vaccines and is expected to reduce the morbidity due to deafness, a serious complication of mumps virus infection. In addition, from 2016, fIPV (fractional IPV) has been included in the EPI to be given at the age of 2 and 4 months. HPV vaccine has been introduced to the NIP from July 2017.

The Expert Committee on Communicable Diseases of the Sri Lanka Medical Association, with the participation of several specialists produced “Guidelines for the use of non EPI vaccines” in 2001. The second edition published in 2004, included the EPI vaccines and was named the “SLMA guidelines on vaccines”. The third edition was published in 2008 and was titled “SLMA guidelines and information on vaccines” and the fourth edition was launched in 2011. In 2014, the fifth edition was published.

The compilation of the sixth edition of the book commenced in September 2016. In addition to the updated information on vaccines included in the previous edition, this edition contains two new chapters, one on the dengue vaccine and the other on immunization following organ transplantation. The chapter on measles vaccine was omitted as it is included in the MMR.

These guidelines are intended to provide assistance to practitioners and represent a consensus opinion arrived at, by committee members and authors of chapters based on current evidence. As new information becomes available this edition will be revised. I wish to express my sincere gratitude to the authors of the chapters and the core group who reviewed them, for their dedicated efforts to formulate the revised guidelines. I am grateful to Dr. Lucian Jayasuriya who spearheaded this activity on behalf of the Expert Committee on Communicable Diseases of the SLMA. I thank GlaxoSmithKline for their sponsorship during the preparation of the manuscript and for its publication.

Sri Lanka has achieved much in terms of health in spite of numerous challenges such as the thirty year old war and a low GDP. Infectious diseases including vaccine preventable diseases have been controlled to a large extent and currently take second place to non-communicable diseases. High immunization coverage throughout the island has

largely contributed to achieving zero or low prevalence rates with regard to vaccine preventable diseases. This has been possible due to availability of effective vaccines and trained staff, government policy on financial commitment and good programme management. The National Immunization Policy that was launched in April 2014 is expected to improve and facilitate the existing processes towards better delivery of services with regard to immunization.

I earnestly hope and believe that this book will contribute to appropriate use of vaccines by medical practitioners so that safe and effective practices with regard to vaccination are observed. It is important to build trust between vaccine recipients and vaccine providers to enable maintenance of high immunization coverage in the island to prevent disease outbreaks and maintain herd immunity.

Dr. Ranjith Perera

Chairperson

Expert Committee on Communicable Diseases of the SLMA

ABBREVIATIONS

ABC	airway, breathing, circulation
ACIP	Advisory Committee on Immunization Practices (of the Centers for Disease Control and Prevention)
AE	accident & emergency
AEFI	adverse events following immunization
AFP	acute flaccid paralysis
AIDS	Acquired Immunodeficiency Syndrome
AMR	antimicrobial resistance
APC	antigen presenting cell
ARSN	Asian Rotavirus Surveillance Network
ART	antiretroviral therapy
ARV	anti-rabies vaccine
ASO4	alum and monophosphoryl lipid
aTd	adult tetanus and diphtheria vaccine
BCG	Bacille Calmette- Guerin
BNF	British National Formulary
CCID ₅₀	cell culture infective dose 50
CDC	Centers for Disease Control and Prevention
CD4	cluster of differentiation 4
CD8	cluster of differentiation 8
CHDR	Child Health Development Record
CIN	cervical intraepithelial neoplasia
CKD	chronic kidney disease
CMVIG	cytomegalovirus immunoglobulin
CRS	congenital rubella syndrome
CYD- TDV	chimeric yellow fever dengue vaccine
DF	dengue fever
DHF	dengue haemorrhagic fever
DNA	deoxyribonucleic acid
DSS	dengue shock syndrome

DTP	diphtheria, tetanus and pertussis vaccine
DTaP	diphtheria, tetanus and acellular pertussis vaccine
DTwP	diphtheris, tetanus and whole cell pertussis vaccine
DTP-HepB	diphtheria, tetanus, pertussis and hepatitis B vaccine
DTaP-HepB	diphtheria, tetanus, acellular pertussis and hepatitis B vaccine
DTP-HepB-Hib	diphtheria, tetanus and pertussis, hepatitis B and <i>Haemophilus influenzae</i> type b vaccine
DTaP-HepB-Hib-IPV	diphtheria, tetanus and acellular pertussis, hepatitis B, <i>Haemophilus influenzae</i> type b and inactivated polio vaccine
DTP-Hib	diphtheria, tetanus and whole cell pertussis and <i>Haemophilus influenzae</i> type b vaccine
DT	diphtheria and tetanus vaccine
ELISA	enzyme linked immunosorbent assay
EPI	Expanded Programme of Immunization
ERIG	equine rabies immunoglobulin
ETU	emergency treatment unit
FA	fluorescent antigen
GAVI	Global Alliance on Vaccination and Immunization
GBS	Guillain Barré Syndrome
GDP	gross domestic product
GVHD	graft vs host disease
HAV	hepatitis A virus
HBV	hepatitis B virus
HBIG	hepatitis B immunoglobulin
HBcAb	hepatitis B core antibody

HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCW	health care worker
HDV	hepatitis D virus
HDC	human diploid cell
HDCV	human diploid cell vaccine (for rabies)
Hep B	hepatitis B
HHE	hypotonic hypo-responsive episode
Hib	<i>Haemophilus influenzae</i> type b
HibMenC	Hib & <i>Neisseria meningitidis</i> sero group C vaccine
Hib-PRP	<i>Haemophilus influenzae</i> conjugated polysaccharide vaccine
PRP-CRM 197	with CRM protein
PRP-D	with diphtheria toxoid
PRP-T	with tetanus toxoid
PRP-OMP	with meningococcal outer membrane protein
HbOC	<i>Haemophilus b</i> oligosaccharide
HIV	human immunodeficiency virus
HNIG	human normal immunoglobulin
HMSO	Her Majesty's Stationery Office
HPV	human papillomavirus
HRIG	human rabies immunoglobulin
HSCT	haemopoietic stem cell transplantation
HTIG	human tetanus immunoglobulin
HTLV	human T cell lymphotropic virus
HZ	herpes zoster
ICU	intensive care unit
ICV	International Certificate of Vaccination
ID	intra-dermal
IDSA	Infectious Diseases Society of America
IFN γ	interferon gamma
IG	immunoglobulin
IgA	immunoglobulin A

ICVP	International Certificate of Vaccination or Prophylaxis
IgG	immunoglobulin G
IgM	immunoglobulin M
IHR	International Health Regulations
IM	intramuscular
IPV	inactivated polio vaccine
ITI	Industrial Technology Institute
ITP	immune mediated thrombocytopenic purpura
IU	international units
IV	intravenous
IVIG	intravenous immunoglobulin
JAMA	Journal of the American Medical Association
JE	Japanese encephalitis
JEV	Japanese encephalitis vaccine
LAIV	intranasal live attenuated influenza vaccine
LJEV	live Japanese encephalitis vaccine
mIU	milli international units
mL	millilitre
MCV4	tetravalent meningococcal conjugate vaccine
MenACWY	tetravalent meningococcal vaccine conjugated with diphtheria toxoid
MHC	major histocompatibility complex
MMR	measles, mumps and rubella vaccine
MMRV	measles, mumps, rubella and varicella vaccine
MPL	monophosphoryl lipid
MPSV4	tetravalent meningococcal polysaccharide vaccine
MSM	men who have sex with men
Mtb	<i>Mycobacterium tuberculosis</i>
NAT	nucleic acid amplification testing
NCD	non communicable diseases

NGO	non governmental organisation
NHIG	normal human immunoglobulin
NIP	National Immunization Programme
NMRA	National Medicinal Drugs Regulatory Authority
NPI	National Policy on Immunization
N saline	0.9% sodium chloride
NTHi	non-typeable <i>Haemophilus influenzae</i>
OCV	oral cholera vaccine
OD	orally daily
OPV	oral polio vaccine
bOPV	bivalent oral polio vaccine
tOPV	trivalent oral polio vaccine
PCEC	purified chick embryo cell vaccine (for rabies)
PCU	primary care unit
PCR	polymerase chain reaction
PCV	pneumococcal conjugate vaccine
PCV7	7 valent pneumococcal conjugate vaccine
PCV10	10 valent pneumococcal conjugate vaccine
PCV13	13 valent pneumococcal conjugate vaccine
PHK	primary hamster kidney cell culture
PET	post exposure treatment
PHN	post herpetic neuralgia
PLHIV	people living with HIV/AIDS
PO	per oral
PPSV23	pneumococcal polysaccharide vaccine
PRP	polyribisoylribitol
PVRV	purified vero cell rabies vaccine
RIG	rabies immunoglobulin
RNA	ribonucleic acid
RRP	recurrent respiratory papillomatosis

SAGE	Strategic Advisory Group of Experts of WHO
SAPNA	South Asia Pneumococcal Network Alliance
SC	subcutaneous
SCID	severe combined immunodeficiency
SLMA	Sri Lanka Medical Association
SLSI	Sri Lanka Standards Institute
ST	sensitivity test
STD	sexually transmitted diseases
TCV	tissue culture vaccine
TCV	typhoid conjugate vaccine
TDV	tetravalent dengue vaccine
Tdap	reduced antigen tetanus, diphtheria and acellular pertussis vaccine
TfH	follicular helper T cells
TIG	tetanus immunoglobulin
TIV	trivalent inactivated vaccine (influenza)
TIV/QIV	trivalent and quadrivalent vaccine (influenza)
TLR	toll-like receptor
TST	tuberculin skin test
TT	tetanus toxoid
UNICEF	United Nations International Emergency Children's Fund
VAPP	vaccine associated paralytic poliomyelitis
VDPV	vaccine derived polio virus
iVDPV	immunodeficiency associated vaccine derived polio virus
VLP	virus-like particles
VVM	vaccine vial monitor
VZIG	varicella zoster immunoglobulin
VZV	varicella zoster virus

WHO	World Health Organization
WPV	wild polio virus
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
YFVC	Yellow Fever Vaccine Centre

PRECAUTIONS BEFORE VACCINATION

1. Vaccines should not be administered

if there was a severe reaction such as anaphylaxis following administration of that particular vaccine or a component of that vaccine. (Exception- refer Chapter 10 Influenza Vaccine)

2. Live vaccines should not be administered

- to a person having a malignancy of the reticulo-endothelial system *
- during pregnancy
- if a live vaccine had been administered within one month

if the person has had blood or blood products including immunoglobulin within three months

- for two weeks after stopping long term oral steroids
($\geq 2\text{mg/kg/day}$ prednisolone or equivalent or 20 mg/day for > 4 weeks in children or 40 mg/day > 2 weeks in adults)
- for three months after stopping immunosuppressive therapy

*varicella vaccine can be administered to leukaemic children in remission (refer Chapter 20 Varicella Vaccine)

3. Postpone vaccination

if the vaccinee is suffering from an acute infection or fever (temperature $> 38.5^{\circ}\text{C}$)

4. Be cautious if there is

- a bleeding disease
- a history of Guillain Barré syndrome
- a progressive neurological disorder

5. Postpone pregnancy

- for three months after varicella vaccination
 - for one month after MMR
6. Vaccination should be given in a hospital if there is a history of severe allergy.
 7. Vaccination should be given only in clinics where the following minimum facilities are available. - adrenaline, syringes, canula, saline and a bed.

It is preferable to have a complete emergency tray. (refer Chapter 27 Management of Anaphylaxis.)

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CHAPTER 1

IMMUNOLOGICAL BASIS OF VACCINATION

Introduction

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

Normal Immune response

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 and CD8⁺ cytotoxic T lymphocytes. The CD4⁺ T lymphocytes are further divided into T_H1 cells producing inflammatory cytokines such as interferon γ (IFN γ) and T_H2 cells, as well as regulatory T cells and T_H17 cells^{1,2}.

The innate immune system recognizes the pathogen and subsequently activates the specific immune system³. These two systems act in concert against the infection. Pathogens that enter the body through skin/mucous membranes are taken up by resident antigen presenting cells in these tissues. The main antigen presenting cell (APC) is the dendritic cell, the macrophage being another APC. Blood borne pathogens are directly taken up by dendritic cells in the white pulp of the spleen. The antigen presenting cells and molecules of the innate immune system have receptors (pattern recognition receptors) that can recognize conserved foreign molecules found only on pathogens (pathogen associated molecular patterns). Recognition is followed by

activation of these cells and molecules. Dendritic cells found in the skin and other sites are crucial in the subsequent activation of the specific immune system¹. The dendritic cell senses potential ‘danger’ when recognizing pathogen associated molecular patterns. Recognition is followed by uptake of the pathogen and activation of the dendritic cell and other antigen presenting cells.

This leads to

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

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

T and B cells have receptors that recognize antigens. Most circulating lymphocytes recognize non-self-antigens². Lymphocytes circulate in the body between blood and peripheral lymphoid tissue (cell trafficking). Activated dendritic cells present peptides derived from pathogens, in conjunction with MHC Class II molecules to CD4+ T cells in the T cell areas of the lymph nodes and spleen. The CD4+ T cell will be activated only if second signals are provided by co-stimulatory molecules on the surface of dendritic cells. These co-stimulators are up regulated only if pathogen associated molecular patterns are recognized by the dendritic cells. As these patterns are only found on pathogens, the dendritic cell will 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 T_H1 or T_H2 cells or memory cells².

Dendritic cells which are activated by microorganisms such as *M. tuberculosis* produce cytokines that switch a naïve CD4⁺ T cell to an activated T_H1 cell, while helminths and some bacterial pathogens induce a T_H2 response. T_H1 cells produce cytokines (IL2, IFN γ) that activate CD8⁺ cytotoxic T lymphocytes, macrophages and B lymphocytes, while T_H2 cells activate B cells by producing IL4, 6 and 13.

B cells that recognize protein antigens need help from CD4⁺ T cells (T_H1 and T_H2) to produce antibody. The initial B cell response takes place extra-follicularly (outside the germinal centre)² and produces low affinity IgM and a small amount of IgG. This occurs within a few days of the infection/immunization and is short lived. This is followed by a response in the germinal centre. B cells move into the germinal centre and encounter their cognate antigen found on the surface of follicular dendritic cells. The B cell proliferates, producing a clone of daughter cells whose antigen binding receptors (immunoglobulin molecules found on the surface of the B cell) 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 plasma cells or memory B cells. With time, high affinity (affinity maturation) IgG, IgA and IgE antibodies are produced (isotype switching) by plasma cells, some being long lived. Memory B cells are capable of producing high affinity, class switched antibody with great rapidity, after re-exposure to the same microorganism. Affinity maturation, isotype switching and memory need T cell help and are hallmarks of antibody responses to protein antigens. T cell help is provided in germinal centers by follicular helper T cells (T_{fh} cells). This response takes 10-14 days to appear and terminates in 3-6 weeks. Peak antibody concentrations occur 4-6 weeks after primary immunization.

Polysaccharide epitopes such as the capsules of *S. pneumoniae* and *H influenzae*, do not activate CD4⁺ T cells (T independent responses)². A subset of B cells in the marginal zone of the spleen, assisted by marginal

zone macrophages, produce low affinity, mainly IgM antibodies and medium affinity IgG (T independent antibodies). Polysaccharides are poorly immunogenic in children under 2 years, till maturation of the marginal zone. As T independent responses do not produce memory cells, subsequent re-exposure evokes a repeat primary response. In some instances, revaccination with certain bacterial polysaccharides may even induce lower antibody responses than the first immunization, a phenomenon referred to as hyporesponsiveness⁴.

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.

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 recognized 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 T_H1 cells activating the macrophage, resulting in intracellular killing of the bacteria.

Vaccines

Different types of vaccines have been produced⁵.

- Live attenuated
- Killed/inactivated
- Subunit
- Recombinant
- Conjugate
- Toxoids

Immune response to vaccines

Vaccine induced immunity is mainly due to IgG antibodies. Antibodies are capable of binding toxins and extra-cellular pathogens. The quality of the antibody (avidity), the persistence of the response and generation of memory cells capable of a rapid response to reinfection are key determinants of vaccine effectiveness. 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. With viruses such as hepatitis B, undetectable antibody titers are seen in many vaccine recipients but due to the long incubation period of the virus, memory B cells can be reactivated in time to combat the infection.

For infections which originate at mucosal sites, transudation of serum IgG will limit colonization and invasion. This is due to pathogens being prevented from binding to cells and receptors in the mucosa. Transudation of IgG is not seen with polysaccharide vaccines. If the pathogens breach the mucosa, IgG in serum will neutralize the pathogen, activate complement and facilitate phagocytosis, thereby preventing spread. Some vaccines (e.g. oral polio, rotavirus and nasal influenza) will stimulate production of IgA antibody at mucosal surfaces, thereby limiting virus shedding.

Live, inactivated and subunit 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 response⁴ 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) evokes a T dependent response.

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

Antibody responses are ineffective against intracellular organisms such as *M. tuberculosis*. There is evidence that a CD4+ T_H1 response, with production of IFN γ leading to activation of infected macrophages is elicited following BCG vaccination⁶.

The quality of the immune response depends on the type of vaccine. Live viral vaccines evoke a strong immune response.

This is due to⁷

- having sufficient pathogen associated molecular patterns to efficiently activate immature dendritic cells, a key requirement for the development of specific immunity.
- the vaccine virus 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 occur. 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 (eg. 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 pathogen associated molecular patterns 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. 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, provided the inoculations are performed at different sites. Booster doses are ineffective with polysaccharide vaccines as memory B cells are not produced.

Determinants of primary vaccine response⁷

- Intrinsic immunogenicity of the vaccine
- Type of vaccine-Live viral vaccines elicit better responses than non-live vaccines. Non-live vaccines rarely induce high and sustained antibody responses after a single dose. Therefore, primary immunization schedules usually include at least two doses, repeated at a minimum interval of 4 weeks to generate successive waves of B cell responses. Even so, the response usually wanes with time.
- Dose - As a rule, higher doses of non-live antigens, up to a certain threshold, elicit higher primary antibody responses. This may be particularly useful when immunocompetence is limited eg. for hepatitis B immunization of patients with end stage renal failure
- Route - The route of inoculation is important. The dermis has many dendritic cells, and for example, the rabies vaccine given intradermally at 1/10th the IM dose can evoke an equally good response. Where the vaccine is not very immunogenic (eg. hepatitis B vaccine), IM injections are preferred over SC^{7,8} as muscle tissue has many dendritic cells, unlike adipose tissue
- Nature of the protein carrier
- Genetic composition of the individual
- Age - responses at the extremes of age are weaker and less persistent

Determinants of duration of vaccine response

Plasma cells which produce antibodies are usually short lasting, while a few plasma cells produced in the germinal centre may survive for long periods in the bone marrow. These cells are responsible for the maintenance of protective antibodies for long periods⁷. This occurs most efficiently with live vaccines, less efficiently with non-live vaccines, but not with polysaccharide vaccines⁷. 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, even live vaccines need booster doses (e.g. varicella, measles, live JE, oral polio, etc)⁹.

The interval between doses may be important. Two doses given one week apart may evoke a rapid short lived response, whereas 2 doses 4 weeks apart may be longer lasting⁷.

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

Adjuvants

For non-live vaccines, adjuvants (Latin *adjuvare* meaning ‘to help’) are incorporated to provide the ‘danger’ signal to the antigen presenting cells¹⁰. Adjuvants improve the magnitude of immune responses to vaccines, including seroconversion rates, dose sparing and reduction of doses¹¹. They are also needed to prolong the antigen delivery at the site of inoculation, thereby recruiting more dendritic cells¹⁰. They should also be non-toxic.

The known adjuvants used in human vaccines are

- Alum - an aluminum salt-based adjuvant
- Oil-in-water emulsions - such as MF59 and AS03

More recently, with the knowledge gained by identifying the molecular targets of adjuvants, a new type of adjuvant was devised¹². Toll-like receptors (TLRs) are innate receptors that recognize pathogen associated molecular patterns. A natural agonist that can be recognized by TLR 4, monophosphoryl lipid A (MPL) was identified which can stimulate 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 vaccines¹³. TLR

agonists enhance the immune response, but the duration of this effect needs further study ⁹.

Summary

All vaccines produce antibodies which can neutralize 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 T_H1 cells, whose cytokines help macrophages control *M. tuberculosis*. Live viral vaccines produce long lasting, even lifelong immunity compared to non-live vaccines.

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CHAPTER 2

BCG

Introduction

Mycobacterium tuberculosis (*Mtb*), the aetiological agent of tuberculosis is an important cause of disease and death particularly in developing countries. In most developing countries the existing strategies for control of TB is inadequate due to the rising number of drug resistant strains, high cost of drugs and other socio-economic conditions.

Primary infection often goes unnoticed clinically in the majority of those infected and may progress to cavitary pulmonary tuberculosis, extra-pulmonary tuberculosis, miliary tuberculosis or meningitis.

The only vaccine currently available for the prevention of tuberculosis is BCG (Bacille Calmette-Guerin), which was developed in 1921. BCG vaccine is effective in protection against meningitis and disseminated TB in children. However, it does not prevent primary infection and more importantly, does not prevent reactivation of latent pulmonary infection, the principal source of bacillary spread in the community. Therefore, the impact of BCG vaccination on transmission of *Mtb* is limited. However, BCG vaccination is considered a life-saving and important component of standard TB control measures in most endemic countries¹.

BCG has a protective effect against leprosy in the range of 26 to 41% based on controlled trials. However, BCG vaccine is not used specifically to control leprosy².

A specific formulation of BCG is used in the treatment of superficial forms of bladder cancer. It mounts a local immune reaction against the tumor³.

In Sri Lanka the coverage of BCG vaccination is 99%⁴.

Type of vaccine

BCG is a live attenuated vaccine which comprises *M. bovis* strain that Calmette and Guérin passed through numerous cycles. All vaccine substrains in use stem from one source, strain Bacille Calmette-Guérin. A number of BCG vaccine strains are available, although the French Pasteur strain 1173 P2, the Danish strain 1331, the Glaxo strain 1077 and the Tokyo strain 172 account for about 90% of BCG vaccinations worldwide. In terms of efficacy, no BCG strain is demonstrably better than another, and there is no global consensus as to which strain of BCG is optimal for general use¹.

Efficacy

BCG shows efficacy in the range of 60-80% in non-endemic countries, but shows a much lower efficacy in endemic countries. However, the average protection against TB meningitis and disseminated disease is 86%¹.

Due to this, childhood immunization with BCG has caused a remarkable reduction in the incidence of miliary tuberculosis and tuberculous meningitis in children⁵.

Indications

- In **endemic countries** such as Sri Lanka vaccine is given at birth, (including low birth weight babies and premature babies before discharge from hospital).
- Children between 6 months to 5 years of age without a BCG scar⁶. A scar is expected to be present by the age of 6 months after successful vaccination. A tuberculin test is not required prior to vaccination.
- In **non endemic countries** vaccination is indicated for children and adults who are at risk of TB exposure and tuberculin negative (less than 10 mm).

Dosage and administration

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

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

During administration of the vaccine, the vaccine should be exposed to light for the shortest period of time possible and never for more than 4 hours. If it is not used immediately after reconstitution, the reconstituted vaccine should be stored between 2°C - 8°C and protected from light. Any vaccine remaining at the end of a vaccination session (maximum 4 hours) should be discarded⁶.

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

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

Contraindications

- Hypersensitivity to any component of the vaccine
- Symptomatic or asymptomatic HIV disease⁷ (infants born to HIV positive mothers could be tested for HIV using HIV RNA test and if results are negative, BCG should be administered)
- Congenital immune deficiency disorders
- Malignant disease
- Persons under immunosuppressive treatment

Precautions

- In cases where infants have been exposed to smear-positive pulmonary TB shortly after birth, BCG vaccination should be

delayed until completion of 6 months of prophylactic isoniazid treatment.

- Children with a family history of immune deficiency disease should be investigated prior to vaccination; if they are inadvertently vaccinated, an infectious disease specialist should be consulted and anti-tuberculous therapy administered if clinically indicated⁸
- If there is a history of unexplained sibling death in infancy, the baby should be investigated for immunodeficiency prior to administration of BCG⁹.

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

A local reaction is normal after BCG vaccination. A few days after vaccination, an induration develops at the point of injection, gradually changing to a small papule and then an ulcer in 2 to 4 weeks. The local reaction usually regresses in 2 to 5 months, leaving a superficial scar⁶. Presence of a scar is used as a marker of previous BCG vaccination but does not indicate protection against TB.

Adverse effects

In rare cases, an abscess may appear at the point of inoculation. Axillary or rarely cervical adenitis (BCGitis) may lead in exceptional cases to suppuration, requiring treatment with anti-tuberculosis therapy.

Faulty injection technique is the most frequent cause of severe injection site reaction.

Storage

2°C – 8°C

New vaccines in the pipeline

Recent advances in areas such as mycobacterial immunology and genomics have stimulated research on several new experimental vaccines. The main vaccine targets are, prevention of infection in naïve individuals, prevention of reactivation of latent infection and therapeutic vaccines to prevent relapses in TB patients. Currently, the most favoured research strategies include development of recombinant modified BCG vaccines, attenuated strains of *Mtb*, subunit vaccines and DNA vaccines. Some of these are currently at the evaluation stages of either phase 2 or phase 3 trials¹⁰.

Until a more effective vaccine becomes routinely available optimal utilization of BCG is highly encouraged.

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CHAPTER 3

CHOLERA VACCINE

Introduction

Cholera is an acute intestinal infection caused by the toxigenic Gram negative bacterium *Vibrio cholerae*. The infection is often asymptomatic or mild and self limited. In severe illness, the patient develops profuse painless diarrhoea with characteristic “rice water stools” associated with vomiting, thirst and muscle cramps. This may lead to rapid volume depletion, sometimes resulting in circulatory collapse. Death may occur in severely dehydrated patients within a few hours after the onset of symptoms. The case fatality rate may exceed 50% among untreated severe cases, but is less than 1% with proper and timely treatment^{1,2,3}.

Infection is acquired primarily by ingesting faecally contaminated water or shellfish and other foods. Person to person spread may occur through the faeco-oral route. The risk to travellers even in infected areas is very small^{3,4}. The incubation period varies from few hours to 5 days, usually 2-3 days³.

Cholera outbreaks can occur periodically in any part of the world where water supplies, sanitation, food safety and hygiene practices are inadequate. Therefore, continued occurrence of cholera outbreaks in the world, emergence of new, more virulent strains of *V. cholerae* O1 (original El Tor is replaced by new and more virulent strain in parts of Africa and Asia)⁵ and, emergence and spread of antibiotic-resistant strains have raised serious concerns. Since 2010, Haiti is fighting the largest cholera epidemic in the world in five decades⁴. Somalia and Yemen reported large cholera outbreaks in 2017 with significant mortality and morbidity. Although cholera has not been reported in our country since 2003, it is a notifiable disease and is under surveillance.

Vibrio cholerae has more than 200 serogroups of which only O1 and O139 cause epidemic disease. Serogroup O1 has two biotypes

(classical and El Tor) and is further divided into subtypes (Ogawa or Inaba). *V. cholerae* El Tor is currently the predominant subtype in the world and is associated with more severe disease ⁵.

Types of vaccine

Two types of inactivated oral cholera vaccines (OCV) are currently available^{5,6}.

- WC-rBS : a monovalent vaccine containing inactivated whole cell (WC) of *V. cholerae* O1 (Classical and El Tor, Inaba and Ogawa) plus recombinant cholera toxin B subunit (rBS)
- bivalent vaccines which contain serogroups O1 and O139.

The use of injectable whole cell cholera vaccine, although still produced in a few countries, is not recommended by the World Health Organization due to its low efficacy, limited duration of protection, unpleasant side-effects in many patients and inability to prevent transmission of the infective agent.

Cholera vaccines are not currently available in Sri Lanka.

Efficacy

The currently available OCVs are safe and offer protection of >50% for at least 2 years among endemic populations⁵.

Since immunization does not provide complete protection against cholera infection, all travellers to a cholera endemic country should be cautioned that the best protection against cholera is to avoid contaminated food and water.

Indications

Oral cholera vaccine is recommended for travellers to endemic or epidemic areas. However, currently there is no mandatory requirement for cholera vaccination as a prerequisite for entry into any country. It could be used specially for high risk populations such as children and pregnant women in outbreak situations⁶.

Immunization should be completed at least 1 week before potential exposure.

Presentation

Oral cholera vaccine is supplied as 3mL of a whitish suspension in a glass vial. A sachet of sodium hydrogen carbonate as white granules is also supplied and this buffer should be mixed with water.

Dosage and administration

The sodium hydrogen carbonate buffer is mixed in 150 mL of cool water in a disposable plastic cup. Full volume should be used for those aged >5 years or half of the solution should be discarded and remaining 75 ml should be used for children aged 2–5 years to prepare the vaccine. The appropriate volume of the solution should then be mixed with the vaccine suspension to obtain a colourless, slightly opalescent fluid. The vaccine must be drunk within two hours of reconstitution.

Cholera vaccine can be given at the same time as injected vaccines.

Product		Primary immunization	Booster
Monovalent vaccine	Adults & children ≥ 6 years of age	2 doses, more than 7 days apart (but less than 6 weeks)*	1 dose after 2 years*
	Children 2-5 years of age	3 doses, more than 7 days apart (but less than 6 weeks)*	1 dose every 6 months*
Bivalent vaccine	Adults & children ≥ 1 year of age	2 doses 14 days apart	Booster after 2 years

** If the interval between doses is longer than indicated, restart primary immunization. The need to repeat a primary course of the immunization is unique to this vaccine³*

Food, drink, and oral medicines should be avoided 1 hour before and after vaccination.

Contraindications

General contra-indications for vaccines are applicable.

Adverse effects

Adverse effects include headache, diarrhoea, abdominal pain, and rarely, nausea, vomiting, loss of appetite, dizziness, fever, and respiratory symptoms.

Storage

2°-8° C. Do not freeze.

Use of cholera vaccine in outbreaks

Vaccination should not be the mainstay of control measures, when an outbreak has already commenced. Pre-emptive vaccination should be considered if the current outbreak is likely to extend to new geographical areas. Reactive vaccination may become relevant as an additional control measure, depending on the previous and present epidemiological situation, local infrastructure, the logistics associated with its use and the ability to clearly identify target populations. Pre-emptive or reactive vaccination should be as quickly as possible with a high coverage.

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CHAPTER 4

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) but only few months of heterotypic cross-immunity¹.

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

The more severe form of dengue infection is dengue haemorrhagic fever (DHF). Although it represents a small proportion of all dengue illnesses, DHF is characterized in its early stages by the signs and symptoms of DF described above, followed by increased vascular permeability and/or haemorrhaging 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 DHF².

Types of vaccine

Live attenuated vaccines

The first dengue vaccine, a tetravalent dengue vaccine (TDV), also known as chimeric yellow fever dengue vaccine (CYD-TDV), is currently registered in several countries in Asia and Latin America.

At the time this edition going into print CYD-TDV is being evaluated for registration in Sri Lanka.

The CYD-TDV dengue vaccine contains no adjuvant or preservatives.

Two other tetravalent candidates, namely, TDV and TV003/TV005 vaccines are in advanced stages of clinical development³.

Efficacy

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

Vaccine efficacy was higher in individuals who were seropositive at baseline compared to those who were seronegative at baseline, with pooled vaccine efficacy of 78.2% and 38.1%, respectively. The protective effect of dose 1 & 2 beyond 6 months is unknown and whether there are different effects in those seropositive and seronegative at baseline remains to be addressed.

During the period of active phase of surveillance, pooled vaccine efficacies against hospitalized dengue illness were 72.7% and 80.8% among participants of all ages and those ≥ 9 years, respectively⁴.

Indications

CYD-TDV is recommended for those 9 - 45 years or 9 - 60 years (depending on the license), living in endemic areas. The lower limit of the indication at 9 years of age was chosen due to safety concern in children aged 2 - 5 years during field trials.

It is still not known, potential for more severe disease (DHF) among individuals 9 years and above, after receiving the vaccine. Therefore, post-registration follow up is necessarily warranted even in eligible vaccine recipients⁵.

Dosage and administration

CYD-TDV should be administered as 3-doses given as a 0/6/12 month schedule. Vaccine is available in a single-dose or in a multi-dose (5-dose) vial. It is a freeze-dried product to be reconstituted before injection with either a sterile solution of 0.4% sodium chloride for the single-dose presentation or a sterile solution of 0.9% sodium chloride for the 5-dose presentation.

After reconstitution, 0.5mL dose to be administered by subcutaneous route. Any reconstituted doses remaining at the end of the session should be discarded within 6 hours of opening/ reconstitution or at the end of a vaccination session, whichever comes first.

Contraindications

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

CYD-TDV vaccination is contraindicated in:

- Individuals with a history of severe allergic reaction to any component of the dengue vaccine or after prior administration of the dengue vaccine or a vaccine containing the same components
- Individuals with congenital or acquired immune deficiency that impairs cell-mediated immunity
- Individuals with symptomatic HIV infection or with asymptomatic HIV infection when accompanied by evidence of impaired immune function
- Pregnant or breastfeeding women
- Individuals with moderate or severe febrile or acute disease

(vaccination should be postponed)

Adverse effects

Local and systemic adverse reactions following CYD-TDV are compatible to those recorded for other live attenuated vaccines. In the Phase 3 trials, the number of serious adverse events was similar in the CYD and placebo groups. Although there was a hypothetical risk of acute viscerotropic and neurotropic disease due to the yellow fever backbone, no cases have been detected.

During hospital-based surveillance of CYD-TDV it was observed that the youngest age group (2-5 year bracket in Asian Trial) had a higher cumulative relative risk which is unlikely to be due to chance. Sero-negative children, of whom there was a higher percentage in the younger age groups, vaccine may act as a silent natural infection that primes sero-negative vaccinees to experience a secondary-like infection upon their first exposure to dengue virus. It is noted that the vaccine may be ineffective or may even increase the future risk of hospitalization or severe dengue illness in those who are seronegative at the time of first vaccination regardless of age. Therefore, even in high transmission settings there may be and increased risk among sero-negative persons despite a reduction in dengue illness at the population level⁵.

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

Storage

2°C-8°C. Protect from light.

Use of dengue vaccine in outbreaks

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

WHO Position

Based on recommendations of the Strategic Advisory Group of Experts (SAGE) on Immunization, the World Health Organization (WHO) published a position paper on the use of CYD-TDV in July 2016.

Accordingly, countries are expected to consider introduction of the vaccine only in geographic areas (national or sub-national) where epidemiological data indicate a high disease burden.

Prior infection with dengue virus of any serotype, as measured by seroprevalence, should be approximately 70% or greater in the age-group considered for vaccination. The vaccine is not recommended when sero-prevalence is below 50%.

Countries/ geographic areas considering vaccination should have a dengue surveillance system to detect and report hospitalized and severe cases consistently over time.

Sero-surveys are currently the best method for selecting populations suitable for vaccination. When defining the target population a combination of sero-prevalence, surveillance data, and programmatic factors is preferred in decision making process.

Dengue vaccine introduction should be part of a comprehensive dengue control strategy including well-executed and sustained vector control, evidence-based best practices for clinical care for all patients with dengue illness and strong dengue surveillance.

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

At the time of introduction, countries should have a functional pharmacovigilance system with at least minimal capacity to monitor and manage adverse events following immunization.

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CHAPTER 5

DIPHTHERIA, TETANUS, PERTUSSIS VACCINE

Introduction

Diphtheria is a potentially acute disease caused by exotoxin-producing *Corynebacterium diphtheriae*. Morbidity and mortality result from the bacterial toxin that may cause obstructive pseudo-membranes in the upper respiratory tract or damage to myocardium and other tissues. Devastating diphtheria epidemics affecting mainly children have been described from many countries throughout history. Diphtheria toxoid is one of the oldest vaccines in current use.

Tetanus is an infectious bacterial disease caused by *Clostridium tetani*. Under favourable anaerobic conditions it may produce tetanospasmin, an extremely potent neurotoxin. The disease may affect any age group and protection against tetanus is antibody-dependent and can be achieved only through active (tetanus vaccine) or passive (tetanus-specific immunoglobulin) immunization. The immunized mother passes antitoxin via the placenta to her fetus, thereby preventing neonatal tetanus.

Pertussis (whooping cough) caused by *Bordetella pertussis* is an important public health concern even in countries with high vaccination coverage. The clinical outcome of pertussis depends on factors such as age and vaccination status. Although most cases of clinically recognizable pertussis occur in older children, adolescents and adults, pertussis is often unrecognized because of its frequent atypical course. However, older age groups represent an important source of infection for susceptible infants. The main aim of pertussis vaccination is to reduce the risk of severe pertussis in infancy.

Types of Diphtheria, Tetanus, Pertussis (DTP) Vaccines

DTP vaccines are available in various formulations and are given in 0.5 mL doses. The five most common formulations are DTwP, DTaP, Tdap, DT, and aTd. Of these vaccines, three (DTwP, DTaP and DT)

are given to children younger than 7 years of age, and two (Tdap and aTd) are given to individuals 7 years or older¹. As indicated by the lower case “d” and “p”, the concentration of diphtheria and pertussis toxoids has been reduced in these “adult” formulations to prevent adverse effects, while the “a” in “ap” indicates that the acellular vaccine contains purified components of *Bordetella pertussis*¹. All DTP vaccines are adjuvanted with aluminium compounds such as aluminium phosphate or aluminium hydroxide.

WHO requirements for potency of each component per single human dose of Diphtheria-Tetanus-Pertussis vaccine formulations²

Vaccine formulation	Composition	Diphtheria toxoid	Tetanus toxoid		Pertussis	Aluminium compounds
			When assayed in guinea pigs	When assayed in mice		
DTwP	Purified diphtheria & tetanus toxoid, suspension of <i>B. pertussis</i> inactivated usually by heating & treated with formalin ³	≥ 30 IU	≥ 40 IU	≥ 60 IU	≥ 4 IU	≤ 1.25µg.
DTaP	Purified diphtheria & tetanus toxoid, inactivated pertussis toxin either alone or in combination with other <i>B.pertussis</i> components such as filamentous haemagglutinin, fimbrial antigens 2&3 and pertactin	≥ 30 IU	≥ 40 IU	≥ 60 IU	≥ 25 µg pertussis toxoid ≥ 25 µg filamentous haemagglutinin ≥ 8 µg pertactin / dose	≤ 1.25µg.
DT	Purified diphtheria & tetanus toxoid	≥ 30 IU	≥ 40 IU	≥ 60 IU		≤1.25µg.
aTd	Purified diphtheria & tetanus toxoid	≥ 2 IU	≥ 40 IU			≤1.25µg.

Tdap	Purified diphtheria & tetanus toxoid, pertussis toxin either alone or in combination with other <i>B.pertussis</i> components such as filamentous haemagglutinin, fimbrial antigens 2&3 and pertactin	≥ 2 IU	≥ 20 IU	≥ 30 IU	≥ 8 µg pertussis toxoid ≥ 8 µg filamentous haemagglutinin ≥ 2.5 µg pertactin / dose	≤1.25µg.
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DTaP-HepB vaccine (Please see Chapter 8 for more details)

DTwP-Hib vaccine (Please see Chapter 6 for more details)

DTwP-HepB-Hib (pentavalent vaccine) (Please see Chapters 6 & 8 for more details)

DTaP-HepB-IPV-Hib (hexavalent vaccine)

Each 0.5 mL dose of hexavalent vaccine contains diphtheria toxoid ≥ 20 IU, tetanus toxoid ≥ 40 IU and *B. pertussis* toxoid 25 µg, FHA 25 µg, inactivated polio virus type 1 (40 D antigen units); type 2 (8 D antigen units); type 3 (32 D antigen units), hepatitis B surface antigen (rDNA) 10 µg and conjugated *H. influenzae* type b 12 µg. It also contains adsorbed aluminium hydroxide. The vaccine may contain traces of neomycin, streptomycin and polymixin B.

Combined triple diphtheria, tetanus and pertussis vaccines (DTwP), has been part of the immunization programme of Sri Lanka from 1961 and in 2008, combined pentavalent DTwP-HepB-Hib vaccine was introduced⁴.

Efficacy

Three doses of DTP vaccine, starting as early as 2 months of age and given at least 8 weeks apart at the age of 4 and 6 months are recommended for primary immunization of infants.

The protection following primary DTP vaccination wanes after 6–12 years due to lack of natural boosting. Therefore, the primary vaccination series of 3 doses should be extended by at least 1 booster dose. The optimal timing for and the number of such booster doses should be based on epidemiological surveillance as well as on immunological and programmatic considerations. Boosting at the age of 18 months (with DTwP), at school entry (with DT) and at 10 to 12 years of age (aTd) is recommended in Sri Lanka. Pertussis component is not included in school entry and older school age groups, because of its high reactogenicity in those age groups.

High-efficacy levels can be obtained with both wP and aP containing vaccines⁵. However, the best aP vaccines have higher efficacy than low-efficacy wP vaccines, but they may be less efficacious than the highest-efficacy wP vaccines in preventing pertussis⁵. Available limited data on the interchangeability of pertussis vaccines shows that changing among or within the wP and aP vaccine groups is unlikely to interfere with the safety or immunogenicity of these vaccines⁵.

Revaccination of adults against diphtheria and tetanus every 10 years may be necessary to sustain immunity in some epidemiological settings^{6,7}. In order to minimize reactogenicity to the protein of diphtheria toxoid, the quantity of the toxoid has been markedly reduced in these adult vaccines.

Indications

(i) Adsorbed diphtheria, tetanus and pertussis vaccine (DTwP, DTaP)

- Primary course of immunization against diphtheria, tetanus and pertussis is recommended for all infants on completion of 2, 4 and 6 months of age, unless there is a contraindication. If the primary course is interrupted it should be resumed but not repeated, allowing appropriate intervals (minimum of 6-8 weeks) between the remaining doses. The booster dose is recommended at 18 months of age.
- There is no contraindication to vaccination of unimmunized older children up to the age of 7 years¹.

- (ii) Adsorbed diphtheria and tetanus vaccine (DT)
 - It is recommended for children immediately before school entry, preferably after at least 3 years from the last dose of the primary course or booster dose.
 - When immunization against pertussis antigen containing vaccine (DTP) is contraindicated, DT can be used for primary immunization.
- (iii) Diphtheria and tetanus vaccine adsorbed for adults and adolescents (aTd)
 - For primary vaccination and re-vaccination of adults and adolescents
 - In the National Immunization Programme (NIP) of Sri Lanka, aTd is given at the age of 10-12 years
- (iv) Reduced antigen tetanus, diphtheria & acellular pertussis vaccine (Tdap)
 - For booster vaccination against diphtheria, tetanus and pertussis of individuals from age seven years onwards¹.
- (v) DTaP-HepB vaccine
 - This is an optional DTP containing vaccine for primary course of immunization against diphtheria, tetanus, pertussis and hepatitis B; recommended for all infants on completion of 2, 4 and 6 months of age, unless there is a contraindication.
- (vi) DTwP-Hib vaccine
 - This is an optional DTP containing vaccine for primary course of immunization against diphtheria, tetanus, pertussis and *Hemophilus influenzae* type b; recommended for all infants on completion of 2, 4 and 6 months of age, unless there is a contraindication.

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

- Primary course of immunization against diphtheria, tetanus, pertussis, hepatitis B and *H. influenzae* type b is recommended for all infants on completion of 2, 4 and 6 months of age, unless there is a contraindication
- In the NIP of Sri Lanka this vaccine is used for primary course of immunization for all infants.

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

- This is an optional DTP containing vaccine for primary course of immunization 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, unless there is a contraindication

Dosage and Administration

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

Contraindications for DTwP

This vaccine should not be given to persons who developed a severe reaction to previous doses of DTwP vaccine. These reactions are mainly due to the wP component in the DTP.

- an extensive area of redness and swelling which becomes indurated and involves most of the antero-lateral surface of the thigh or a major part of the circumference of the upper arm
- bronchospasm, laryngeal oedema
- encephalopathy within 7 days of administration of a previous dose of DTwP and not attributable to another identifiable cause

- prolonged inconsolable crying/screaming lasting more than 3 hours
- convulsions occurring within 72 hours
- progressive neurological disorders

These reactions may increase in severity with each subsequent injection. DT or DTaP should be used for subsequent vaccinations.

Contraindications for DTaP

- anaphylaxis to previous dose of DTaP
- anaphylactic reaction to any component of the vaccine which may be present even in trace amounts (such as neomycin, polymyxin B)

In the case of encephalopathy within 7 days of administration of a previous dose of DTwP/DTaP which is not attributable to another identifiable cause, subsequent immunization is recommended with DT vaccine.⁸

Personal or family history of allergy or non-progressive neurological conditions such as cerebral palsy or spina-bifida are not contraindications for immunization with DTP.

Precautions

There are certain groups of children to whom the administration of pertussis vaccine requires special consideration. Appropriate advice should be obtained from a specialist before a decision is made to administer the vaccine to them.

- Temperature of 40.5° C or higher within 48 hours after vaccination with a previous dose of DTwP/DTaP
- Collapse or hypotonic hyporesponsive episode (HHE) within 48 hours after receiving a previous dose of DTwP/DTaP

- Convulsions within 72 hours after receiving a previous dose of DTaP
- Children with a documented history of cerebral damage in the neonatal period
- Children with a history of convulsions

Acute illness is not a contraindication. Vaccination should be postponed until child has recovered.

Adverse Reactions

Both DTaP and DTwP vaccines have high level of safety. Mild adverse reactions are relatively common with DTwP vaccine⁵.

Whole-cell pertussis vaccines are not recommended for use in adolescents and adults due to high reactogenicity. Therefore, a vaccine containing acellular pertussis antigen is recommended. Vaccines containing lower dose of diphtheria toxoid (aTd, Tdap) are recommended for adolescents and adults to provide satisfactory immune response with lower risk of reactions.

DTP Vaccine

- **Local reactions**

Pain, redness and swelling at the injection site may occur and persist for several days. Persistent nodules at the injection site may arise if the injection is not given deep enough.

- **Systemic reactions**

Headache, lethargy, malaise, myalgia and pyrexia may occur. Anaphylactic reactions and urticaria may occur occasionally and rarely peripheral neuropathy

The common, non-specific reactions such as crying, screaming and fever may occur for the pertussis component in DTP vaccine. These reactions may also occur after vaccines which do not contain the

pertussis component. Attacks of high pitched screaming, episodes of pallor, cyanosis, limpness, and convulsions as well as local and general reactions have been reported. Neurological events including convulsions and encephalopathy may rarely occur after the pertussis component. Although encephalopathy is included as a rare adverse reaction to DTP vaccine, it is not certain whether DTP vaccines in fact cause encephalopathy^{1,9}.

DT Vaccine

- **Local reactions**

Reactions are generally mild and confined to the site of injection. Occasionally a painless nodule may develop at the site of injection but usually disappears without sequelae.

- **Systemic reactions**

Transient fever, headache, malaise and irritability. Anaphylactic reactions are rare. Neurological reactions have been reported occasionally.

Storage

The vaccine should be stored in a dry place and stored and transported at 2°C - 8°C. Vaccines should **not be frozen** or come into direct contact with ice or ice packs during transport or storage. DTP vaccines can be irreversibly damaged by either inadvertent freezing or heat.

WHO recommended Open Vial Policy is practiced for multidose vials for all DTP containing vaccines.

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CHAPTER 6

***HAEMOPHILUS INFLUENZAE* TYPE B VACCINE**

Haemophilus influenzae type b (Hib) is a common cause of bacterial meningitis, pneumonia and septicemia in children¹. The incidence of meningitis due to Hib in children in Sri Lanka prior to introduction of the Hib vaccine was estimated to be one of the highest in Asia². With the growing antibiotic resistance, immunization has become an increasingly effective means of preventing Hib disease. By mid 2016, 191 countries had Hib vaccine in their National Immunization Programmes (NIP)³. Out of these 191 countries, two countries (Belarus and India) have partially introduced this vaccine. Thailand, Russian Federation and China are yet to introduce Hib vaccine in to their NIP.

Types of Vaccine

All currently licensed Hib vaccines are conjugated vaccines. In conjugated Hib vaccines the Hib capsular polysaccharide, polyribosylribitol (PRP) is conjugated to a protein carrier. The conjugated protein carrier induces a long lasting T cell dependent B cell immune response to the PRP polysaccharide and immunological memory⁴. The type of protein conjugate to PRP differs in the three vaccines which are currently available^{5,6}.

- (i) Non-toxic mutant diphtheria toxin CRM 197 (PRP-CRM197)
- (ii) Tetanus toxoid (PRP-T)
- (iii) Meningococcal outer membrane protein (PRP-OMP)

A diphtheria toxoid (PRP-D) conjugated vaccine was withdrawn from the market because it was less immunogenic in children under 18 months of age⁷.

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

Available Hib vaccines in combination are as follows⁵.

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

Efficacy

Hib conjugated vaccines are efficacious from early infancy. Though there is evidence of a decrease in antibody levels over time, in most instances the immunity following the primary series is protective during the years of the highest susceptibility to invasive Hib disease. All conjugate Hib vaccines have demonstrated remarkably high, consistent efficacy and effectiveness against Hib invasive disease⁵.

All Hib conjugated vaccines induce a strong response when given as a booster dose in the second year of life. There is no difference in the immune response to monovalent or combined Hib vaccines⁸. However, Hib conjugate vaccines in combination with acellular pertussis antigen induce a lower antibody response than Hib conjugate vaccines in combination with whole cell pertussis antigen or Hib conjugate vaccines separately administered with the DTP containing acellular pertussis antigen⁵.

Use of Hib conjugate vaccine has led to virtual elimination of Hib invasive disease in countries where the vaccine was introduced. Nasopharyngeal colonization has been drastically reduced in populations with high Hib vaccine coverage. This has resulted in greater reduction in the Hib disease incidence than can be directly attributed to the effects of the vaccine suggesting that herd protection is induced by the widespread use of the Hib vaccine⁵. These vaccines do not protect against infection caused by *Haemophilus influenzae*

strains without capsules, termed non-typeable *Haemophilus influenzae* (NTHi), and therefore do not prevent the great majority of otitis media, recurrent upper respiratory tract infections, sinusitis or bronchitis.

Indications

- Infants and children under 5 years of age
- Older children and adults who are at risk of invasive Hib disease due to the following conditions⁶
 - HIV/AIDS
 - Complement deficiency
 - Certain antibody deficiency syndromes e.g. IgA deficiency, specific antibody deficiency
 - Hodgkin's disease
 - Recipients of stem cell transplants
 - Patients undergoing chemotherapy for malignant neoplasia
 - Anatomic or functional asplenia
 - Sickle cell anaemia or thalassaemia
 - Children with nephrotic syndrome

The response to the vaccine in children with partial immunoglobulin deficiency, Hodgkins's disease and following chemotherapy is likely to be sub-optimal⁶.

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

Dosage and administration

In general, a three dose primary series is given at the same time with the primary series of DTP. The first dose may be given as early as 6 weeks of age and the second and third doses may be given at 4-8 weeks intervals along with the DTP. If a booster dose is required, it should be given at least 6 months after the completion of the primary series. This normally coincides with 12-18 months of life. Sri Lanka National Immunization Programme recommends administration of Hib vaccine at 2nd, 4th and 6th months of life without a booster⁸.

For children aged 1-5 years who have not received a primary series of Hib vaccine, one dose is sufficient. Hib vaccine is not required for healthy children after 5 years of age⁵.

If the vaccination course has been interrupted, the schedule should be resumed without repeating the previous doses⁵.

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

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

Hib vaccine, as a separate vaccine, can be given at the same time as other routine vaccines at a different site. However, it should not be mixed in the vial or syringe with any other vaccine⁵.

Contraindications

Hypersensitivity or anaphylaxis to any component of the vaccine

History of hypersensitivity to a previous dose of vaccine

Adverse effects

Serious adverse events following immunization with Hib vaccine are uncommon. However, some local and systemic reactions have been reported. In general these reactions appear within 24-72 hours after

vaccination and are mild and resolve spontaneously^{5,6}.

Local reactions - redness, pain and swelling at the injection site

Systemic reactions - fever, loss of appetite, restlessness, irritability, vomiting, diarrhoea and unusual crying

Storage

2°C -8°C

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CHAPTER 7

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. In children <16 years, about 70% of the infections are asymptomatic compared to 10 – 25% of adults. A person is most infectious from 14-21 days before and through 1 week after the onset of symptoms.

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

Globally, an estimated 1.5 million clinical cases of hepatitis A occur each year. The anti-HAV seroprevalence is decreasing in many parts of the world, with a majority of adults and adolescents susceptible to the disease. Studies in Sri Lanka, from 1976 to 2005 have shown the same trend, a shift towards a lower seroprevalence rate¹. Outbreaks of hepatitis due to HAV continue to occur in Sri Lanka and several large outbreaks have been reported in the recent past.

Types of vaccines

Two types of vaccines are available worldwide.

- Inactivated vaccines (formaldehyde inactivated)
- Live, attenuated vaccines (available only in China and India)²

The preparations of inactivated vaccines available in Sri Lanka include

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

Efficacy

- Pre-exposure - 94% to 95% (The duration of protection is estimated to be as long as 45 years³)
- Post exposure - 79%⁵

Indications

Pre-exposure prophylaxis:

- For individuals over 12 months of age

Recommended for

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

Post exposure prophylaxis

Passive or active immunization or a combination of the 2 methods can be used for post exposure prophylaxis.

Human normal immunoglobulin (HNIG)

This is recommended for children aged <12 months and persons over 40 years of age, immunocompromised persons, persons who have had chronic liver disease and persons for whom the vaccine is contraindicated. When administered IM before or within 2 weeks after exposure to HAV, HNIG is >85% effective in preventing infection⁴.

If HNIG is administered to persons for whom hepatitis A vaccine also is recommended, a dose of vaccine should be administered simultaneously with HNIG at a different site. The second vaccine dose should be administered 6-12 months after the first dose to complete the series³.

Hepatitis A vaccine

This is recommended for healthy persons over the age of 1 year who have been exposed to hepatitis A infection within the last 14 days³. The vaccine is preferred over HNIG as it gives long term protection⁵. 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 prophylaxis³.

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 can be interchanged.

Combined vaccine: A combination vaccine containing inactivated hepatitis A and recombinant hepatitis B vaccine is available for use in persons over one year. The combination vaccine is given as a 3-dose series, at 0, 1 and 6 months. Alternatively, a 4-dose schedule may be used, administered on days 0, 7, and 21–30 followed by a booster dose at 12 months⁶.

1-15 years - 0.5 mL

≥16 years – 1.0 mL

It is recommended that the full series should be continued with the combination vaccine, and not interchanged with the monovalent vaccines.

Hepatitis A vaccines (both the monovalent and the combined) can be administered simultaneously with vaccines against diphtheria, tetanus, pertussis (DTP), polio (oral and inactivated), *Haemophilus influenzae* type b (Hib), measles, mumps, rubella, typhoid (oral and intramuscular), hepatitis B, Japanese encephalitis, rabies and yellow fever. This can be safely administered to immunocompromised patients including HIV^{5,7}. It can also be given safely to pregnant women at risk of developing hepatitis A⁷.

Contraindications

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

Adverse Effects

No serious events attributed to hepatitis A vaccine have been reported.

- 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.

Storage

2°C-8° C. Do not freeze.

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CHAPTER 8

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 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. Fulminant hepatitis could occur in 0.1 – 0.6% of acute cases¹. The sequelae of chronic HBV infection vary from an asymptomatic chronic carrier state, to the development of chronic hepatitis, cirrhosis and hepatocellular carcinoma. The rate of progression from acute to chronic hepatitis B is primarily determined by the age of infection, the rate being. 80-90% for those infected during the first year of life, 30-50% for infections between the ages 1-4 years, and 5-10% for infection acquired in adulthood¹. Immune tolerance to viral antigens acquired at birth is believed to play an important role in neonatal HBV persistence. By preventing HBV infection, hepatitis B vaccine also protects against hepatitis D virus (HDV) infection. Worldwide, an estimated 2 billion people have been infected including 350 million with chronic hepatitis B infection.

Hepatitis B vaccine has had a significant impact on reducing morbidity and mortality due to HBV and its complications. In a study conducted in Korea, it was demonstrated that after implementation of the national vaccination program, HBV prevalence declined from 6-8% to 2-3%. This study also demonstrated that the national vaccination program has contributed to the reduction of liver cancer mortality beyond just a natural decrease in Korean children and adolescents².

Carrier prevalence of HBV varies in different parts of the world, and may be quite variable within countries. Sero-epidemiological studies done in Sri Lanka have shown varying HBsAg prevalence rates ranging from 0.1 to 2.5%³. A more recent study conducted prior to

introduction of the HBV vaccine in to the NIP, showed that the HBV prevalence in the community to be 0.46%⁴.

HBV, though similar to HIV in its primary routes of transmission, is hundred times more infectious than HIV. It is transmitted parenterally, sexually, vertically and horizontally. However, in a significant proportion of patients, the route of transmission cannot be determined. The hepatitis B virus can survive outside the body for at least seven days and can be a source of infection¹.

Types of vaccine

Recombinant hepatitis B vaccine was introduced in 1986 and has replaced the plasma-derived hepatitis B vaccine. The recombinant vaccine contains hepatitis B virus surface antigen (HBsAg) and alum is used as an adjuvant. In certain preparations, thimerosal is present as a preservative. A recombinant hepatitis B vaccine that is intended for adult patients with renal insufficiency uses alum and lipid A as adjuvants. These potentiate the immune response and thereby elicit a long standing antibody response after vaccination¹. The vaccine is available as monovalent formulations or in combination with other vaccines, including DTwP, DTaP, Hib, hepatitis A and IPV (please refer Chapter 5). When immunizing against HBV at birth, only monovalent hepatitis B vaccine should be used¹.

Efficacy

Protective efficacy is determined by the presence of anti-HBs antibodies. An anti-HBs concentration of 10 mIU/mL assessed 1–2 months after administration of the last dose of the primary vaccination series is considered a reliable marker of protection against infection. Following vaccination, a protective antibody titre is present in >95% of infants, children and young adults. The duration of protection is over 20 years in healthy persons.

Efficacy of vaccination in immunocompromised individuals

Some infants born prematurely with low birth weight (<2000 g) may not respond well to vaccination at birth. Immunosuppressive illnesses,

including advanced HIV infection, chronic renal failure, chronic liver disease and diabetes, are associated with reduced immunogenicity following vaccine administration. The antibody response rate reduces primarily with ageing, in chronic disease, HIV infection, smoking and obesity¹.

Post vaccination efficacy should be tested in

- Persons at risk of occupationally acquired infection, e.g. healthcare workers (HCW)
- Infants born to HBsAg-positive mothers
- Chronic renal disease patients undergoing haemodialysis
- Persons with HIV and other immunocompromised conditions
- Patients undergoing multiple transfusions
- Sex partners or needle-sharing partners of persons who are HBsAg positive

Testing should be performed 1–2 months after administration of the last dose of the vaccine series and anti-HBs titre of ≥ 10 mIU/mL is considered protective.

Indications

- All children, adolescents and adults
- 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
 - persons interned in prisons
 - dialysis patients
 - persons who frequently require blood or blood products
 - recipients of solid organ transplantation

- those at occupational risk eg healthcare and emergency care staff
- travellers to HBV-endemic countries
- All previously unvaccinated adults aged 19 through 59 years with diabetes mellitus (type 1 and type 2) as soon as possible after the diagnosis⁵
- At birth, for babies born to mothers who have had hepatitis B infection during pregnancy or are hepatitis B surface antigen positive (refer post exposure prophylaxis (PEP) for additional information)
- 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 yrs) receive 50% of the adult dose.

The vaccine is administered by IM route. The antero-lateral 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 to the buttock is not recommended as this is associated with decreased protective antibody levels.

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

Minimum interval between doses is 4 weeks. There is no evidence to support the need for a booster dose following 3 (or 4) doses of hepatitis B vaccine in routine immunization programmes.

Vaccination schedules

Infants : In the national immunization programme three doses are given to all infants at 2, 4 and 6 months of age. Infants born to mothers who are HBsAg positive should receive both the HBV vaccine and

hepatitis B specific immunoglobulin (HBIG) within the first 24 hrs simultaneously with the BCG vaccine at different injection sites as there is no immune interference. Vaccine alone is sufficient when the mother is positive for HBeAb (please refer post exposure prophylaxis)

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

Travellers and high risk groups : The accelerated schedule of 0,1,2 months and a booster at 12 months. The British National Formulary (BNF) recommends 0, 7, 21 days and booster at 12 months for travellers

Contraindications

Hypersensitivity to any of the vaccine components

Anaphylactic reaction to a previous dose of hepatitis B vaccine

Allergy to common bakers yeast

Neither pregnancy nor lactation are contraindications for use of the vaccine.

Adverse effects

The vaccine has a proven safety record. Adverse effects, when they occur, are transient and minor. They include local soreness, redness, nausea, diarrhoea, malaise and fever¹.

Storage

2°C - 8°C. Do not freeze.

POST-EXPOSURE PROPHYLAXIS (PEP)

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

- 1) Per-cutaneous or per-mucosal exposure to HBsAg-positive blood
- 2) Perinatal exposure of an infant born to an HBsAg-positive mother.

- 3) Sexual exposure to a HBsAg- positive person
- 4) Household exposure

1) Perinatal exposure

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

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

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

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

2) Sexual partners of persons with acute hepatitis B virus infection

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

3) Household contacts of persons with acute Hepatitis B virus infection

Prophylaxis of an infant less than 12 months of age with HBIG and hepatitis B vaccine at 0, 1 and 6 months is indicated if the mother or primary 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.

4) Sexual partners and household contacts of chronic carriers

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 & 6 month schedule.

5) Percutaneous or permucosal exposure to HBsAg positive blood⁶

Management is as in table below.

Exposed person Status	Management when source is found to be		
	HBsAg+	HBsAg-ve	HBsAg status unknown
Unvaccinated	HBIG x 1 and initiate HBV vaccination (preferably within 24 hrs)	Initiate HBV vaccination	Initiate HBV vaccination
Vaccinated responder (a person with Anti HBs of ≥ 10 mIU/mL)	No immunization	No immunization	No immunization
Vaccinated nonresponder [#]	HBIG x 2 one month apart	No immunization	If high risk source treat as if source was HBsAg+ve
Vaccinated with unknown response or partially vaccinated	Test exposed person for anti HBs. If inadequate ** HBIG x 1 + hepatitis B vaccine dose If adequate no immunization	No immunization	Test exposed person for anti-HBs. If adequate no immunization If inadequate ** initiate revaccination

** Anti HBs titre of < 10 m IU/ mL

Post vaccination testing of HCW for anti HBs titres should be done 1-2 months after completion of vaccination. If titres are < 10 mIU/

mL the response to vaccination is inadequate. In such an instance, the person should be evaluated for HBs antigen positivity. If HBs antigen is negative, a second three dose vaccine series should be given. A vaccine non-responder is a person who does not develop protective HBs antibodies after completing 2 full series of hepatitis B vaccine and for whom an acute or chronic hepatitis B infection has been ruled out.

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CHAPTER 9

HUMAN PAPILLOMAVIRUS VACCINES

Introduction

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

Low risk (non-oncogenic) HPV genotypes 6 and 11 are associated with 90% of genital warts (*condylomata accuminata*) and 100% of recurrent respiratory papillomatosis (RRP) cases. High risk (oncogenic) HPV genotypes 16 and 18 are associated with 70% of cervical cancers and >80% of other anogenital cancers ^{1,2,3}.

Anogenital cancer preventive HPV vaccines are available to immunize adolescents in prevention of HPV genital infection. Currently, 3 types of HPV vaccines (bivalent, quadrivalent and 9-valent) are available of which 2 vaccine types (bivalent and quadrivalent) are currently available in Sri Lanka. These vaccines are prepared using recombinant technology. Both are prepared from purified L1 structural proteins that self assemble to form HPV type-specific empty shells or virus-like particles (VLP). Neither vaccine contains live biological products or viral DNA, so they are non-infectious. HPV vaccines are designed for prophylactic use only and do not clear existing HPV infection or treat HPV-related disease^{1,2,3}.

Quadrivalent vaccine consists of a mixture of four HPV geno type specific L1 virus like particles (VLP) of genotypes 6, 11, 16 and 18. The substrate of the vaccine is based on recombinant yeast technology

(*Saccharomyces cerevisiae*). Each 0.5 ml dose of quadrivalent vaccine contains 20µg HPV 6 L1 protein, 40 µg HPV 11 L1 protein, 40 µg HPV 16 L1 protein and 20 µg HPV 18 L1 protein with 225 µg aluminum hydroxyphosphate sulphate as an adjuvant. This vaccine has been licensed for use in young adolescents as young as 9 years of age¹.

Bivalent vaccine includes L1 VLP of HPV genotypes 16 and 18. This is produced using a baculovirus technology that uses Hi-5 Rix4446 insect cells with an adjuvant known as ASO4 that contains aluminium hydroxide plus mono phosphoryl lipids (alum and MPL). This vaccine has been licensed for use in females as young as 10 years of age¹.

Efficacy

Both vaccines are generally safe, well tolerated and with high efficacy and immunogenicity. Overall sero-conversion observed is 99-100% for both vaccines. Long lasting immunity after vaccination has been observed for at least 10 years which includes 100% efficacy against HPV type 16/18 related persistent HPV infection and CIN 2/3.

Lower sero-conversion and lower vaccine efficacy has been observed among immunocompromised individuals.

Indications

Bivalent HPV vaccine is indicated for use in females 9- 26 years of age and quadrivalent HPV vaccine is indicated for use in both males and females 9-26 years.

Bivalent vaccine is indicated for the prevention of:

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

In addition to above indications quadrivalent vaccine is indicated for the prevention of:

- ano-genital warts(condylomata acuminata) caused by genotype 6 and 11

Benefits are observed especially among previously unvaccinated and sexually unexposed individuals

Dosage and administration

Two types of schedules are available for different age categories

0.5 ml is administered IM as

- 2 doses for 9-13 years : 0 and 6 months
- 3 doses for 14-26 years :
 - 0, 1 and 6 months for bivalent HPV vaccine
 - 0, 2 and 6 months for quadrivalent HPV vaccine

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

Vaccination of sexually active women

Vaccination of sexually active women is not a contraindication. However there is no evidence of preventing vaccine preventable HPV genotype associated pre-cancers among women with previous HPV exposures.

Cervical cytology screening

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

Immunocompromised persons

HPV vaccine can be administered to immunocompromised and / or HIV-infected women though there is limited data on immunogenicity. However, the immune response and vaccine effectiveness might be less than that of immunocompetent persons.

Contraindications

HPV vaccines should not be given to people who have experienced severe allergic reactions after a previous dose or to a component of the vaccine. As for other vaccines, it is recommended that HPV vaccination be delayed for individuals who have severe acute illnesses.

Use in pregnancy

HPV vaccine is not recommended to be given during pregnancy even though teratogenicity has not been observed in animal studies. Vaccines can be administered to lactating mothers. Antigen or antibody excretion in breast milk has not yet been observed^{1,4}.

Adverse Effects:

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

Preventing syncope after vaccination

Syncope may occur after vaccination among adolescents and young adults. This is described as a preventable event after injection among adolescents and vaccine can be administered in the seated position for prevention of syncope. It is required to observe the vaccine recipients for 15-20 minutes after vaccination as for all other vaccines¹.

Storage

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

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CHAPTER 10

INFLUENZA VACCINE

Introduction

Influenza is a viral infection that is associated with seasonal outbreaks of respiratory illness during the winter months in regions with temperate climates and during rainy seasons in tropical regions. The reasons for seasonal epidemics of influenza are not definitely known.¹

In Sri Lanka, for the last few years, it has been generally observed during April to June and from again in November to January. There could be shift of a month or two either way in this seasonality.² Vaccination is currently the only effective means of reducing the burden of influenza in the community.²

Trivalent influenza vaccine contains three influenza viruses; two influenza A virus strains, A (H1N1) virus and A (H3N2) and one influenza B virus strain in the trivalent vaccine. There are four influenza viruses; two influenza A virus strains, A (H1N1) virus and A (H3N2) and two influenza B virus strains from each lineage in the quadrivalent vaccine. The virus strains in the vaccine change each year based on global surveillance and scientists' estimations, with regard to the types and strains of virus that will circulate during the next season.

There are two types of vaccine formulations for northern and southern hemispheres. For countries in equatorial region, epidemiological considerations influence the choice of the vaccine. Currently southern hemisphere vaccine is registered in Sri Lanka.

Types of vaccine-

1. Inactivated vaccine*

Trivalent and quadrivalent inactivated vaccines TIV/QIV include killed viruses. These injectable vaccines are approved for use in persons older than 6 months.

2. Live attenuated vaccine **

Intra nasal live attenuated influenza vaccine LAIV- is recommended for individuals between the age of 2 years and 50 years and not recommended during pregnancy.

* whole virus/ split virus/ subunit

** cold adapted/ genetically re-assorted

Efficacy

Efficacy varies with the recipient's age and the antigenic match between the virus strains in the vaccine and those in circulation. The vaccine will prevent illness in 70-90% of healthy adults provided that there is a good antigenic match.³

Estimates of the efficacy or effectiveness of inactivated vaccine among children vary by age, season and study design (confirmation of influenza, outcome parameters etc).

The efficacy has been estimated as 40% -58% for those aged 6-23 months and 60% -74% for those aged 2-5 years^{3,4}

Indications:

1. General population

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

2. People at high risk for complications

- Residents of institutions for the elderly or disabled
- Elderly, non-institutionalized individuals with chronic conditions e.g. chronic cardiovascular, pulmonary, metabolic, renal disease, or immunocompromised.
- All individuals > 6 months of age with any of the conditions listed above.
- All persons over 65 years

- e. Pregnant women - Pregnant and postpartum women are at higher risk for severe illness and complications⁵.
Influenza vaccine containing the killed virus is safe and is recommended for all pregnant women during an influenza season. It is safe in all trimesters of pregnancy ⁶

3. Special groups

- Healthcare workers
- Household members who are in close contact with high risk persons
- Essential services

Dosage and administration:

Inactivated vaccine.

Age	Dose	Route/site
Children 6 months to 3 years	Half the adult dose	IM/ anterolateral aspect of thigh
Previously unvaccinated child < 9 yrs	Two doses 1 month apart	IM/deltoid muscle
Children > 9 yrs and adults	Single dose	IM/ deltoid muscle

Contraindications:

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

Precaution

Egg allergy ^{7,8}

Acute febrile illness- vaccination should be postponed

Recent published studies (n=28) involving a large number of individuals allergic to egg protein revealed that influenza vaccine can be administered without any serious reactions. The reason that such

patients tolerate the vaccine is due to very low amount of egg protein in the vaccine. ^{9,10}

Adverse effects:

- Local reactions at the site of the injection – pain, erythema or induration
- Systemic effects – low grade fever and body aches lasting for 1-2 days.
- Guillain–Barré Syndrome –very rare ⁷

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

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CHAPTER 11

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 JE¹. It is caused by a flavivirus transmitted to man through mosquitoes. Several strains of JE viruses identified. It is an infection of the central nervous system characterized by coma, seizures, paralysis and abnormal movements. Death occurs in one third of cases and serious sequelae in 40% of survivors². This disease primarily occurs in children and most infections are asymptomatic. The ratio of infection to symptomatic illness has been estimated to vary between 1:25 and 1:300. The incubation period is 4-14 days. There is no specific antiviral treatment for JE.

The virus is transmitted in an enzootic cycle among mosquitoes and vertebrate amplifying hosts, mainly domestic pigs and aquatic birds. *Culex* mosquitoes, *Culex tritaeniorhyncus* and *Culex gelidus* are the principal vectors. Humans are dead end hosts and no human to human transmission has been reported¹. JE cases have been identified from various parts of Sri Lanka throughout the year. It shows a marked increase with the north-east monsoonal rains (November-February) as a result of increased mosquito breeding, due to water logging of rice fields and other collections of water.

Types of vaccine

There are four classes of JE vaccines

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

WHO recommends that mouse brain derived vaccines should be gradually replaced by new generation JE vaccines, given their advantageous safety profile¹.

- **Inactivated mouse brain derived vaccine - (2 types)**

Vaccine prepared from suspension of mouse brain infected with JE virus (JEV)

- Nakayama strain - Freeze dried or liquid

- Bejjin strain - Liquid

Both strains of vaccines are not available in Sri Lanka at present.

- **Inactivated vero cell derived vaccine**

Formalin inactivated alum adjuvanted vaccine - SA 14-14-2 strain is licensed in several countries including US. It does not contain any preservatives or stabilizers. This vaccine is not available in Sri Lanka.

- **Live attenuated vaccine (LJEV)**

Freeze dried (SA-14-14-2 strain)

The vaccine is prepared in primary hamster kidney cell culture (PHK). This vaccine 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^{3,4}.

In the National Immunization Programme, all children are immunized with the live JE vaccine on completion of 12 months. This is the only JE vaccine available in Sri Lanka and is WHO pre-qualified.

- **Recombinant yellow fever- Japanese encephalitis chimeric vaccine (YF-JE)**

A promising approach for a future JE vaccine has been developed, based on the attenuated 17D YF virus genome, This YF-JE chimera virus, was grown in vero cells and was shown to elicit JEV neutralizing antibodies. Vaccine was tested in the US, showing good safety and immunogenicity with 94% of the vaccinees in the phase II trial developing protective neutralizing antibodies after a single dose⁵.

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

Efficacy

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

Due to the likely interference with passively acquired maternal antibodies during the first months of life, vaccination is not recommended for children before the age of 6 months.

In endemic settings, among children aged 1-2 years, seroprotection was 95.7% one month following the second dose of vaccine⁶.

- **Live attenuated vaccine (LJEV)**

Efficacy trials in children 1-10 year olds have yielded high protection rates above 98% following a single dose of vaccine after 1 year. Case control and numerous large scale field trials in China have consistently shown an efficacy of at least 95% following 2 doses administered at an interval of 1 year^{2,4}.

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 vaccine². Based on this study presently, a single dose has been recommended to be used in Sri Lanka⁴.

- **Live recombinant vaccine**

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 dose⁷.

Indications

LJEV - Children above 12 months of age and adults.

Dosage and administration

- **Inactivated vero cell derived vaccine in JE endemic countries**

Primary immunization consists of two doses 0.5 mL each administered intramuscularly 4 weeks apart. For children < 3 years dose is 0.25 mL. Currently, the manufacturer does not recommend any booster doses for the paediatric age group¹.

For travellers visiting JE endemic countries

For travellers aged >17 years who have received primary immunization >1 year previously, may be given a booster dose if traveling to a JE endemic country¹.

- **Live attenuated vaccine (LJEV)**

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

The primary immunization is recommended for children above 12 months of age given SC. A booster dose after 1 year is recommended by the manufacturer.

The National Advisory Committee on Communicable Diseases approved the use of the live JE vaccine in children who had not completed the inactivated JE vaccine course⁸.

- **Live recombinant vaccine**

Primary immunization is recommended for children above 9 months of age. One dose administered SC and a booster dose is recommended by the manufacturer 12-24 months later for those < 18 years of age. Currently, no booster doses are recommended for adults.

Contraindications

Inactivated JE vaccine

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

Live JE vaccine

- Hypersensitivity to any component of the vaccine
- Pregnancy
- Immunodeficiency states (refer Chapter 29)
- Leukemia, lymphoma and other malignancies (refer Chapter 29)
- History of convulsions during the past 1 year

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

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

The following conditions are NOT contraindications:

- Minor illnesses such as common cold, diarrhoea with temp. below 38.5°C
- Stable neurological conditions. e.g. cerebral palsy, Down's syndrome
- Treatment with topical steroids or systemic use of steroids at low dosages, less than 0.5 mg/Kg body wt.⁴
- 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 anaphylactoid reactions are rare.

Encephalitis/meningitis have not been reported following LJEV³.

Storage

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

Instructions on the product leaflet should be followed.

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CHAPTER 12

MEASLES, MUMPS AND RUBELLA VACCINE (MMR)

Introduction

Measles, mumps and rubella (MMR) is a live attenuated combined vaccine which prevents measles, mumps, rubella and congenital rubella syndrome (CRS). MMR vaccine was included in the National Immunization Programme (NIP) of Sri Lanka in 2011. In accordance with the World Health Organization's (WHO) regional elimination of measles, rubella and CRS strategic plan, Sri Lanka has set the goal of achieving elimination by 2018¹.

Measles

Measles is one of the most highly contagious of all infectious diseases. Humans are the only host for the virus. Measles virus is a 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 spreading. The incubation period is approximately 10 days, but varies from 7 to 18 days from exposure.

Measles is characterized by fever, cough, coryza, and conjunctivitis, followed by a maculopapular rash appearing on the face and spreading cephalocaudally and centrifugally. During the prodromal period, a pathognomonic enanthema (Koplik's spots) may be detected. Case-fatality rates are higher among children younger than 5 years, the immunocompromised and in the severely malnourished, including in states of vitamin A deficiency².

The disease remains one of the leading causes of death among young children globally, despite the availability of a safe and effective vaccine. Approximately 134,200 people died from measles in 2015 – mostly children under the age of five. Accelerated immunization activities

have had a major impact on reducing measles deaths. During 2000-2015, measles vaccination prevented an estimated 20.3 million deaths. Global measles deaths have decreased by 79% from an estimated 651,600 in 2000 to 134,200 in 2015¹.

Complications of measles

Complications of measles include otitis media, bronchopneumonia, laryngotracheobronchitis (croup), keratomalacia and diarrhoea, particularly among young children. Acute encephalitis occurs in approximately 1 in 1000 cases and often leads to permanent brain damage. Subacute sclerosing panencephalitis which is a rare degenerative central nervous system disease characterized by behavioural and intellectual deterioration and seizures, occurs 7 to 11 years after wild-type measles virus infection occurring at a rate of 4 to 11 per 100 000 measles cases.

Mumps

Mumps generally occurs during childhood. The incubation period of mumps is 14–18 days (range : 14–25 days). The clinical case definition of mumps is an acute onset of unilateral or bilateral, tender, self-limiting swelling of the parotid or other salivary glands lasting more than 2 days and without any other apparent cause². Mumps is caused by an RNA virus in the Paramyxoviridae family and transmitted by respiratory droplets. 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%). It 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 patients³.

Complications of mumps

Infections occurring in adults are more likely to cause complications than in children. Asymptomatic occurrence of aseptic meningitis is common (50-60%). Symptomatic meningitis occurs in up to 10% of patients and resolves without sequelae in 3–10 days. In children, boys

are more commonly affected than girls (3:1). Orchitis is a commonly reported complication among post-pubertal males, but sterility is rare². Oophoritis occurs in 5% of post pubertal females. However, there is no association with impaired fertility. Nerve deafness caused by mumps virus occurs in approximately 1 per 20,000². Encephalitis is rare -less than 2 per 100,000. Other rare complications include arthritis, thyroiditis, mastitis, glomerulonephritis, myocarditis, pancreatitis, cerebellar ataxia and transverse myelitis. Mumps during the first trimester of pregnancy is associated with an increased incidence of spontaneous abortions. Nevertheless, there is no evidence to suggest any link with congenital malformations⁴.

Rubella

Rubella is an acute viral infection which generally results in a mild disease in children and adults. It is characterised by low grade fever, a generalised erythematous maculopapular rash, which is transient and lymphadenopathy, commonly suboccipital or post auricular. 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; 25- 50% of rubella infections are subclinical.

Rubella is of great significance if it occurs in a pregnant woman, as it can cross the placental barrier and cause teratogenic effects. Rubella infection in pregnancy may lead to miscarriage or stillbirth. Some infants may be born with congenital rubella syndrome (CRS) which includes ophthalmic, cardiac, auditory and neurological abnormalities.

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

The risk of congenital defects in the first trimester is approximately 80%, with the risk falling to 10-20% by the 16th week of pregnancy^{2,4}.

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)
Urabe
All grown in chick embryo tissue culture

Rubella strain - Wistar RA27/3 grown in human diploid cells

Immunogenicity and vaccine efficacy

A single dose of MMR at 15 months of age causes seroconversion for measles in 98%, mumps 97% and more than 95% for rubella. Studies conducted in the US during 1973–1989 determined that 1 dose of MMR vaccine was 75%–91% effective. A study from the United Kingdom documented that vaccine effectiveness was 88% with 2 doses⁵.

The effectiveness of the mumps component of the MMR vaccine is lower than that of the measles or rubella components⁶. It is strongly suggested that elimination targets of measles, mumps and rubella can be reached with sufficiently high coverage with a 2 dose MMR vaccination programme. Maintaining high MMR vaccination coverage remains the most effective way to prevent outbreaks and also to limit their extent when those occur⁷. However, based on the recent outbreaks of measles and mumps in the US and the Netherlands, a third dose has been suggested as a control measure, among the close contact communities^{8,9}.

Indications

- Susceptible individuals more than 9 months of age, adolescents and adults
- When any of the individual components is indicated

Dosage and administration

0.5 mL SC. It could also be given IM

In Sri Lanka, measles vaccine was first introduced in 1984 at the age of 9 months.

Two doses of MMR vaccine has been recommended since 2011. Initially, the 1st dose was given at one year and a second dose at 3 years. As there is a susceptible infant population for measles, the first dose of MMR vaccine has been advanced to 9 months since 2015¹⁰.

Catch up vaccination programme

Children presenting at pre-school age who have not received the first dose of MMR, should be given a dose of MMR, followed by a second dose after three months.

The age of 11–12 years also could serve as a catch-up opportunity to verify vaccination status and MMR vaccine should be administered to children who have not yet received the 2nd dose of MMR. The second dose of MMR may be administered as early as 4 weeks after the first dose⁷. Furthermore, individuals of both sexes at school leaving age who have never received MMR, should be offered a single dose of vaccine¹¹.

Post exposure prophylaxis

MMR vaccine is not routinely recommended for prophylaxis following exposure to mumps, measles or rubella as the antibody response to mumps or rubella components is too slow for effective prophylaxis. However, vaccination after exposure is not harmful and may possibly avert later disease. Recent studies have shown that although two MMR doses are adequate in the prevention of mumps in most settings, administering a third dose may be worthwhile in specific outbreak situations. This may lead to shorter duration of virus shedding, boosting of antibody titres and milder clinical manifestations⁸.

Contraindications

- Pregnancy
- Persons with immunodeficiency, HIV/AIDS (please refer Chapter 22)
- Individuals with a history of allergy to any of the vaccine components (gelatin, neomycin or kanamycin)
- Persons who have received immunoglobulin injections, blood or blood products within three months⁷.

Precautions

- Pregnancy should be avoided for one month after vaccination⁹. 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 beef, pork or mutton, should be vaccinated in a hospital setting where emergency facilities are available, as there can be cross reactions between gelatin and proteins present in meats.
- Vaccination should be deferred in persons with an acute febrile illness
- Tuberculin skin testing (TST) - it is recommended to perform the TST before or on the same day or 4 weeks later as measles component can depress the cell mediated immunity⁷

Adverse effects

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

Parotitis may occasionally occur in the third week after vaccination. Thrombocytopaenic purpura has been rarely reported within six weeks after the first MMR. However, the risk of developing thrombocytopaenia after MMR vaccination is much less than the risk

of developing it after an infection with measles, rubella or mumps virus⁶. Adverse reactions are less common after the second dose of vaccination than the first dose.

Concerns about the probable associations of MMR vaccine and infantile autism and inflammatory bowel disease have been evaluated. Many epidemiological studies have firmly disproved the remotest possibility of a cause and effect phenomenon with regard to the MMR vaccine and pervasive and regressive developmental disorders in children¹².

Storage

2°C-8°C

MMRV Vaccine

Combination vaccine against measles, mumps, rubella and varicella (MMRV) vaccine was made available in 2005 and currently is being used in Europe, North America and Australia. Seroconversion rates and antibody titers after the first and second doses were similar to those observed after concomitant administration of the MMR and varicella vaccines¹³.

However, in 2010, studies revealed a greater risk of febrile seizures in children between 12 -23 months of age, 5-10 days following MMRV vaccination. No increased risk of seizures was observed among children receiving the first dose of the vaccine at or older than 48 months of age².

The MMRV vaccine is currently not available in Sri Lanka.

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CHAPTER 13

MENINGOCOCCAL VACCINE

Introduction

Invasive meningococcal disease due to *Niesseria meningitidis* causes substantial morbidity and mortality and has a case fatality rate of 10-20% in industrialised countries¹. Approximately 10-20% of survivors of meningococcal meningitis are left with permanent sequelae such as mental retardation, deafness and epilepsy.

N. meningitides is a Gram-negative diplococcus which causes disease only in humans. It is classified into 12 serogroups (A, B, C, 29E, H, I, K, L, W135, X, Y and Z) based on the structure of the polysaccharide capsule. The majority of invasive meningococcal infections are caused by serogroups A, B, C, X, W135 and Y. 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 world¹.

Crowding is an important risk factor. Tobacco smoke, functional or anatomic asplenia, complement factor deficiencies, HIV infection, and travel to epidemic areas are associated with an increased risk for meningococcal disease.

Meningococcal meningitis is uncommon in Sri Lanka and the cases encountered are mostly imported.

Types of vaccine

The capsular polysaccharide vaccines are less immunogenic than the conjugated vaccines. Conjugated vaccines are vaccines containing capsular polysaccharides joined to a protein to enhance immunogenicity.

Polysaccharide vaccines¹ (unconjugated)

- a) Bivalent vaccine – contains polysaccharides to serogroups A+C

- b) Trivalent vaccine - contains polysaccharides to serogroups A, C, W135,
- c) Tetravalent vaccine - containing polysaccharides to serogroups A, C, W135, Y(MPSV4)

The vaccine contains 50 µg each of the purified bacterial capsular polysaccharides. The duration of protection is 3–5 years.

Conjugated vaccines

A vaccine against serogroup B (MenB) has been approved for use in the European Union. This vaccine has also been approved for use in Australia, USA and Canada². MenB vaccine may be administered to adolescents and young adults aged 16–23 years to provide short-term protection against most strains of serogroup B meningococcal disease.

In countries where a vaccine is not available for use in serogroup B outbreaks, chemoprophylaxis is recommended for the close contacts and should be ideally given within 24 hours of diagnosis of the primary case. Rifampicin, ceftriaxone or ciprofloxacin is recommended for adults while rifampicin is recommended for children¹.

There are several other conjugated vaccines used in different parts of the world depending on the endemicity of the serotype¹.

- a) Group A conjugate vaccine (conjugated to TT) mainly intended for the African Meningitis belt
- b) Group CY vaccine (conjugated either to tetanus or diphtheria toxoid)
- c) Tetravalent vaccine, conjugated with diphtheria toxoid (MenACWY-D)
- d) Tetravalent vaccine, conjugated with CRM protein (MenACWY-CRM)
- e) A combination vaccine based on *H.influenzae* type b and *N. meningitides* serogroup C vaccine (HibMenC).

There is no vaccine against serogroup X-disease.

Efficacy

Efficacy varies between 85-93% for both conjugated and unconjugated vaccines. Antibody response to serogroup C is the lowest following vaccination with unconjugated vaccines. With conjugated vaccines, the lowest antibody titres were observed against the Y serogroup. On the whole conjugated vaccines are more immunogenic³.

Indications

Not recommended for routine immunization

Current vaccines are recommended for use in :

- epidemic or outbreak situations
- travellers to endemic countries
- pilgrims to Saudi Arabia (Mecca) during the annual Hajj & Umrah pilgrimage
- persons exposed to patients
- patients undergoing splenectomy
- patients with complement component deficiencies
- laboratory workers handling meningococci
- students entering overseas universities in countries where the disease is endemic

The conjugated vaccines are recommended for children 2 months to 2 years of age who are at risk of developing meningococcal disease. These include infants with complement factor deficiencies, anatomical or functional asplenia, infants travelling to hyperendemic areas and when exposed to disease outbreaks⁴. Conjugated vaccines are recommended to persons infected with HIV and dosing schedules vary depending on the age of the person⁵.

Dosage and administration

Unconjugated vaccine

Dose 0.5 mL subcutaneously.

The lyophilised preparation of purified polysaccharides should be reconstituted with the diluent.

- Children ≥ 2 years & adults – one dose is adequate. It protects up to 3 – 5 years.

After 3–5 years, one booster dose may be given to persons considered to be at continued risk of exposure including healthcare workers

Meningococcal polysaccharide vaccine is not recommended for children < 2 years of age

- Children 3 months to 2 years – 2 doses 3 months apart, with meningococcal MenACWY vaccine
- Persons aged 2-55 years - A booster dose is recommended to those who are at continued risk of acquiring the disease and adolescents in particular. Persons with functional or anatomical asplenia should receive a booster dose every 5 years³
- Adults ≥ 56 yrs - MPSV4 is the only licensed meningococcal vaccine for those aged ≥ 56 years in the US. For persons aged ≥ 56 years who have not previously received a meningococcal vaccine (e.g. travellers) MPSV4 is preferred. For persons now aged ≥ 56 years who were vaccinated previously with MenACWY and require revaccination (e.g. persons with asplenia), MenACWY is preferred⁶.

Conjugated vaccines

Dose 0.5 mL IM

Both conjugated and unconjugated meningococcal vaccines are not contraindicated in pregnancy

Contraindications

- Acute febrile illness
- Hypersensitivity to any component of the vaccine
- A history of Guillane-Barre Syndrome (GBS) is a contraindication for receiving MenACWY (A history of GBS continues to be listed as a precaution in the package although in

June 2010, after reviewing the two safety studies, ACIP voted to remove the precaution for persons with a history of GBS because the benefits of meningococcal vaccination outweigh the risk for recurrent GBS in these persons, and MPSV4 can be given for short term protection (3-5 years)².

Adverse effects

- Local - erythema, slight induration, tenderness or pain at the injection site
- Systemic – Febrile reactions and chills have rarely been observed within 24 hours of vaccination.
- GBS has been reported after MenACWY

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

Storage

2°C– 8°C

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CHAPTER 14

PNEUMOCOCCAL VACCINE

Introduction

Over one third of deaths among children under five, are caused by pneumonia and diarrhoea. Pneumonia is the single largest cause of death in children globally killing more than 1.5 million children every year. *Streptococcus pneumoniae* remains the most common cause of bacterial meningitis and subdural hydromas in infants and children over two years of age in the United States.¹ According to WHO, immunization against pneumococcus, *H. influenzae type b* (Hib), measles and pertussis is the most effective way to prevent pneumonia. Vaccines are available against all four infections. Pneumococcal disease (pneumonia, meningitis and septicaemia) is recognised as the world's leading vaccine preventable child killer, which is estimated to cause up to one million deaths in children under 5 years of age annually^{2,3}.

After introduction of the pneumococcal conjugate vaccine (PCV) in 2000, several studies described a decrease in invasive pneumococcal disease in the United States. One year after its introduction, there was a 69% decrease in the rate of invasive disease in those less than two years of age.⁴ By 2004, all cause admission rates had declined by 39% and rates of hospitalisation for pneumococcal meningitis decreased by 66% in children younger than two years of age^{5,6}. Interestingly rates of invasive pneumococcal disease among adults also decreased since the introduction of the vaccine^{6,7}. There are about 90 distinct serotypes. Globally about 20 serotypes are associated with > 80% of invasive pneumococcal disease occurring in all age groups.

The introduction of the 7-valent pneumococcal conjugate vaccine (PCV 7) has changed significantly the epidemiology of pneumococcal infections, including invasive pneumococcal disease. PCV 7 was first introduced to children in 2000 in USA and within a decade, pneumococcal infections were almost eliminated in that age group⁶.

Furthermore, herd immunity has significantly reduced the incidence of such infections in the over 65 year age group, as well as in older children. Although there has been some increase in the incidence of pneumococcal infections caused by serotypes not covered by PCV 7, especially serotype 19A, the overall incidence of pneumococcal disease has been significantly reduced ².

In 2009, PCV 10 and in 2010, PCV 13 were introduced. Data suggest that changing from 7-valent to 10-valent vaccine would increase the proportion of serotypes covered from 80% to 88% in the USA and from 74-84% in Europe. In developing countries, in Africa the corresponding increase would be from 67-81% and in parts of Asia it could increase from 43-66%. Changing from 10-valent to 13-valent vaccine would further improve coverage of serotypes by 4% to 7% globally^{8,9,10,11}. In developed countries the newer vaccines are fast replacing PCV 7 which is being phased out.

The South Asian Pneumococcal Network Alliance (SAPNA) surveillance revealed that in Colombo, the common serotypes isolated were 6B, 14, 19F and 23F¹². There was a very high degree of resistance to commonly used antibiotics, penicillin (91%), cotrimoxazole (70%), erythromycin (67%), chloramphenicol (28%).

Types of Vaccine

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

1. Pneumococcal polysaccharide vaccine (PPSV 23)

It contains purified polysaccharide for 23 capsular types of pneumococci.

Efficacy

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

Indications

- Adults over 65 years
- Persons aged over 2 years who are at increased risk of pneumococcal infection
 - Asplenia or severe dysfunction of the spleen
 - Splenectomy – in elective splenectomy, at least two weeks prior to surgery
 - 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

Administration of PCV under special categories – Please refer Chapter 29

Dosage and administration

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

Contraindications

Severe reaction to a previous dose of vaccine

Precautions

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

Adverse effects

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

Storage

2°C - 8°C. Do not freeze

2.Pneumococcal conjugate vaccine (PCV)

PCVs are more immunogenic than polysaccharide vaccine, especially in children under 2 years of age. Currently 2 types of vaccines are available PCV 10 and PCV 13, as PCV 7 has been discontinued. In developed countries PCV 7 is being replaced by PCV 13, due to its formulation. PCV 10 provides protection against some non-typeable Hib (NTHi) infections such as acute otitis media. PCV 10 contains serotypes 1, 5 and 7F, in addition to the 7 serotypes found in PCV 7.

Indications

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

Efficacy

PCV 10 provides cover against serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F. It provides cover against 70% of serotypes globally and also against non-typeable *H. influenzae*(NTHi).

PCV 13 provides cover against serotypes 1, 3, 4, 5, 6A. 6B. 7F, 9V, 14, 18C, 19A, 19F and 23F. It provides cover against serotype 19A which became an important pathogen after the introduction of PCV 7 in 2000, in some countries.

Dosage and Administration

0.5 mL IM per dose.

- For infants - In USA a 3 dose primary series at 2, 4, 6 months and a booster dose at 12-15 months.
 - In Europe a 3 dose schedule at 2, 4 and 12 months.
- 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.

Minimum intervals – 4 weeks between doses given before 12 months
– 8 weeks between doses given at/after 12 months

Transitioning from PCV 7 to PCV 10 or PCV 13

Children aged 2 months to 5 years who have not completed the course, complete the course with PCV 10 or PCV 13.

Children under 5 years of age who have completed a PCV 7 series – one dose of PCV 10 or PCV 13 should be administered.

Contraindications

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

Precautions

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

Adverse effects

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

Storage

2°C-8°C. Do not freeze

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CHAPTER 15

POLIOMYELITIS VACCINE

Introduction

Poliomyelitis is a highly infectious viral disease caused by polio virus, resulting in acute flaccid paralysis. Polio virus is an enterovirus that is mainly transmitted person-to-person through the faeco-oral route. It multiplies in the intestine, spreads to the central nervous system through the blood stream and affects motor neurones. It initially causes generalized symptoms such as fever, headache, vomiting and muscle pains and results in irreversible paralysis among 1 in 200 infected persons. Among them, 5-10% will die due to respiratory failure. The paralysis can occur at any age but mainly affects children below 5 years of age¹.

There are three antigenic types (type 1, 2, and 3) of wild polio virus (WPV) and paralysis can be caused by all three types². At present, WPV type 1 and type 3 are continuing to circulate, the most prevalent strain being type 1. Infection due to WPV type 2 has not been detected since 1999³ and the eradication of WPV type 2 was declared in September 2015⁴.

Poliomyelitis occurred worldwide in epidemic form in the first half of the 19th century. The Global Polio Eradication Programme has dramatically reduced polio virus transmission throughout the world. At present only 3 countries remain endemic for polio namely Afghanistan, Pakistan and Nigeria. The WHO South East Asia Region was declared polio free in 2014, three years after the last polio case in India⁴.

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 Endgame Strategic Plan developed by the World Health Assembly 2012, required the withdrawal of OPV containing OPV type

2 and the introduction of at least one dose of inactivated polio vaccine (IPV) as a risk mitigation measure. Intradermal IPV administration with fractional doses (0.1 mL, which is 1/5th of a full dose) is recommended as two fractional doses of IPV provide higher seroconversion rates than a single full dose⁵. This recommendation was considered by the Advisory Committee on Communicable Diseases in Sri Lanka and the National Immunization Schedule was changed accordingly to replace a single dose of IPV with two fractional doses from July 2016.

Types of vaccine -

- Live attenuated oral polio vaccine (OPV) (Sabin Vaccine)
- Bivalent oral polio vaccine (bOPV) (contains types 1 and 3)
- Trivalent oral polio vaccine (tOPV) (contains types 1, 2 and 3) is discontinued
- Inactivated (injectable) polio vaccine (IPV) (contains types 1, 2 and 3)(Salk Vaccine)

IPV is available as stand alone or combined with other antigens e.g. hexavalent vaccine

Efficacy

Oral Polio Vaccine (Bivalent OPV/ bOPV)

bOPV is highly effective in producing immunity in the mucosa of the intestine and serum 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 maximize the immunity³. As with other live virus vaccines immunity from OPV is probably lifelong.

Inactivated Poliovirus Vaccine (IPV)

IPV is highly effective in producing immunity against polio virus and protection from paralytic poliomyelitis by providing immunity in the serum. Ninety percent or more of vaccine recipients develop

protective antibody to all three types of poliovirus after 2 doses and at least 99% are immune following 3 doses³.

Indications

Infants at 2, 4 and 6 months as primary immunization.

Boosters at 18 months and school entry at the age of 5 years.

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

After eradication of polio which is expected by 2018, gradual shifting over from bOPV to IPV is recommended³.

Dosage and Administration

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

One multi dose vial contains 1 mL and contains 10 doses

Open vial policy is applicable to OPV (see Chapter 30.)

Additional doses are recommended during mass campaigns

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

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

When IPV is given in combination with other vaccines such as diphtheria, tetanus and pertussis or hepatitis B the vaccine should be administered intramuscularly.

Contraindications

- Severe allergy to vaccine or a component of the vaccine
- Moderate or severe acute diarrhoea (bOPV)
- 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 must be substituted for bOPV in these circumstances

Adverse Effects:

- Local reactions are uncommon
- Allergic reactions are very rare

Vaccine Associated Paralytic Poliomyelitis (VAPP)

The vaccine virus carries a small risk (2–4 cases/million birth cohort per year) of causing paralytic poliomyelitis in the vaccine recipient and unimmunized close contacts³. VAPP risk is increased in persons with immunodeficiency and in under-immunized populations².

Vaccine Derived Polio Virus (VDPV)

In very rare instances, the vaccine virus can change genetically. These mutated viruses may be excreted and could cause paralysis or outbreaks, if a population is under-immunized – circulating vaccine derived polio virus (cVDPV). cVDPV type 2 is the commonest type identified³. 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 no cases have been reported to date among contacts³.

Storage

OPV

-20°C up to two years

2°C - 8°C up to three months

IPV

2°C - 8°C. Do not freeze.

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CHAPTER 16

RABIES VACCINE

Introduction

Rabies is an acute encephalomyelitis caused by a rhabdovirus. It is 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 rabies¹. Humans are occasionally infected by wild animals, but domestic dogs and cats are responsible for the majority of cases². In Sri Lanka rabies has been detected in mongoose, cattle, goats, pigs, bandicoots, jackals, pole cats, civet cats, squirrels, monkeys, horses and elephants. House rats have not been implicated in the transmission of rabies in Sri Lanka. Human to human transmission also has not been documented².

The virus can penetrate broken skin or intact mucous membranes. Humans are usually infected when virus laden saliva is inoculated through the skin by the bite of a rabid animal. Saliva can also infect if the skin is already broken e.g. by the claw of the animal. The virus has been isolated in an animal's saliva even up to 14 days before it exhibits the first signs of rabies. Intermittent excretion of the virus in the saliva continues throughout the illness. The incubation period in humans averages 1 to 3 months but can range from 5 days to more than one year^{3,4,5}.

Infection with rabies virus characteristically produces an acute illness with rapidly progressive central nervous system manifestations, including anxiety, dysphagia and seizures. Some patients may present with paralysis. Illness almost invariably progresses to death.

Types of Vaccine

Inactivated anti rabies cell culture vaccine

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

* Vaccines available in Sri Lanka at present.

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

Efficacy

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

Indications

Pre-exposure immunization

Pre exposure immunization is recommended for the following risk groups

- 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 by IM or ID route⁵.

Primary immunization

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

One booster to be taken 01 year later.

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

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

If an exposure takes place, medical advice should be sought immediately regarding booster doses of vaccine.

Following an exposure, irrespective of severity, additional doses of ARV are recommended. A single IM dose /2 site ID 0.1mL doses on day 0 and day 3 as boosters should be administered depending on the route of pre-exposure schedule which has been initiated in the primary immunization⁶.

Administration of rabies immunoglobulin is contraindicated in persons on pre-exposure therapy.

Post exposure immunization

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

Choice of therapy depends on the screening of the person exposed and also the animal involved in the incident.

Screening the patient - Categorization of the exposure

Major exposures:

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

Minor exposures:

- a. Single, superficial bite with oozing of blood or scratches with bleeding on the lower limbs, upper limbs, abdomen and back

- b. Multiple bites without bleeding or scratches with oozing of blood on any part of the body
- c. Nibbling of uncovered skin
- d. Contamination of open wounds with saliva
- e. Drinking of raw milk of rabid cow or goat
- f. Superficial bites and scratches of wild animals without bleeding

Screening the animal

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, with the last vaccination given within 1 year of the incident, PET can be delayed while observing the animal for 14 days. If the animal goes missing, becomes sick, is having 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 unobservable (missing, stray or dead) initiate PET and continue the full course of vaccine.

In case of **minor** exposure to dogs and cats:

- If the animal is healthy, observable and 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 can be delayed while observing the animal for healthiness or behavioral changes for 14 days from the day of the exposure.

If an animal concerned is a dog or cat, is healthy and alive for 14 days following the bite, the person is not at risk of developing rabies^{3,4,5}.

- PET for superficial scratches, under provocation, caused by healthy observable domestic animals (irrespective of vaccination status of the animal) also can be delayed while observing the animal for 14 days⁶.
- When the animal is suspected to have rabies or is sick, but observable, initiate PET while observing the animal. Discontinue PET if the animal is healthy after 14 days.
- If the animal is having rabies, confirmed by laboratory diagnosis or unobservable (missing, stray or dead) initiate PET and continue the full course of vaccine.

The patient must be clearly advised that the animal should be put in a cage or leashed during the observation period. If the animal becomes sick, develops any abnormal behavior 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 of rabies⁷.

The following are not considered as exposures:

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

Anti Rabies PET when indicated :

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

Rabies Immunoglobulin (RIG)

RIG available in Sri Lanka at present:

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

Rabies immunoglobulin should be given immediately after the incident. However if the patient reports late, RIG could be given up to 3 months after exposure if he has not taken more than 2 doses of anti rabies vaccine^{3,4,8}.

It is necessary to test for sensitivity before administering ERIG. HRIG does not require sensitivity testing prior to its administration.

Method of sensitivity testing (ST) for ERIG

Control: Inoculate 0.1mL of sterile N saline ID on flexor aspect of the forearm.

Test: Prepare a 1:10 dilution of rabies equine serum with sterile N saline and inoculate 0.1ml ID on flexor aspect of the opposite forearm.

Initial diameter of the indurated area should be measured in mm and recorded.

Patient is kept under observation and the ST should be read after 20 minutes. Examine for itching, induration or urticaria or any systemic

effects of anaphylaxis. If the initial diameter of the induration is less than 6 mm and the induration after 20 minutes is over 10 mm or if there is any systemic reaction, ST should be considered as a positive⁸.

Separate fixed needle-syringes should be used for each patient.

The drug of choice in anaphylaxis is 1:1000 adrenaline 0.5 mL given IM immediately. (Dosage for children - refer Chapter 27).

Mild sensitivity reactions could be managed with antihistamine therapy. **Oral or parenteral steroids should be best avoided as it could depress the immune response.**

If a patient with a major exposure is ST positive for all available products of ERIG, HRIG should be considered⁸.

However⁶,

1. If the animal is **healthy and observable**, the modified 4 site ID ARV schedule could be considered while observing a healthy animal for 14 days⁶. Report to hospital immediately, if the animal goes missing, falls sick or dies during this period.
2. If the animal is **suspected of having rabies or is not observable**, in a situation where HRIG is not available, the WHO recommended method of using ERIG under adrenaline and antihistamine in an emergency care facility (ETU, PCU, A & E or ICU) should be considered⁷. In this situation, modified 4 site ID ARV should not be considered as equivalent for RIG and a course of ARV.
3. 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. In such situations, additional doses of ARV could be considered after seeking expert opinion.

Dosage and Administration of RIG

HRIG 20 IU/kg body weight

ERIG 40 IU/kg body weight

Part of the dose (as much as possible depending on the site) should be infiltrated in and around all wounds. After infiltration if there is any remaining RIG, it should be given deep SC or IM on the thighs. Administration of RIG on the buttocks is not recommended as absorption is unpredictable. Deltoids should be spared for ARV when giving RIG. Vaccine should be administered preferably on the same day after RIG, but at a different site.

In situations with multiple bites, where the volume of RIG is insufficient for infiltration of all wounds, RIG could be diluted with sterile N. Saline up to a maximum of 3 times.

Anti rabies vaccines (ARV)

Intramuscular schedule

Patients with major exposures should be given rabies cell culture vaccine IM 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 should be given a total of 4 doses of rabies cell culture vaccine IM 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 inoculation of rabies cell culture vaccine

ID vaccination schedule has been recommended by the WHO to be used in developing countries where cost is a major limiting factor^{1,8}.

Recommended ID dose is 0.1mL per site for both PCEC and PVRV

2 Site ID Schedule (2-2-2-0-2)

Standard schedule used in government hospitals

One dose (0.1mL) given ID at each of 2 sites in the deltoids on days 0, 3, 7 and 30.

2 site schedule is routinely used in all patients irrespective of the use of rabies immunoglobulins.

Example: Major exposure - rabies immunoglobulin + 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)

Gives an early antibody response when compared to the 2 site ID schedule.

The modified 4 site schedule is helpful in patients with major exposure, with a reliable history, who are sensitive to ERIG and the animal is healthy and observable and for patients with a minor exposure who come late for treatment.

One dose of (0.1mL) given ID at each of 4 sites on day 0 (both deltoids and lateral thighs) and 0.1mL given at 2 sites on days 3, 7 and 30.

Please note: In a patient with a major exposure, modified 4 site ID ARV should not be considered as equivalent for RIG and a course of ARV.

Precautions that should be taken when using ID ARV schedules.

All ID injections should be **administered only by trained staff** under supervision of a medical officer. Once the vaccine is reconstituted the contents should be used as soon as possible (preferably within 6 hours stored at 2^o - 8^oC). Separate disposable syringes and needles should be used for each patient to prevent contamination.

Sterile 1mL fixed needle-syringes should be used for administration of ID ARV to minimize wastage.

Post exposure therapy for immunocompromised patients

ID schedules of ARV is not recommended for these patients. Often these patients may require RIG even for minor exposures with IM schedule of ARV after expert advice.

In high risk situations, after expert advice is obtained from the Dept. of Rabies, MRI, rabies antibody assessment could be offered to these patients.

Management of patients who have subsequent exposure to rabies infection

A. With documented evidence of a full course of ARV

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.

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

- for individuals who are not immunocompromised
- who have been previously vaccinated with a full course of a potent and effective rabies vaccine
- have adequate documentation
 - should receive 2 booster doses of ARV on days 0 and 3 (one IM dose /2 site ID 0.1mL)⁹
 - patient may be offered a one visit “4 site” ID doses consisting of 4 injections of 0.1mL, over left and right deltoids and supra-scapular / antero-lateral thigh areas. These patients do not require administration of RIG⁵

In any doubtful or complicated situations, expert opinion should be sought.

B. After a partial course of ARV

The management will depend on the time duration from previous course of ARV. Expert opinion should be sought from Dept. of Rabies, MRI.

If a person develops an allergic reaction to one type of cell culture rabies vaccine, switching over to the other type of cell culture ARV is recommended.

Contraindications

In view of the gravity of the disease, all contraindications are secondary in cases of exposure to suspected rabies infections. 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^o-8^o C

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CHAPTER 17

ROTAVIRUS VACCINE

Introduction

Globally, rotavirus is the leading cause of severe dehydrating diarrhoea in children less than 5 years of age. It causes 138 million diarrhoeal episodes, 2 million hospitalizations and an estimated 453,000 deaths, each year. About 90% of the deaths occur in low income countries in Africa and Asia¹. Worldwide it is estimated that almost every child has had at least one episode of diarrhoea due to rotavirus by the age of 5 years.

The incidence of rotavirus infection is comparable in the developing and developed world showing that increased disease awareness, improved sanitation and hygiene and safe water supply is not effective in controlling the spread of the disease².

The World Health Organization (WHO) has recommended that rotavirus vaccine for infants should be included in all national immunization programmes, and in countries where diarrhoeal deaths account for $\geq 10\%$ of mortality among children aged < 5 years, the introduction of the vaccine is strongly recommended¹.

Rotavirus infection in Sri Lanka is a significant cause of morbidity. Several studies and the ongoing rotavirus surveillance studies show that rotavirus causes about 24% of the watery diarrhoeal infections³. Of this, 80% of the infections occur in the age group < 2 years. However, mortality due to rotavirus infection in Sri Lanka 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 out 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. 27 G types and 35 P types have been identified. Out of this 5 G types are seen

commonly 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 varying scenario. The Sri Lankan genotypes found commonly are G1-3 and G9^{3,4}.

Rotavirus is shed in very high numbers during acute 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 can survive in the environment for days and in stools for months.

The incubation period is 1-3 days and an infected child will excrete the virus a few days before and after the clinical illness. The clinical spectrum of the disease is wide, with transient loose stools to severe diarrhoea with dehydration leading to death. Typically, the clinical illness is of sudden onset, with fever, vomiting and explosive watery diarrhoea up to 10 times a day. There is no blood in the stools but it may be mucoid. The illness usually lasts about 3-7 days but may be prolonged up to 2-3 weeks. About 50% of the infections could be subclinical.

The first infection which occurs around 3 months of age, is the most likely to cause severe gastroenteritis with dehydration. The primary infection confers protection for rotavirus gastroenteritis in 77% of patients and against severe gastroenteritis in 87% of patients. The primary infection confers homotypic immunity and subsequent infections confer a broader heterotypic immunity.

Types of vaccine

Two types of live, attenuated vaccines are available. One is a human monovalent vaccine (RV1) against G1P[8] and the other is a bovine-human reassortant pentavalent vaccine (RV5) against G1-4 and P[8]. However, both vaccines give cross immunity to other genotypes of rotavirus². Both are administered orally.

Efficacy

The vaccine will prevent about 74-87% of all rotavirus gastroenteritis, >80% of severe cases, and about 95-100% of hospitalizations due to rotavirus².

Indications

Prevention of childhood gastroenteritis due to rotavirus.

Dosage and administration

- *Human monovalent vaccine (2 doses)*

Lyophilised vaccine to be reconstituted with the diluent (supplied with the vaccine), 1 mL/dose at 2 and 4 months of age. The minimum age for the first dose is 6 weeks and the minimum interval between the doses is 4 weeks. The second dose should be given before 6 months 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. All 3 doses should be administered before 8 months of age.

The maximum age for the first dose in the series is 14 weeks, 6 days. Vaccination should not be initiated for infants aged 15 weeks 0 days or older. The maximum age for the final dose in the series is 8 months, 0 days. If any dose in the series was pentavalent vaccine or vaccine product is unknown for any dose in the series, a total of 3 doses of vaccine should be administered. If monovalent vaccine is administered for the first and second doses, a third dose is not indicated⁵.

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 vaccination⁶.

Contraindications

- Life-threatening allergy to any component of the rotavirus vaccine
- Children with severe immunodeficiency including severe combined immunodeficiency (SCID)¹
- Children who are moderately or severely ill. This includes children who have acute moderate to severe gastroenteritis

Precautions

There is a low risk of intussusception with both vaccines (1-5 cases/100,000 infants)⁷. It is accepted that the benefits of the vaccine outweigh the risk of intussusception^{1,8}. The manufacturers recommend that the vaccine is contraindicated in children with a history of intussusceptions or an abnormality of the gastro-intestinal tract which can predispose to intussusception (eg. Meckel's diverticulum).

Adverse effects

Diarrhoea, vomiting, otitis media and nasopharyngitis

Storage

2°C-8°C. Protect from light.

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CHAPTER 18

TETANUS VACCINE

Introduction

Tetanus is an acute disease caused by the action of tetanospasmin, an extremely potent neuro-toxin released following infection by the anaerobic spore bearing bacterium, *Clostridium tetani*.

Tetanus spores are present in soil and may be introduced into the body through a contaminated puncture wound, burn or even a trivial scratch injury. Neonatal tetanus is caused by the infection of the baby's umbilical stump. Tetanus does not spread from person to person. The incubation period of tetanus is between 4-21 days, usually about 10 days.

The disease is characterised by generalised rigidity and spasms of skeletal muscles. The muscle stiffness initially involves the jaw (lockjaw) and the neck, then becomes generalised. The case-fatality rate ranges from 10-90% and is highest in infants and the elderly¹.

Early diagnosis, prompt intensive care and treatment will reduce mortality. However, the case-fatality rates are high even where modern intensive care is available.

Tetanus can never be eradicated, because the spores are commonly present in the environment.

Protection against tetanus is antibody-dependent and can be achieved only through active (tetanus vaccine) or passive (tetanus-specific immunoglobulin) immunization².

Adequate immunization coverage is the key strategy for prevention of tetanus, as there is no place for herd immunity. Passive immunization using tetanus antitoxin, preferably of human origin, is essential for treatment and occasionally for prophylaxis (e.g. in cases of

contaminated wounds in incompletely immunized people). While tetanus antitoxin is useful in the management of tetanus, its use cannot substitute the need to achieve and sustain high tetanus vaccination coverage².

Type of vaccine

Inactivated toxoid.

The vaccine is made from a cell-free purified toxin extracted from a strain of *C.tetani*. This is treated with formaldehyde that converts it into tetanus toxoid and is adsorbed to an adjuvant, either aluminium phosphate or aluminium hydroxide, to improve its immunogenicity.

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.

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

Vaccine efficacy

Efficacy ranges from 80-100% following a full course of vaccination².

Indications

- To prevent tetanus in all age groups
- To prevent neonatal tetanus by immunizing pregnant women

Immunization schedule for pregnant women^{3,4}		
A. 1 st Dose	Tetanus toxoid (TT)	During 1 st pregnancy, after 12 weeks of POA
B. 2 nd Dose	Tetanus toxoid	During 1 st pregnancy, 6-8 weeks after the 1 st dose (at least 2 weeks before delivery)
C. 3 rd Dose	Tetanus toxoid	During 2 nd pregnancy, after 12 weeks of POA
D. 4 th Dose	Tetanus toxoid	During 3 rd pregnancy, after 12 weeks of POA
E. 5 th Dose*	Tetanus toxoid	During 4 th pregnancy, after 12 weeks of POA
F. One booster dose of tetanus toxoid (TTb)	Tetanus toxoid	During 1 st pregnancy with written evidence of previous immunization with 6 doses of tetanus toxoid as per National Immunization Programme (3 doses of DPT in infancy + DPT at 18 months + DT at 5 years + aTd at 12 years) during childhood and adolescence and a gap of 10 years or more after the last tetanus toxoid containing vaccine.
G. Tetanus toxoid immunization not indicated	<ol style="list-style-type: none"> 1. Mothers who have received 5 doses of tetanus toxoid during previous pregnancies are protected and do not need further tetanus toxoid immunization for the present pregnancy. 2. Mothers who have received 6 doses of tetanus toxoid according to the NIP during childhood and adolescence and if the gap between the last tetanus toxoid containing vaccine and the current pregnancy is less than 10 years, are protected and do not need further tetanus toxoid for the current pregnancy. 3. Mothers who have received 6 doses of tetanus toxoid according to the NIP during childhood and adolescence and have received at least 1 booster dose of tetanus toxoid during pregnancy or due to trauma within last 10 years, are protected and do not need further tetanus toxoid for the current pregnancy. 	

* A total of 2 doses of TT should be given in first pregnancy. One dose of TT is recommended for each subsequent pregnancy up to a maximum of 5 doses

Vaccines containing tetanus toxoid⁵.			
	Diphtheria	Tetanus	Pertussis
Diphtheria, tetanus and whole cell pertussis vaccine DTwP	≥ 30 IU/dose	≥ 40 IU/dose	≥ 4 IU/dose
Diphtheria, tetanus and acellular pertussis vaccine DTaP	≥ 30 IU/dose	≥ 40 IU/dose	≥ 25 µg pertussis toxoid ≥ 25 µg filamentous haemagglutinin ≥ 8 µg pertactin / dose
Diphtheria and tetanus vaccine DT	≥ 30 IU/dose	≥ 40 IU/dose	-----
Low antigenic diphtheria, tetanus and acellular pertussis vaccine Tdap for 6 years and above	≥ 2 IU/dose	≥ 20 IU/dose	≥ 8 µg pertussis toxoid ≥ 8 µg filamentous haemagglutinin ≥ 2.5 µg pertactin / dose
Diphtheria and tetanus vaccine for adolescents and adults aTd	≥ 2 IU/dose	≥ 40 IU/dose	-----
Tetanus toxoid vaccine TT for adults	-----	≥ 40 IU/dose	-----
Diphtheria, tetanus, pertussis, Hib, hepatitis B vaccine (pentavalent) DTP-HepB- Hib	≥ 30 IU/dose	≥ 40 IU/dose	≥ 4 IU/dose
Diphtheria, tetanus, acellular pertussis, Hib, hepatitis B, and inactivated polio vaccine (hexavalent) DTaP-HepB-Hib-IPV	≥ 30 IU/dose	≥ 40 IU/dose	≥ 25 µg pertussis toxoid ≥ 25 µg filamentous haemagglutinin ≥ 8 µg pertactin / dose

Active immunization with tetanus toxoid (TT) is indicated for all persons who have not been adequately immunized.

In children, initial tetanus immunization is administered with DTP, DT, DTP-HepB-Hib (pentavalent vaccine) or DTaP-HepB-Hib-IPV (hexavalent vaccine). A total of 5 doses are recommended.

The primary series of 3 doses of a tetanus toxoid containing vaccine should be given in infancy at 2, 4 and 6 months (pentavalent/hexavalent) with a booster at 18 months of age (DTwP/DTaP/pentavalent/hexavalent) followed by the second booster before school entry around 5 years (DT/Tdap), so that the school going child is completely immunized against tetanus.

However, WHO recommends that in addition to the above 5 doses of vaccine, an extra tetanus toxoid or tetanus toxoid containing vaccine should be administered to adults, as immunity after 5 doses wanes in adult life². This will provide additional assurance of long lasting, possibly lifelong protection against tetanus. Therefore, a sixth dose is recommended for adolescents at age 12-15 years as aTd or Tdap and for young adults as TT. This can be routinely and conveniently given at the time of first pregnancy, induction to military service, the medical examination before first employment or admission to higher education institutes.

For details on dosage and administration refer Chapter 5

Dosage - 0.5 mL of tetanus toxoid or tetanus toxoid containing vaccine.

- A history regarding tetanus immunization should always be taken before tetanus toxoid is given for wound prophylaxis.
- For persons who have not been vaccinated properly or whose vaccination status is unknown - 3 injections are recommended as follows – 1st dose stat, 2nd dose 4 - 6 weeks later and 3rd dose 6 months later.
- A single dose of TT given to a person who is not immunized against tetanus, will not produce effective immunity.
- Tetanus toxoid need not be given to children with a history of complete immunization with 5 doses of tetanus containing vaccine.
- Young adults with a history of immunization with only 5 doses of tetanus toxoid in childhood need 1 booster dose.
- Adults with a history of immunization with 6 doses of tetanus toxoid including the 5 doses received in childhood do not need further tetanus toxoid for wound prophylaxis.

- Persons who have had initial tetanus immunization in adolescence or adulthood with 5 doses of tetanus toxoid, do not need any doses for prophylaxis².
- There is no minimum interval required or advised between a given dose of TT or aTd and a dose of Tdap when it is indicated⁶.
- A patient who recovers following tetanus will not have adequate natural immunity, and should be started on a full 3 dose vaccine schedule at the time of discharge from hospital.

Route of administration - Deep intramuscularly into deltoid or antero-lateral aspect of thigh.

Contraindications

Hypersensitivity to any component of the vaccine

Adverse effects

Subcutaneous injection can cause local irritation, inflammation, granuloma formation and necrosis.

Anaphylactic reactions, Guillain-Barre syndrome and brachial neuritis have been rarely reported.

Storage

2°C - 8°C. Do not freeze.

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CHAPTER 19

TYPHOID VACCINE

Introduction

Enteric fever (typhoid and paratyphoid fever) is an acute febrile illness, endemic in developing countries with occasional outbreaks. The prototype of this syndrome is typhoid fever caused by *Salmonella enterica* serotype Typhi. However paratyphoid fever due to *Salmonella enterica* serotype Paratyphi A is replacing typhoid fever in many South Asian countries including Sri Lanka^{1,2,3,4}.

Transmission is by food and water contaminated by faeces. The incubation periods are 7-14 days for typhoid and 1-10 days for paratyphoid. Typhoid and paratyphoid fever cannot be differentiated clinically². Clinical features include continued fever, headache, abdominal pain, constipation or diarrhoea and splenomegaly. Bacteraemia is present and blood cultures are positive in 50-70% of cases.

Resistance to the commonly used antimicrobials, especially to ciprofloxacin, is emerging worldwide⁵. Infection with multi drug resistant strains increases the severity of illness, treatment costs, mortality and the rate of subsequent chronic carriage. This has increased the need to control the disease through effective vaccination⁶.

Types of vaccine

Two safe and moderately efficacious vaccines against typhoid fever are currently recommended by the WHO and licensed widely. In addition, two typhoid conjugate vaccines are registered for use in India. The currently available typhoid vaccines do not protect against paratyphoid fever. Ideally, a bivalent vaccine protecting against both typhoid and paratyphoid is required.

Vi polysaccharide (parenteral): purified Vi capsular polysaccharide vaccine (ViPS) is licensed for persons over 2 years of age.

Ty21a (oral): A live-attenuated vaccine, manufactured from the S. Typhi Ty21a strain, as an enteric-coated capsule is licensed for persons over 5 years. This vaccine is not available in Sri Lanka.

Newer generation typhoid conjugate vaccines (TCVs): The Vi polysaccharide antigen is conjugated to a carrier protein so as to convert a T-independent immune response to a T-dependent response. This renders the vaccine effective in infants. Two TCVs have been licensed in India for parenteral use in infants, older children and adults (Report of the WHO Informal Consultation of experts on Typhoid Fever, South East Asia Region, 28-29 September, 2016 New Delhi, India).

Efficacy:

Vaccine efficacy is not adequate to protect against a high inoculum of bacteria, as may occur in food borne exposure¹. Therefore, vaccination is only an adjunct to avoidance of high risk food and drink. Protection lasts only for a limited period.

Vi polysaccharide vaccine:

Efficacy for 3 years is around 55-72%⁷. Protection occurs 7 days after vaccination. Revaccination is recommended every 3 years⁶.

Oral Ty21a vaccine:

Efficacy for 3 years is around 48% after 3 doses⁷. Protection commences 7 days after taking the third dose⁶. Those living in endemic areas should be revaccinated every three years and travelers from non-endemic areas need annual revaccination⁶. Herd protection of non-vaccinated population and moderate cross protection against Paratyphi B is also seen^{6,8,9}.

Newer generation typhoid conjugate vaccines (TCVs):

Vaccine trials conducted in India have shown immunogenicity in infants^{10,11}.

Indications

In view of the public health burden of typhoid fever and increasing antibiotic resistance the WHO recommends programmatic use of vaccination in high risk groups and populations to control endemic disease^{6,9}. For each country, data on sub-populations at risk and age-specific rates should be obtained and such groups targeted.

Although such data for Sri Lanka is limited, the Epidemiology Unit has identified high risk groups in high risk areas. These groups include food handlers, people who do not use or do not have proper toilet facilities, close contacts of typhoid patients and communities who do not have access to safe water¹⁰.

- Vaccination is also recommended for outbreak control^{6,9}
- Travellers visiting typhoid endemic areas, especially if staying for more than one month, visiting locations where antibiotic resistant strains are prevalent or travelling to areas where sanitation and food hygiene are likely to be poor⁶
- Household contacts of typhoid carriers
- Laboratory personnel who may handle *S. Typhi* in the course of their work¹¹

Dosage and administration

Vi capsular polysaccharide vaccine:

Single 0.5 mL (25µg) dose IM or SC. Booster doses every 3 years⁶.

Oral Ty21a vaccine:

The Ty21a vaccine is administered in 3-4 doses.

Contraindications

- Previous severe hypersensitivity reaction to any component of the vaccine.
- immunocompromised patients

Adverse effects

Local reactions such as pain, induration and erythema may be seen 48 to 72 hours after administration of the Vi capsular polysaccharide vaccine.

Storage

2°C-8°C. Do not freeze.

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CHAPTER 20

VARICELLA VACCINE (Chickenpox Vaccine)

Introduction

Chickenpox in childhood is characterized by fever and a pruritic vesicular rash of generalized distribution. Although in temperate climates, the majority of the population is immune to the varicella zoster virus by 5 years of age, the epidemiology is remarkably different in Sri Lanka. In Sri Lanka, only 77.3% had had chickenpox by the age of 60 years. In addition, 39.7% of women of child bearing age were not immune to chickenpox¹.

Complications of chicken pox, such as pneumonia, are 25 times commoner in adults than in children and mortality rates are far higher². VZV infection associated viral pneumonia has an incidence of 0.3-50% and a reported mortality of 2-20% in adults². Chickenpox during pregnancy is associated with many serious complications such as maternal pneumonia, congenital varicella and neonatal chickenpox, which are associated with a high morbidity and mortality³. Chickenpox is prolonged (more than 10 days) in the immunosuppressed and many have complications. Visceral dissemination and multi-organ failure subsequently leading to death has been reported in many².

Types of Vaccines

All varicella vaccines contain the Oka strain of live attenuated VZV. The lyophilized vaccine is supplied with sterile diluent.

Efficacy

Two doses of vaccine are effective in preventing any form of clinical disease in 98% of recipients and 100% effective against severe disease, up to 10 years after vaccination². With the use of two doses, individuals have not shown any waning of immunity even 14 years after receiving the vaccine⁴. Immune responses are influenced by the number of doses given, immune status and age at receiving the vaccine.

- Age at receiving the vaccine: seroconversion rates are between 77-96% in adult vaccinees, which is lower than the seroconversion rates in children.
- Immune status: seroconversion rates are lower in children with malignancies.
- Number of doses: One dose is thought to offer protection against approximately 80% for all types of varicella. However, break through varicella is observed in 20-30% of children who only received one dose of the vaccine⁵.

Indications ^{4,5}

- Susceptible children over 1 year of age, adolescents and adults
- It is strongly recommended in the following groups: Health-care 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 3 months 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 human immunodeficiency virus (HIV) infection, if CD4 > 200 cells/ μ L or if CD4 counts >25% of the total lymphocyte count (in children).

Dosage and administration

- 0.5 mL given subcutaneously

Aged 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 aged 4-6 years
- The second dose may be administered at an earlier age provided that the interval between the first and second dose is more than 3 months

- Those who have received only one dose of the vaccine during childhood based on earlier guidelines are recommended another dose of the vaccine

Persons Aged >13 Years

- should receive two 0.5-mL doses of varicella vaccine, 4-8 weeks apart

Post exposure prophylaxis

The varicella vaccine is effective in preventing illness or modifying the illness if given to children within 3 days following exposure to the rash. Vaccination within 3 days of exposure to the rash was >90% effective in preventing varicella whereas vaccination within 5 days of exposure to rash was approximately 70% effective in preventing varicella and 100% effective in modifying severe disease. Therefore, the varicella vaccine is recommended for post exposure administration for unvaccinated persons without other evidence of immunity. (see Chapter 25 Passive Immunization).

Herpes zoster

The incidence of herpes zoster (HZ) among persons older than 75 years of age is > 10/1,000 person-years and the lifetime risk of HZ following chickenpox is estimated to be 10-20%. The incidence is significantly higher in individuals with impaired cell mediated immune responses such as those with malignancy, organ transplant recipients and those on immunosuppressant treatment². The most common complication of HZ, particularly in older persons, is postherpetic neuralgia (PHN). 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 0.9/1,000 person-years, which is significantly less than the prevalence of HZ following natural infection².

Herpes Zoster vaccine

There is currently a safe and effective vaccine for the prevention of herpes zoster, in which the varicella virus concentration is at least 14 times more than that of the VZV vaccine. This vaccine is administered as a single subcutaneous dose and is recommended to be used in individuals over 60 years of age. The vaccine was found to reduce the risk of zoster by 51.3% and PHN by 66.5%, three years following vaccination⁶. However, the protection offered by this vaccine was shown to wane 5 years following vaccination⁶.

Absolute contraindications for the varicella vaccine

- Those suffering from cellular immune deficiencies including individuals who have any malignant condition
- Persons receiving high-dose systemic immunosuppressive therapy, including persons on oral steroids >2 mg/kg of body weight
- Patients with human immunodeficiency virus (HIV) infection can receive the vaccine if CD4 > 200 cells/ μ L or if CD4 counts >25% of the total lymphocyte count
- Pregnancy. Although pregnancy is an absolute contraindication, no adverse effects have been reported in instances where the vaccine has been mistakenly administered
- Those who are allergic to any components of the vaccine such as fetal bovine serum or porcine gelatin⁷

Relative contraindications

- Impaired humoral immunity: vaccine can be given after obtaining specialist opinion
- Patients on steroids <2 mg/kg of body weight per day
- Those with leukemia, lymphoma, or other malignancies whose disease is in remission and when chemotherapy has been terminated for at least 3 months

Adverse effects

- Mild pain, redness at the site of administration
- Causes a varicella type rash in 3% of recipients⁴. These rashes are mostly macular papular and occur within 2 weeks of immunization
- The virus is able to establish latent infection in the vaccinated host, and zoster due to the vaccine virus has been reported. However, reactivation of the vaccine virus occurs less frequently than in those following natural infection and zoster and episodes are reported to be milder⁶

Storage

2°C-8°C. Please refer to the manufacturer's instructions.

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CHAPTER 21

YELLOW FEVER VACCINE

Yellow fever

Yellow fever is a viral haemorrhagic fever which is endemic in the tropics of Africa and South America. It poses a significant hazard to unvaccinated travelers to these areas. The case fatality rate may reach 20-50% of persons with severe disease^{1,2,4}. Yellow fever (YF) is transmitted in a cycle involving monkeys and mosquitoes but human beings can also serve as the viraemic host for mosquito infection. Although the vector mosquito, *Aedes aegypti*, is found in Sri Lanka, yellow fever has not been reported. The emphasis is on preventive vaccination as there is no specific therapy.

Type of vaccine

Live attenuated vaccines from the 17D strain of the yellow fever virus produced in embryonated chicken eggs. Two 17D sub strain vaccines are manufactured today: 17DD & 17D-204YF vaccines. The yellow fever strains in these two vaccines share 99.9% sequence homology^{1,2}.

Only the 17D- 204YF vaccine is available in Sri Lanka.

The immunizing dose of live attenuated YF vaccine should not be less than 3.0 log₁₀ international units according to WHO recommendations².

Efficacy

Studies have demonstrated that a single primary dose of yellow fever vaccine induces neutralizing antibodies by 10 days in 80-100% of vaccinees² and protection appears to last for 20-35 years and is probably lifelong^{2,3,4}.

Indications

The following groups should be immunized:

1. Persons aged nine months or older who are travelling to countries that require an International Certificate of Vaccination or Prophylaxis (ICVP) for entry
2. Persons aged nine months or older who are travelling to or living in infected areas or countries in the yellow fever endemic zone even if these countries do not require evidence of immunization on entry
3. Persons travelling from a country with risk (list of countries available at the end of the chapter) of YF virus transmission and ≥ 9 months of age, including transit >12 hours in an airport located in a country with risk of YF virus transmission
4. Laboratory workers handling infected material

Immunization should be performed at least ten days prior to travel to an endemic area to allow protective immunity to develop and for the ICVP to become valid. However, vaccine should still be considered for last minute travellers who should be counseled about the importance of insect bite precautions and possible implications of an invalid ICVP.

Reinforcing immunization

Revaccination should be offered to certain groups believed to be at increased risk for yellow fever disease either because of their location and duration of travel or because of more consistent exposure to virulent virus⁴.

- Persons travelling to an area with an ongoing out break
- Persons travelling for a prolonged period in an endemic area
- Laboratory workers who routinely handle wild type yellow fever virus
- Those needing a valid ICVP
- Those who received their initial yellow fever vaccination

- When age is less than two years old
- During pregnancy
- When infected with HIV
- When immune suppressed
- Before undergoing a bone marrow transplant

International Certificate of Vaccination or Prophylaxis (ICVP)

Under the reviewed International Health Regulations (IHR) 2005, member states may require immunization against yellow fever as a condition of entry. Yellow fever vaccine can only be administered at a designated yellow fever center as established by the International Health Regulations of WHO. The yellow fever vaccination centre (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. Following immunization, an International Certificate of Vaccination or Prophylaxis (ICVP) is issued. Sri Lanka considers the certificate of YF vaccination to be valid for life, beginning from the tenth day after primary immunization and immediately after re-immunization.

For the ICVP to be valid, it must contain the following:

- The signature of the clinician supervising the administration of the yellow fever vaccine
- The official stamp of the designated YFVC where the vaccine was administered

Note: In February 2015, the CDC Advisory Committee on Immunization Practices (ACIP) approved a new recommendation that a single dose of yellow fever vaccine provides long-lasting protection and is adequate for most travellers. The updated recommendations also identify specific groups of travellers who should receive additional doses and others for whom additional doses may be considered⁵.

Although ACIP no longer recommends booster doses of yellow fever vaccine for most travellers, clinicians and travellers should review

the entry requirements for destination countries because changes to the IHR have not yet been fully implemented. Individual country requirements are subjected to change at any time and updates can be found at <http://www.who.int/ith>.

Dosage and schedule

Single dose of 0.5 mL of reconstituted vaccine. Further doses should be given at the recommended intervals if required².

Freeze dried vaccine, once reconstituted, should be used immediately. The reconstituted vaccine could be stored for a maximum of 3 hours at 2°C - 8°C.

Administration

0.5 mL subcutaneous

Contraindications

- Infants below the age of 6 months
- Pregnant women – except during a yellow fever outbreak when the risk of infection is high⁵
- Confirmed anaphylactic reaction to a previous dose of yellow fever vaccine or to any of the component of the vaccine
- Confirmed anaphylactic reaction to eggs
- Thymus disorder
- Malignancy
- Immunocompromised persons

Patients with any of the conditions described above who must travel should be informed of the risk of yellow fever and instructed in mosquito avoidance measures. For those who intend to visit countries where an ICVP against yellow fever is required for entry, a letter of exemption should be issued by the YFVC.

Precautions

- Minor illness without fever or systemic upset is not a valid reason to postpone immunization. If an individual is acutely unwell, immunization should be postponed until fully recovered.

- Persons over 60 years of age

The risk of neurological and viscerotropic adverse events increases with age

- Pregnancy

Yellow fever vaccine should not generally be given to pregnant women because of the theoretical risk of fetal infection from the live virus vaccine. Pregnant women should be advised not to travel to a high risk area. When travel is unavoidable, the risk from the disease and the theoretical risk from the vaccine have to be assessed on an individual basis and vaccination considered⁶.

- Breast feeding

There is some evidence of transmission of live vaccine virus to infants less than two months of age from breast milk^{4,7}. Administration of yellow fever vaccine for women who are breast feeding children under the age of nine months should be done with caution³.

- Infants

Risk of vaccine associated encephalitis is inversely proportional to age. Infants aged six to nine months should only be immunized if the risk of yellow fever during travel is unavoidable. Infants aged less than six months should not be immunized.

- Immunosuppression and HIV infection

Unless the yellow fever risk is unavoidable, asymptomatic HIV infected persons should not be immunized. However yellow fever vaccine may be given safely to HIV infected persons with a CD4 count ≥ 200 and a suppressed viral load^{5,7}.

Adverse effects

Common adverse reactions

Reactions to yellow fever vaccine are generally mild; reported events typically include low-grade fever, headache, myalgia and / or soreness at the injection site that begin within 1-5 days following vaccination and last for 5–10 days.

Severe adverse reactions

Hypersensitivity

Immediate hypersensitivity reactions are uncommon. Anaphylaxis after yellow fever vaccine is reported to occur at a rate of 1.8 cases per 100,000 doses administered. Urticarial rash or bronchospasm rarely occurs, most likely related to egg protein or gelatin in the vaccine.

Yellow fever vaccine associated neurologic disease (YEL-AND)²

YEL-AND is a serious but rarely fatal adverse event² which includes meningoencephalitis, Guillain-Barre syndrome, acute disseminated encephalomyelitis, bulbar palsy, and Bell's palsy². Four to six cases occur per 1 million doses distributed. The illness occurs 3 – 28 days after vaccination, and almost all cases were in first-time vaccine recipients. YEL-AND is commoner in people aged > 60 years.

Yellow fever vaccine-associated viscerotropic disease (YEL-AVD)²

YEL-AVD is a severe illness similar to wild-type disease, with vaccine virus proliferating in multiple organs and often leading to multisystem organ failure and death. YEL-AVD appears to occur after the first dose of yellow fever vaccine, rather than with booster doses. The onset of illness for YEL-AVD cases averaged 3 days (range, 1–8 days) after vaccination. The case fatality ratio for reported YEL-AVD cases is 65%. The rate is higher for people aged >60 years. The frequency is 3-5 cases per 1 million doses distributed⁸.

Storage

2°C – 8°C. Do not freeze

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CHAPTER 22

IMMUNIZATION OF HIV INFECTED PERSONS

Immunization is an important measure to protect people living with HIV/AIDS (PLHIV) against certain vaccine preventable diseases. PLHIV often have an increased risk of infection and they could experience more severe disease compared to HIV uninfected persons. However as HIV infection alters immune function, vaccination of HIV-infected persons may not confer the same degree of protection gained by immunocompetent persons. The antibody response is frequently impaired in PLHIV, as the virus attacks the CD4 T cell, which is important in antibody formation. However, many of these vaccines still afford protection but the immunity may remain lower and decline more rapidly compared to HIV negative individuals. To overcome this issue, some vaccines could be administered with a modified schedule such as higher or more frequent doses which improves the immunogenicity¹. In addition certain vaccines enhance HIV virus replication and transiently increase HIV viral load but this does not preclude vaccination².

Theoretically, for PLHIV, the vaccine 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/ μ L.

In general all inactivated vaccines could be administered safely to persons with altered immunocompetence³.

However live vaccines such as BCG, oral polio, measles, mumps, rubella, varicella and yellow fever vaccines may pose a risk to HIV infected individuals. Nevertheless, antiretroviral therapy (ART) induced immunorestitution reduces the possibilities 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 with CD4 T lymphocyte cell percentage >15% and those aged >5 years with CD4 counts ≥ 200 cells/ μL)³. Before administering live vaccines consultation with an immunologist or a vaccinologist is advised.

* HIV-infected persons >5 years of age with CD4 percentage <15% and CD4 counts <200 cells/ μL . Children ≤ 5 years of age with CD4 percentage <15% are considered to have severe immunosuppression

General principles of immunization in HIV-infected children

Vaccines may be less effective in HIV infected children. However, these children also have an increased risk of disease and may have more severe illness if they are infected. Therefore, HIV infected children should be protected from vaccine preventable diseases. Hence completing immunization is important, but consideration should be given to the most appropriate time for immunization. It is important to immunize the HIV infected children prior to the impairment of their immune system or after immune reconstitution occurs with ART.

Table 1: Immunization schedule for HIV infected children**

Age	Standard schedule	Child with HIV	Remarks
0-4 weeks	BCG	HIV infected infants should not receive BCG vaccine. BCG should be postponed till HIV is excluded in HIV exposed infants	
On completion of			

2 months	Pentavalent (DTP-HepB-Hib) & OPV (1 st dose) fIPV (fractional IPV) (1 st dose)	Pentavalent (DTP-HepB-Hib)+inactivated polio vaccine*** (1 st dose) Pneumococcal conjugate vaccine (PCV-1 st dose)	
4 months	Pentavalent (DTP-HepB-Hib) & OPV (2 nd dose) fIPV (fractional IPV) (2 nd dose)	Pentavalent (DTP-Hep-Hib)+inactivated polio vaccine*** (2 nd dose) (PCV -2 nd dose)	
6 months	Pentavalent (DTP-HepB-Hib)& OPV (3 rd dose)	Pentavalent (DTP-HepB-Hib)+ inactivated polio vaccine*** (3 rd dose) (PCV -3 rd dose)	
9 months	MMR	MMR	MMR- should be postponed in severe immuno deficiency
12 months	Live JE Hep A	Hep A 1 st dose (2nd dose 6-12 months apart)	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 who are severely immunosuppressed should not receive the varicella vaccine.

18 months	DTP& OPV (4 th dose)	DTP+Inactivated Polio vaccine***	
3 years	MMR 2 nd dose	MMR 2 nd dose	Patients who are severely immunosuppressed should not receive the vaccine.
5 years	DT+OPV	DT+Inactivated polio*** Pneumococcal polysaccharide vaccine (PPSV) booster	
10 years (females and males)	HPV (quadrivalent) 2 doses (0,6 months)	HPV (quadrivalent) 3 doses (0,2,6 months)	
11 years	aTd	aTd	

** Adopted from National Immunization Programme

*** IPV- 0.5 mL intramuscular

General principles of immunization in HIV-infected adults

Live vaccines

- Persons with symptomatic HIV infection or CD4 counts <200 cells/ μ L should not be given live vaccines. Vaccination may be reconsidered when immune restoration occurs with ART¹.
- HIV infected adults with a CD4 count of 200-300 cells/ μ L have a moderate immunodeficiency¹. When administering live vaccines to them it is important to weigh the risk and benefits before vaccination.
- Co-administration of multiple live vaccines to HIV infected individuals is not recommended due to issues related to safety, immunogenicity and efficacy. It is recommended to have at least an interval of four weeks between vaccination¹.

Inactivated vaccines

- In persons with CD4 counts <200 cells/ μ L, the response to inactivated vaccines is reduced¹. Delaying vaccination till immunorestitution could be considered in these patients. However if the risk of exposure is high, vaccination could be done. If indicated vaccination could be repeated following immunorestitution on ART.

Recommendation for pre-exposure vaccination in HIV-infected adults¹

***Haemophilus influenzae* type b vaccine (Hib)**

Vaccine has been shown to produce protective antibodies in HIV infected individuals but the response can vary with the CD4 cell count. It is recommended that HIV positive individuals with asplenia, splenic dysfunction, or complement deficiency should receive one dose of a Hib containing vaccine whether or not they were immunized previously and regardless of CD4 count, ART use and viral load¹.

Hepatitis A vaccine

It is recommended to do pre-vaccination screening for hepatitis A immunity in HIV positive adults who are at risk of hepatitis A. Following categories could be considered as at risk for hepatitis A infection.

- Close contacts with hepatitis A patients
- Men who have sex with men
- Injecting and non-injecting drug users
- Those with occupational exposure to Hepatitis A
- Persons who require frequent blood /blood products transfusions
- Persons with special needs living in residential institutions and their carers

If serologically negative for hepatitis A, they should be offered monovalent hepatitis A vaccine. The immune response to hepatitis A vaccine is generally reduced in HIV positive individuals compared to

HIV negative individuals. But the response improves with increasing CD4 cell counts and viral load suppression on ART. The vaccine is safe and well tolerated in HIV positive individuals including those who receive three doses over 6 months.

Hepatitis B vaccine

HIV infection affects the response to Hepatitis B vaccine and the HBsAb seroconversion strongly correlates with CD4 cell count and viral load. Revaccination of non-responders once the CD4 count is >350 cells/ μL , suppression of viral load with ART and the use of larger and more frequent vaccine doses are some strategies available to improve the vaccine response among HIV infected individuals. Duration of vaccine induced protection is unknown in HIV positive individuals and in general, post vaccination antibody levels are lower and disappear more quickly than in HIV uninfected individuals.

When using recombinant vaccines, high dose (40 μg -2 doses of 20 μg /mL vaccine) vaccination should be offered. Four vaccine doses should be given at 0, 1, 2, and 6 months¹. It is recommended to measure the HBsAb levels 4-8 weeks after the last vaccine dose.

Antibody level >100 IU/L are regarded as ideal, whereas a level <10 IU/L is classified as non-responsive. It is recommended that individuals with HBsAb levels ≥ 10 but <100 IU/L should receive one booster dose¹. If retesting of HBsAb level shows antibody level between ≥ 10 -100 IU/L regular annual HBsAb testing is needed to guide subsequent boosting requirement.

Individuals who have HBsAb levels <10 IU/L after the primary vaccine course should receive three further vaccine doses at monthly intervals. It is better to delay the revaccination until the viral load is suppressed on ART and the CD4 count has increased > 350 cells/ μL .

Screening of HBsAb levels with longer intervals (2-4 yearly) are indicated for individuals with initial HBsAb levels >100 IU/L, CD4 count >350 cells/ μL and viral load suppression on ART. Other individuals should undergo yearly HBsAb screening.

Human papillomavirus vaccine

HIV infected individuals are at higher risk of HPV acquisition, persistence and at increased risk of HPV related malignancies. The response to vaccine is highest in those receiving ART and showing high CD4 cell count and suppressed viral load. Studies are still ongoing to demonstrate the duration of vaccine induced protection. Even though younger individuals are more likely to benefit from the vaccine, older men and women may continue to have at least a partial benefit from vaccination.

It is recommended that previously unvaccinated HIV infected men and women aged up to 26 years be offered HPV vaccination regardless of CD4 count, ART use and viral load. Previously unvaccinated HIV positive men having sex with men aged up to 40 years be offered HPV vaccination regardless of CD4 count, ART use and viral load¹.

It may be useful to offer HPV vaccination for previously unvaccinated HIV positive women aged up to 40 years regardless of CD4 count, ART use and viral load¹. In ART naïve patients with CD4 cell count <200 cells/ μ L, vaccination may be postponed until the patient is established on ART.

Inactivated polio vaccine

Inactivated polio vaccine can produce neutralizing antibodies in HIV positive adults and children and in patients with CD4 count <300 cell/ μ L. It is safe and well tolerated. It is recommended that individuals who are unvaccinated should receive 3 vaccine doses at monthly interval followed by 2 reinforcing doses after 5 and 10 years¹. Fully vaccinated individuals could receive booster doses every 10 years if at risk of exposure.

Influenza vaccine

Vaccine response is lower compared to HIV negative individuals and correlate with CD4 cell count and viral load. As patients with HIV infection are at higher risk of complications of influenza, it is recommended to offer annual inactivated influenza vaccine to all HIV infected individuals especially for HIV infected pregnant women.

Japanese encephalitis vaccine

Live JE vaccine is not recommended in HIV infected patients. There is insufficient evidence on the safety, immunogenicity and clinical efficacy of JE vaccination in HIV positive adults. However it is recommended that HIV infected individuals be offered an inactivated vero cell derived JE vaccine with two doses given 1 month apart. A booster dose could be given 1-2 years later for those at continued risk with a further booster planned after 10 years¹. This vaccine is not available in Sri Lanka at present.

Meningococcal vaccine

Patients with HIV infection are at higher risk of invasive meningococcal infection especially those with CD4 cell count <200 cells/ μ L and viral load >400 copies/mL. However HIV infection alone is not currently an indication for meningococcal vaccine. It is recommended that HIV positive individuals who are close contacts of patients with meningococcal disease should be offered antibiotic prophylaxis and appropriate vaccination.

MMR vaccine

The prognosis of rubella and mumps does not show much difference between HIV infected individuals and the general population. However measles could be life-threatening in persons with advanced HIV infection. Therefore, it is recommended to offer two doses of MMR vaccine at least 1 month apart to measles seronegative HIV infected patients with CD4 cell counts >200 cells/ μ L. However, based on the likelihood of exposure, vaccination may be postponed in patients with CD4 cell count >200 cells/ μ L who have not started on ART.

After a significant exposure to measles, HIV infected individuals should be screened for measles IgG within 3 days regardless of a history of previous vaccination. After a risk assessment about the need and the mode of post exposure prophylaxis, measles seronegative adults:

- with CD4 count >200 cells/ μ L preferably on ART with a stable viral load could receive MMR vaccine within 3 days of contact or IM preparation of human immunoglobulin (HNIG) within 6 days of contact¹.
- with CD4 counts <200 cells/ μ L could be given HNIG within 6 days¹.

However the protection afforded with HNIG/IVIG will be short lived.

It is also recommended to give MMR vaccine to rubella sero-negative HIV positive women of child bearing age provided their CD4 count is >200cells/ μ L and they are not pregnant. Vaccine responses are reduced in HIV infected individuals but effective ART can improve the response.

Pneumococcal vaccine

HIV infected individuals are at higher risk of developing pneumococcal disease and show an increased risk of mortality. Studies conducted on clinical efficacy of pneumococcal polysaccharide vaccine (PPSV23) in HIV positive adults have shown inconsistent findings. However, serological studies conducted on pneumococcal conjugate (PCV) vaccine have shown immunogenicity in HIV infected persons¹. With both vaccines, the response is low in HIV positive individuals compared to HIV negative individuals. However, PCV vaccine has demonstrated superiority with certain serotypes over PPSV in serological studies¹.

It is recommended to give pneumococcal vaccine to HIV infected individuals irrespective of the CD4 cell count, ART use and viral load. One dose of PCV 13/10 could be administered followed by one dose of PPSV23 at least 8 weeks later. Second dose of PPSV23 should be administered at least 5 years after the previous dose. One final dose of PPSV23 should be administered at 65 years or older. This dose should be given at least 5 years after the most recent dose of PPSV23⁴.

Rabies vaccine

When giving post exposure prophylaxis, each case should be assessed individually. Following categories should be considered as non-

immune for rabies and should be given rabies immunoglobulin (RIG) and five doses of a cell culture derived vaccine intramuscularly at 0, 3, 7, 14 and 30 days¹.

- 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/ μ L and not receiving ART

In patients who previously received 5 doses of the vaccine and had adequate antibody response with a CD4 count >500 cells/ μ L, viral suppression (>6 months) and on ART may be managed with 2 intramuscular doses given at 0 and 3-7 days without RIG¹.

After full course of vaccination all patients should undergo serological testing 2 weeks after the last vaccine dose and non-responders are offered double dose or more frequent vaccine doses after obtaining specialist advice.

Tetanus-Diphtheria vaccine (aTd)

The HIV infected adults who require vaccination against tetanus and diphtheria could be given aTd vaccine regardless of CD4 cell count, ART use and viral load. It is recommended to give three vaccine doses at 1 month intervals, followed by 2 reinforcing doses after 5 and 10 years¹.

Tetanus toxoid

The vaccine has been shown to be immunogenic in HIV infected individuals even though the response is less compared to non-infected individuals. However the immunity improves following successful ART.

If the patient is unvaccinated for tetanus, it is recommended to give the adult tetanus vaccine regardless of CD4 count, ART use and viral load in three vaccine doses given at 1 month intervals, followed by two reinforcing doses after 5 and 10 years. Fully vaccinated individuals should receive a booster dose every 10 years.

Following a potential exposure,

- Individuals with uncertain or incomplete vaccination, 3 vaccine doses at monthly intervals should be given regardless of type of wound and level of risk
- Individuals who have previously received three vaccine doses with a clean wound and negligible risk should receive one dose if the last dose received was >10 years previously
- Individuals who received at least three vaccine doses with tetanus prone wound should receive tetanus immunoglobulin and 1 dose of vaccine if the last dose received was >10 years previously

Typhoid vaccine

HIV infected individuals are at higher risk of developing infections with Salmonella and more likely to develop complications. It is recommended to offer Vi capsular polysaccharide vaccine to HIV infected individuals who are likely to be exposed to poor sanitary conditions. The vaccine should be given at least 2 weeks before the expected exposure. The booster dose could be given every 3 years for those who remain at risk.

Varicella zoster vaccine

HIV infected individuals who acquire chickenpox are at higher risk of developing severe and fulminant disease. In addition, they are at increased risk of developing VZV reactivation especially with low CD4 count 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.

Chickenpox vaccine has shown to be safe and immunogenic in children with asymptomatic or mildly symptomatic HIV infection. However, only limited data are available in HIV positive adults¹.

Two doses of the varicella vaccine 3 months apart are recommended for varicella seronegative patients who have CD4 cell count >200cells/ μ L, and on ART¹.

Yellow fever vaccine

It is recommended that HIV infected individuals aged <60 years and with CD4 cell count >200 cells/ μ L who are planning to travel to countries in which there is risk of exposure should be offered the vaccination after counseling on benefits and risks of vaccination. One vaccine dose at least 2 weeks before travel is recommended¹. Higher CD4 counts and a suppressed viral load on ART are likely to maximize safety and the efficacy of vaccination.

Table 2: Vaccination of adults with HIV

Vaccine	Indication	Primary course	Boosting	Remarks
Haemophilus influenzae type b (Hib)	At risk	Single dose	None	Could be given regardless of the CD4 cell count
Hepatitis A	At risk	2 or 3 doses	Ten yearly if at risk	3 doses at 0,1, and 6 months if the CD4 cell count is <350 cells/ μ L and two doses at 0 and 6 months if the CD4 cell count is >350 cells/ μ L
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 \leq 10 IU/L need three further vaccine doses and retesting	Could be given at all CD4 cell counts. Screen HBsAb levels according to initial response
Human papillomavirus (HPV)	Age and gender related	3 doses of quadrivalent vaccine 0,2 and 6 months apart	None	Could be given regardless of the CD4 cell count
Inactivated polio (IPV)	To all non immune	5 doses (at 0,1,2 months, 5 years and 10 years)	Ten yearly 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 account count
Japanese encephalitis Inactivated vero cell derived	At risk	2 doses 1 month apart for those at continued risk with a further boost after 10 years.		Could be given regardless of the CD4 cell count
Meningococcal (conjugated)	At risk	2 doses 2 months apart	Five yearly 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/ μ L
Pneumococcal (polysaccharide) PPSV23 and Pneumococcal (conjugate) PCV13/10 is preferred	For all	1 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 ⁴ .	None	Could be given regardless of the CD4 cell count
Rabies vaccine	For exposed non-immune	Rabies immunoglobulin + 5 doses of the vaccine IM at 0,3,7,14 and 30 days	None	Could be given regardless of the CD4 cell count

Tetanus-Diphtheria (aTd)	To all non-immune	5 doses at 0,1,2 months,5 years and 10 years	Ten yearly if at risk	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	Ten yearly if at risk	Could be given regardless of the CD4 count
Typhoid	At risk	Single dose	Three yearly if at risk	Could be given regardless of the CD4 count
Vi capsular polysaccharide Varicella	All non immune	2 doses 3 months apart	None	Could be given when the CD4 cells count is >200 cells/ μ L
Yellow fever	At risk age <60 years and CD4 cell count is >200 cells/ μ L	Single dose	Ten yearly if at risk	Age >60 years , CD4 cell count is <200cells/ μ L and pregnant women should not receive the vaccine

***Yeast based vaccine 40 μ g/dose

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CHAPTER 23

IMMUNIZATION FOR THE ELDERLY

Introduction

A person over the age of 65 years is considered elderly. The percentage of this group is gradually increasing in developed and developing countries, due to advances in medical care and better living conditions.

The elderly are at a higher risk of contracting vaccine preventable infections and complications due to advancing age and waning immunity. They often may have other medical conditions such as diabetes, hypertension, chronic respiratory diseases, chronic renal and liver disease which makes them more susceptible to infections.

An active life style and increasing local and international travel, makes them even more susceptible to infections.

Aging could cause waning immunity for certain infections for which they may have had immunity during their younger days, either following natural infection or immunization. Hence, certain vaccines are recommended routinely for the elderly.

Data from USA shows, even though influenza is a very common, mild to moderate and self limiting viral infection, there could be serious complications in the elderly and approximately 90% of influenza related deaths occur in this group¹.

Pneumococcal disease is a significant cause of morbidity and mortality in the elderly. The case fatality rate of invasive pneumococcal disease increases from 20% for those >65 years of age to 40% for those > 85 years¹. The risk of multidrug-resistant pneumococcal infections is increasing in this group due to prolonged hospitalization and long term antibiotic therapy².

The morbidity and mortality following varicella and its complications are also higher with advancing age. The reactivation disease of

varicella (herpes zoster (HZ)/shingles) occur in up to 25% of persons following primary infection and the incidence of zoster and post-herpetic neuralgia (PHN) is markedly higher in the elderly¹. More than two-thirds of the cases of HZ occur in persons >50 years of age.

Routinely recommended vaccinations for the elderly include

- Influenza vaccine
- Pneumococcal vaccine
- Tetanus, diphtheria and pertussis booster
- Varicella vaccine – if the person has not had the natural infection or received 2 doses of vaccine in the past or absence of serological evidence of immunity
- Zoster vaccine

By immunizing the elderly, there will be substantial reduction in morbidity and mortality due to these infections and thereby will reduce the burden of health care cost.

Influenza vaccine:

- Only the inactivated influenza vaccine is recommended for the elderly³
- Seasonal influenza vaccine with a good match for prevailing viral strains are effective
- Single dose of vaccine given intramuscularly followed with annual boosters
- Can be given simultaneously with other vaccines

Pneumococcal vaccine:

- 23 valent purified bacterial capsular polysaccharide vaccine (PPSV23) is recommended
- A single dose of vaccine is given intramuscularly
- Only a single booster dose is recommended after 5 years for adults >65 years of age, if the first dose has been given before the age of 65 years³

- One time re-vaccination after 5 years is recommended for older adults with chronic renal failure, nephrotic syndrome and immunocompromised situations^{3,4}
- Can be given simultaneously with other vaccines

For immuno-competent adults who previously received pneumococcal vaccine when aged <65 years and for whom an additional dose of PPSV23 is indicated when aged ≥ 65 years, this subsequent PPSV23 dose should be given ≥ 1 year after PCV13 and ≥ 5 years after the most recent dose of PPSV23. For adults aged ≥ 65 years with immunocompromising conditions, functional or anatomic asplenia, cerebrospinal fluid leaks, or cochlear implants, the recommended interval between PCV13 followed by PPSV23 is ≥ 8 weeks⁵.

Tetanus, diphtheria and pertussis booster (Tdap / aTd):

Adults are recommended to get the Tdap vaccine once, if they did not receive it as an adolescent to protect against pertussis (whooping cough), and then aTd (tetanus, diphtheria) booster dose, every 10 years⁶.

- Tdap is given as a single intramuscular dose
- Booster dose of aTd is recommended every 10 years as antitoxin titres drop gradually to the minimal protective level by 10 years after the last dose¹
- Can be given simultaneously with other vaccines

Varicella vaccine:

- Two doses of varicella vaccine are recommended for non-immune adults
- Live attenuated varicella vaccine is given subcutaneously
- A second dose is recommended with a gap of 4–12 weeks
- An adult who has received a single dose of varicella vaccine in the past, should be offered a booster dose

Zoster vaccine : Not available in Sri Lanka at present.

- A single dose of live attenuated zoster vaccine is given subcutaneously.
- Zoster vaccine reduces the risk of HZ by 51% and PHN by 67% by increasing VZV specific cell mediated immunity¹.
- The vaccine is not 100% effective in preventing HZ. However, cases of HZ and PHN after vaccination appear to be much milder, than in persons who have not had the vaccination.

For details of these vaccines including contraindications, please refer the relevant chapters.

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CHAPTER 24

IMMUNIZATION OF TRANSPLANT RECIPIENTS

Transplantation includes both solid organs such as kidney, liver, heart and lung transplants and bone marrow or stem cell transplants.

Solid organ transplantation

Solid organ transplant 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 risk³. Infections may be responsible for graft failure as well as other effects. Influenza infection can result in graft rejection. Hepatitis B infection, from the donor, as well as from transfusions may lead to fulminant hepatic failure³. A 20–100 fold increase in carcinoma-in-situ due to human papillomavirus infection following transplantation has been noted⁴. Disseminated varicella infection, measles encephalitis and pneumonitis and interstitial nephritis due to mumps infection in renal transplant recipients may increase mortality³.

The humoral and cellular responses after transplantation however are decreased compared to normal people or even transplant candidates with organ dysfunction⁵. As organ failure reduces the “take” of vaccines, immunization should be provided early in the disease process before transplantation if possible. All patients with chronic or end stage kidney, liver, heart and lung disease should be given age appropriate vaccines⁶. Live vaccines should be given at least 4 weeks before transplantation^{1,2} and are not generally recommended after transplantation due to the risk of vaccine induced infection due to the reduced immune status of the patient. Inactivated vaccines can be given 3–6 months after transplantation, **if not administered pre transplantation**. This should be followed by monitoring responses serologically 4 weeks later.

Donor immunization

Living donors should have been immunized according to the current immunization schedule. Vaccination of donors solely for the recipient's benefit is not recommended. Live vaccines should be avoided within 4 weeks of organ donation⁶.

Immunization of close contacts and healthcare personnel

House hold 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 MMR and varicella vaccines. 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 changes². Pets should also be fully immunized. There is little or no risk of transmission following immunization of pets with live vaccines².

Influenza vaccine

The inactivated influenza vaccine should be administered annually. The American Transplant Society recommends vaccination 3–6 months after transplantation. Some guidelines recommend it even earlier (at one month)². However, the immunogenicity is less, compared to vaccination at 3–6 months⁷. As delaying vaccination may leave some patients vulnerable to seasonal influenza, Medicare/Medicaid in the US recommend vaccination before discharge, and giving another dose at 3–6 months² if within the influenza season.

MMR vaccine

The MMR vaccine is contraindicated after transplantation. If the vaccine is given inadvertently or the patient is exposed to wild type measles, passive immunization with pooled immunoglobulin (HNIG) should be administered⁵. The MMR vaccine should be administered at least 4 weeks before transplantation. It can be given after 6 months of age. All children should complete a two-dose MMR series if possible, with at least 4 weeks between doses^{1,2}. It should also be given to sero-negative adults.

Pneumococcal vaccine

The risk of pneumococcal disease is 13 times more in the transplanted population compared to normal people. The conjugated 7 valent vaccine evoked a better response rate compared to the 23 valent polysaccharide vaccine (PPSV23). However, the antibody titres returned to baseline after 3 years, with both vaccines⁵. Theoretically, administering the 13 valent vaccine followed 8 weeks later by the PPSV23 vaccine leads to a prime boost response: ie. The T and B cell responses evoked by the conjugate vaccine are further boosted by the PPSV23, 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 does not occur in transplant recipients⁵. The 13 valent vaccine is not available in Sri Lanka, and the 10 valent vaccine can be substituted, instead.

Herpes zoster vaccine

Transplant candidates aged ≥ 60 years and varicella-positive candidates aged 50–59 years who are not severely immuno-compromised should receive the vaccine up to 4 weeks before transplantation. However, the effectiveness of the vaccine in this population is not known. It is contraindicated post-transplant. This vaccine is not available at present in Sri Lanka.

Human papillomavirus vaccine

While it was expected that cancer due to human papillomavirus (HPV) would be increased in transplant recipients, it was observed in a review of transplant recipients that while there was an increase in vulval and penile cancers, the incidence of invasive cervical cancer was not increased compared to the general population⁸, even though carcinoma in situ is increased. This is probably due to increased surveillance in this population⁸. The quadrivalent HPV vaccine is recommended for normal persons from 9-45 years in females, and 9–26 years in males⁵. 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 performed⁵.

Hepatitis B vaccine

Sero-negative candidates should receive the Hepatitis B vaccine series. Those who are on hemodialysis and aged ≥ 20 years, should receive the high-dose (40 μ g 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 (alternative: 1 dose of Hepatitis B vaccine after which anti-HBs is tested) should be administered, using adult dose or high dose for children and high dose for adolescents and adults⁶. Intradermal vaccination has been successful in those who do not seroconvert following repeated vaccinations⁵. Non-responders should be counseled, and given post exposure prophylaxis with hepatitis B immune globulin.

Meningococcal vaccine

All patients at risk of invasive disease (i.e. after splenectomy) or on complement inhibitors such as eculizumab should be given the quadrivalent conjugated meningococcal vaccine⁵.

Varicella vaccine^{1,2,6}

Varicella vaccine should be administered ≥ 4 weeks before transplantation, for children over one year of age and sero-negative adults, with 2 doses, at least 3 months apart⁶. Those who do not seroconvert, should be given another dose. Non-responders should be given varicella zoster immune globulin after exposure.

Table 1 Recommended vaccine (paediatric and adult) adapted from^{1,2}

Vaccine*	Inactivated(I) or live (L)	Before transplantation	After transplantation	Monitor titre
Influenza *	I	Yes	Yes	No
Hepatitis B **	I	Yes	Yes ^a	Yes ^l
Hepatitis A ^{b*}	I	Yes	Yes	Yes
DTP (paediatric < 7 years)* Tdap (> 7 years and adult)*	I	Yes	Yes	For tetanus
Inactivated polio *	I	Yes	Yes	No
H influenza type b*	I	Yes	Yes	Yes ^c
Inactivated polio *	I	Yes	Yes	No
<i>H influenzae</i> type b*	I	Yes	Yes	Yes ^c
<i>S. pneumoniae</i> conjugate ^d	I	Yes	Yes	Yes ^e
<i>S. pneumoniae</i> polysaccharide ^d	I	Yes	Yes	Yes ^e
<i>N. meningitidis</i> ^{f*}	I	Yes	Yes	No
Human papillomavirus (HPV) ^{g*}	I	Yes	Yes	No
Rabies ^{h*}	I	Yes	Yes	Yes ⁱ
Varicella ^{j *}	L	Yes	No	Yes
MMR* ^j	L	Yes	No	Yes
Zoster vaccine ^k	L	Yes	No	No

* Follow National Guidelines for dosage

** Refer text

^aRoutine vaccine schedule recommended prior to transplant and as

early in the course of disease as possible; vaccine poorly immunogenic after a transplantation, and accelerated schedules may be less immunogenic. Serial hepatitis B surface antibody titers should be assessed both before and every 6–12 months after transplantation to assess ongoing immunity

^b For children, routine recommendation for all transplant candidates and recipients, if unvaccinated, under-vaccinated or sero-negative⁶. In adults, it is routinely recommended for liver transplant candidates and recipients.

^c Serologic assessment recommended if available. *Haemophilus influenzae* type b titer greater than 0.15 mg/L is considered protective in the general population. Test is not available in Sri Lanka

^d Children older than 5 years of age and adults should receive

- one dose of PCV followed by one dose of PPSV 23 two months later, with a booster dose of PPSV23 after 5 years

Children less than 2 years of age should receive

- Two doses of PCV with a gap of 2 months, with a booster dose of PPSV 23 after 5 years

Children aged 2–5 years

- who have taken a full course of PCV should be given one dose of PPSV 23. One booster dose of PPV23 after 5 years
- who have taken a partial course, or are unvaccinated, should be given 2 doses of PCV with an interval of 2 months, and one dose of PPSV 23, 2 months after last dose of PCV. One booster dose of PPSV23 should be given after 5 years.

^e However, the absolute protective titer for pneumococcus is unknown and may vary by serotype. Assay is not available in Sri Lanka

^f Travelers to high-risk areas, properdin deficient, terminal complement component deficient, those with functional or anatomic asplenia

should be vaccinated

^g Recommended for all females aged 9–45 years, males 9–26 years. See text

^h Recommended for exposures or potential exposures due to vocation. IM schedule to be administered. Intra dermal vaccination is not recommended

ⁱ Checking the titre post vaccination is recommended in high risk patients (DGHS/Circular/2016-127 (MRI-ARPET))

^j See text

^k Vaccine is indicated for persons ≥ 60 years. However, no studies of the herpes zoster vaccine are available in the pre-transplant setting

Hematopoietic stem cell transplantation (HSCT)

HSCT includes autologous and allogeneic 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, where delayed as specific immune reconstitution may take 1–2 years⁹. T cell depends on donor memory cell expansion, which occurs in the first few months, followed by de novo T cell expansion after thymic selection, wherein CD 4 cells are generated. The risk of post-transplant infections is dependent on the CD 4 count⁹. 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, whereas CD4 counts normalize 6–9 months post HSCT in the paediatric recipients, and twice as long in adult patients resulting in decreased response to vaccines. In the absence of revaccination, antibody titers to vaccine-preventable diseases decline during the first decade after autologous or allogeneic HSCT^{9,10, 11}. 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 transplantation¹⁰. 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^{9,10}.

While immune reconstitution after HSCT depends on source of cells and immune suppressants used, guidelines for immunization are based on timing after HSCT. Thus, delayed immune reconstitution due to donor (cord blood), conditioning regimes, age, T cell depletion, use of rituximab, graft vs host disease (GVHD) and use of immunomodulatory agents are not considered [10]. Inactivated vaccines and toxoids are administered 3 – 6 months post-transplant, irrespective of immune status¹⁰. Live vaccines are delayed for 24 months, based on insufficient safety and efficacy data on earlier immunization⁹. Inactivated vaccines can be given during immune suppression, and with ongoing GVHD, where 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 antigens¹⁰.

Immunization prior to HSCT⁶

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 can be administered up to 2 weeks before the conditioning regime. Children aged 12 months or over can receive the varicella vaccine, with a 2nd dose if time permits.

Donor immunization

There is limited data as to whether immunization of donor or recipient before transplantation is beneficial¹². The Infectious Diseases Society of America guidelines recommend against immunizing the donor solely for the benefit of the recipient⁶. Live vaccines should be avoided within 4 weeks of stem cell harvest⁶.

Table 2 Recommended vaccine (paediatric and adult) adapted from^{1,2*}

Vaccine Recommended for use after HSCT	Earliest time post-HSCT to initiate vaccine	Dosage ^a	Improved by donor vaccination (practicable only in related-donor setting)
Pneumococcal conjugate (PCV)	3–6 months	3–4 doses ^b	Yes; may be considered when the recipient is at high risk for chronic GVHD
Tetanus, diphtheria, acellular pertussis ^c	6–12 months	3 doses	Tetanus: likely Diphtheria: likely Pertussis: unknown
<i>H. influenzae</i> type b	3 months	3 doses	Yes
Meningococcal ^d	6–12 months	2 doses	Unknown
Inactivated polio	6–12 months	3 doses	Unknown
Hepatitis B ^e	6–12 months	3 doses	Likely
Inactivated influenza ^f	6 months, yearly thereafter	1–2 ^g	Unknown
MMR ^h	24 months	2	Unknown

*Joint updated Guidelines from European Group of Blood and Marrow Transplantation (EBMT), Centers for Disease Control (CDC), Infectious Diseases Society of America (IDSA) and American Society for Blood and Marrow Transplantation (ASBMT)

^aA 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 given at 12 months after HSCT 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

^cDTaP is preferred. However, if only Tdap is available (for example, because DTaP is not licensed for adults), administer Tdap. Acellular pertussis vaccine is preferred, but the whole-cell pertussis vaccine should be used if it is the only pertussis vaccine available

^dRefer Chapter 13

^eIf a post vaccination anti-HBs concentration of ≥ 10 mIU/mL is not attained, a second 3-dose series of HepB vaccine (alternative: 1 dose of HepB vaccine after which anti-HBs is tested), a standard dose or high dose (20 μ g) for children and high dose (40 μ g) for adolescents and adults should be administered⁶.

^fstarting at 4 months of age during an outbreak of influenza

^gFor children aged 6 months to < 9 years, who are receiving influenza vaccine for the first time, 2 doses should be administered ≥ 4 weeks apart⁶

^hAfter 24 months, if sero-negative for measles, without GVHD and not on immuno-suppressives, and 8–11 months (or earlier, if there is a measles outbreak) after intravenous immunoglobulin

Table 3 Optional vaccines adapted from^{6,11}

Vaccine	Recommendations for use
Hepatitis A	Follow recommendations for general population Two doses given at 6–12 month intervals
	HNIG should be administered to hepatitis A-susceptible HSCT recipients for post-exposure prophylaxis
Varicella	Limited data regarding safety and efficacy 2 dose schedule 6–8 weeks apart For varicella sero-negatives, >24 months after transplantation, without active GVHD and not on immuno-suppressives and 8–11 months (or earlier if there is a varicella outbreak) after intravenous immunoglobulin

Human papillomavirus (HPV)	Follow recommendations for general population No data exists regarding the time after HSCT when vaccination could be expected to induce an immune response
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 12–24months after HSCT Post-exposure administration – Rabies immunoglobulin should be given in all instances, irrespective of the severity of the exposure followed by a course of vaccine. Post vaccination antibody titres should be measured ^b

^aAdvisory Committee on Immunization Practices (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 administered intramuscularly (IM) on days 0, 3, 7, 14 and 28 post-exposure

^bChecking the titre post vaccination is recommended in high risk patients (DGHS/Circular/2016-127 (MRI-ARPET))

The following vaccines are contraindicated.

- Bacille Calmette– Guerin (BCG)
- OPV
- Intranasal influenza vaccine (live)
- Rotavirus vaccine
- Zoster vaccine (live)

Table 4 Vaccinations for family, close contacts and healthcare workers (HCW) of HSCT recipients

Vaccination should be completed at least 4 weeks before transplantation

Vaccine	Recommendation
Hepatitis A	Routine vaccination is recommended for: <ul style="list-style-type: none"> • 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 for all 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. OPV contra-indicated
Rotavirus	Vaccination not contraindicated in contacts of HSCT transplant patients.
MMR	Vaccination is recommended for all indicated persons and 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 <07 years and with Tdap for adolescents and adults
Varicella ^c	Vaccination should be administered to susceptible >12 months old, who are not pregnant or immuno-compromised Note: Two doses should be given separated by at least 28 days ⁴

^a Children aged 6 months to 9 years, who are receiving influenza vaccination for the first time require two doses and those who have received only one dose in the first year should receive two doses the following year.

^b Vaccine-strain polio virus in the oral polio vaccine can be transmitted from person-to-person; therefore, oral polio vaccine administration is contraindicated among household contacts of immunocompromised persons. If OPV is inadvertently administered to a household contact of an HSCT recipient, minimize close contact with the immunocompromised person for 4–6 weeks after vaccination.

^c HCW, family members, close contacts and visitors who do not have a documented history of varicella-zoster infection or who are seronegative should receive varicella vaccine before being allowed to visit or have direct contact with an HSCT recipient. Ideally, varicella-zoster-susceptible HCW, family members, household contacts and potential visitors of immunocompromised HSCT recipients should be vaccinated as soon as the decision to perform an HSCT is made. The vaccination should be completed 4 weeks before the conditioning regimen begins or 6 weeks (42 days) before contact with the HSCT recipient is planned. If a varicella vaccinee develops a post-vaccination rash within 42 days of vaccination, the vaccinee should avoid contact with HSCT recipients until all lesions are crusted or the rash has resolved.

^d Children 12 months to 12 years should receive two doses at least 3 months apart; adolescents >13 years and adults should receive two doses at least 4 weeks apart.

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CHAPTER 25

PASSIVE IMMUNIZATION

Introduction

Passive immunization involves administration of immunoglobulins to individuals in order to prevent or reduce the severity of infection. Immunoglobulins used in passive immunization may derive from pooled human plasma, obtained from immunizing donors to obtain specific and highly concentrated specific immunoglobulins (hyper immune immunoglobulins) or produced as monoclonal antibodies. Pooled immunoglobulins are usually given for individuals with congenital or acquired immune deficiencies and specific hyper immunoglobulins are prophylactically administered following exposure to infection or used to treat an infection (e.g. botulism, tetanus, rabies).

Immunoglobulin products used in passive immunization include pooled or specific immunoglobulins (hyperimmune) or monoclonal antibodies given intramuscularly or intravenously. Immunoglobulins are a sterile solution, derived from pooled plasma from adults that have been tested negative for hepatitis B surface antigen, antibodies to HIV and HCV, HCV RNA, syphilis, HTLV-1 and HTLV-2. During the manufacturing process, all viruses that may be present are destroyed.

The main immunoglobulins are of the IgG type (96%) with trace amounts of IgM and IgA. Hyperimmune immunoglobulins are prepared from donors who have high antibody titres to the specific organism. Optimal serum concentrations of antibodies are usually achieved 3-5 days after IM administration.

Administration

Intramuscular: Immunoglobulin for passive immunization (to be used for the prevention of infection) is licensed to be administered intramuscularly. It should be administered into a large muscle mass such as the gluteal region (upper outer quadrant) in an adult or the lateral

thigh region in a child. No more than 5 mL should be administered at one site in an adult, and an adolescent; a lesser volume per site (1–3 mL) should be given to small children and infants.

Subcutaneous: This route is safe and effective in adults and children with primary immune deficiencies. It is used to administer smaller amounts of immunoglobulins at weekly intervals. Immunoglobulins should not be administered intradermally.

Intravenous: This route is used in the replacement of immunoglobulins at 3 to 4 weekly intervals in patients with primary immune deficiency states. Intravenous route is also used in certain diseases such as Kawasaki disease, immune mediated thrombocytopenia (ITP), autoimmune diseases (e.g. Guillain-Barré syndrome, myasthenia gravis), paediatric HIV infection, prevention of graft versus host disease and infection in patients who receive bone marrow transplants.

Indications for use of pooled human immunoglobulins (given IM)

1. Hepatitis A prophylaxis: Indicated as post exposure prophylaxis of infants, individuals older than 40 years, in immunocompromised individuals and in individuals with chronic liver disease. When administered within 2 weeks of exposure, it is >85% effective in preventing infection, though protection rates are higher when administered early¹. In individuals from 12 months to 40 years old, hepatitis A immunization is preferred to administration of immunoglobulins in post exposure prophylaxis¹.

2. Measles prophylaxis: MMR vaccination in individuals who are >12 months of age is preferred to administration of immunoglobulin in the post exposure prophylaxis of measles². The MMR vaccine can offer some protection and modify the course of the disease if administered within 72 hours of exposure².

Administration of immunoglobulins as post exposure prophylaxis is recommended for the following groups of individuals:

- Infants younger than 12 months of age However, in infants from 6 to 11 months of age the MMR can be given in place of immunoglobulins, if it is given within 72 hours of exposure.

- Pregnant women without evidence of measles immunity
- Severely immunocompromised persons. These individuals should receive immunoglobulins regardless of previous vaccination status due to the possibility of very severe infection.

Any non-immune individual exposed to measles who received IG should subsequently receive MMR vaccine (no earlier than six months after intramuscular immunoglobulin or eight months after IVIG), provided the individual is then ≥ 12 months and the vaccine is not otherwise contraindicated².

3. Rubella prophylaxis: Following possible exposure to rubella, the immune status of pregnant women should be recorded by routinely performing rubella specific IgM and IgG antibodies. Neither the rubella vaccine nor immunoglobulins are effective in preventing rubella following exposure and therefore, are not recommended³.

Indications for specific (hyperimmune) immunoglobulins (given IM)

1. Hepatitis B immunoglobulin (HBIG): should be administered as soon as possible after an exposure and preferably within 24 hours. The effectiveness of HBIG given after 7 days of exposure is unknown. The hepatitis B vaccine should be administered at the same time as immunoglobulins (different sites). Indications are as follows⁴:

- Babies born to HBsAg positive mother: HBIG should be given intramuscularly (IM), preferably within 12 hours of birth. This is 85 to 95% effective in preventing infection due to HBV
- Percutaneous (bite or needle stick) or mucosal exposure to HBsAg positive blood or body fluids
- Victim of sexual abuse

Individuals with a history of completed hepatitis B vaccination schedule should receive a booster dose of the vaccine, if exposed to a known patient who is Hepatitis B surface antigen positive. However, in exposure to a patient with an unknown hepatitis B status, no further action is required in individuals who have completed the vaccination

schedule⁴.

2. *Varicella zoster immunoglobulin (VZVIG)*: should be administered within 10 days following exposure although the greatest protection is seen when given within 96 hours of exposure. It is recommended that VZIG should be given to the following groups of individuals⁵.

- Immunocompromised individuals
- Newborn infant whose mother developed chickenpox within 5 days before delivery or within 48 hours after delivery
- Hospitalized preterm infant whose mother lacks a reliable history of chickenpox or serologic evidence of protection against varicella
- Pregnant women without evidence of immunity
- Premature infants if exposed during the total duration of time spent in hospital

It should be given intramuscularly. Please refer manufacturer's instructions for dosing. As administration of VZV-immunoglobulin may result in asymptomatic infection, testing for VZV-specific antibodies 2 months after administration is recommended for subsequent management of the patient (e.g. in immunocompromised patients). Incubation period of varicella can be prolonged following administration of immunoglobulins. The varicella vaccine should be given to all eligible individuals 3 months after administration of VZV-IG.

The varicella live attenuated vaccine is recommended in post exposure prophylaxis in immunocompetant individuals and in those who have no contraindications to the vaccine⁵. Please see chapter on the varicella vaccine for details on post exposure prophylaxis in immunocompetant individuals.

3. Rabies immunoglobulin: see Chapter 16 Rabies

4. Tetanus immunoglobulin: Human tetanus immunoglobulin should be given as a single dose intramuscularly with part of the dose infiltrated around the wound as soon as possible, in the treatment

of tetanus. If tetanus immunoglobulin is not available intravenous immunoglobulin (IVIG) should be used, as it contains antibodies to the tetanus toxoid. It is also recommended that a vaccine containing the tetanus toxoid should be given at the same time (but to a different site) when administering the tetanus immunoglobulin. Please refer manufacturers' instructions for dosing.

5. Botulism immunoglobulin: The antitoxin only neutralises toxin that is still unbound to nerve endings and therefore, it most effective when given early. Antitoxin does not reverse paralysis but can arrest the progression and decrease the duration and dependence on mechanical ventilation. Antitoxin should be given early in the course of illness, ideally within 24 hours of illness. There is no data available regarding the efficacy when given later. Skin testing should ideally be done before administration. Re-administration of the anti-toxin is not recommended as it has a half-life of 5-8 days⁶.

Subsequent administration of other vaccines

Immunoglobulins and blood products can interfere or inhibit the immune response to live vaccines. Therefore, live vaccine should not be given for at least 3 months after administration of immunoglobulins or blood products. In some instances, especially following administration of IVIG as an antibody replacement therapy or for autoimmune conditions, it is recommended to delay administration of live vaccines for at least 8 months. Immunoglobulins and blood products do not generally inhibit immune responses to inactivated vaccines.

Adverse effects

- Many experience pain and discomfort at the site of administration, Flushing, headache, nausea and vomiting may occur less frequently
- Serious reactions: these are uncommon but chest pain, constriction, dyspnoea and anaphylaxis may occur

Precautions

- Caution should be used when administering immunoglobulins to individuals with a past history of adverse reactions
- The intramuscular route should not be used in individuals with thrombocytopenia and coagulation disorders

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CHAPTER 26

ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI)

The goal of immunization is to protect the individual and the public from vaccine preventable diseases. Although modern vaccines are safe, no vaccine is entirely without risk. Some persons experience adverse events following immunization (AEFI) ranging from non serious mild adverse reactions to life-threatening but rare serious adverse reactions. Most non-serious minor adverse reactions caused by vaccines are self limited. In the majority of serious cases, these events are merely coincidences and there is no causal relationship.

Surveillance of AEFIs is an effective means of monitoring immunization safety. It allows for proper management of AEFIs and avoids inappropriate responses to reports of AEFIs. To increase acceptance of immunization and improve quality of services, surveillance of AEFIs must become an integral part of both public and private sector immunization services in the country.

What is an adverse event following immunization (AEFI)?

AEFI is *any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine*. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease. Reported adverse events can either be true adverse events, i.e. a result of the vaccine or immunization process, or coincidental events that are not due to the vaccine or immunization process but are temporally associated with immunization¹.

Cause-specific categorization of adverse events following immunization (CIOMS/WHO, 2012)

Cause-specific Type of AEFI	Definition
Vaccine product-related reaction	An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product.
Vaccine quality defect-related reaction	An AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product including its administration device as provided by the manufacturer.
Immunization error-related reaction	An AEFI that is caused by inappropriate vaccine handling, prescribing or administration and thus by its nature is preventable.
Immunization anxiety-related reaction	An AEFI arising from anxiety about the immunization.
Coincidental event	An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety

Vaccine Reactions

Vaccine reactions may be classified into common, minor reactions and rare, more serious reactions². Most vaccine reactions are minor and settle on their own. More serious reactions are very rare and in general do not result in long term problems.

Common, minor vaccine reactions: The purpose of a vaccine is to induce immunity by causing the recipient's immune system to react to the vaccine. A safe and good quality vaccine reduces these reactions to a minimum while producing the best possible immunity. The occurrence of minor vaccine reactions is expected and observed with all vaccines. The expected rates of vaccine reactions are available in medical literature³. In addition, some of the vaccine components, excipients (e.g. aluminium adjuvant, stabilizers or preservatives) can also lead to vaccine reactions².

Rare serious vaccine reactions: A serious adverse event or reaction is any untoward medical occurrence following any dose of vaccine that

- results in death
- requires hospitalization or prolongation of hospital stay
- results in persistent or significant disability/incapacity
- is life-threatening

Most of the rare and more serious vaccine reactions [e.g seizures, thrombocytopenia, hypotonic hyporesponsive episodes (HHE), persistent inconsolable screaming] do not lead to long term problems. Anaphylaxis, while potentially fatal, is treatable without having any long term effects. Vaccine adverse reactions previously unknown or partially known are called ‘signals’. All signals need a comprehensive scientific evaluation to establish the causality.

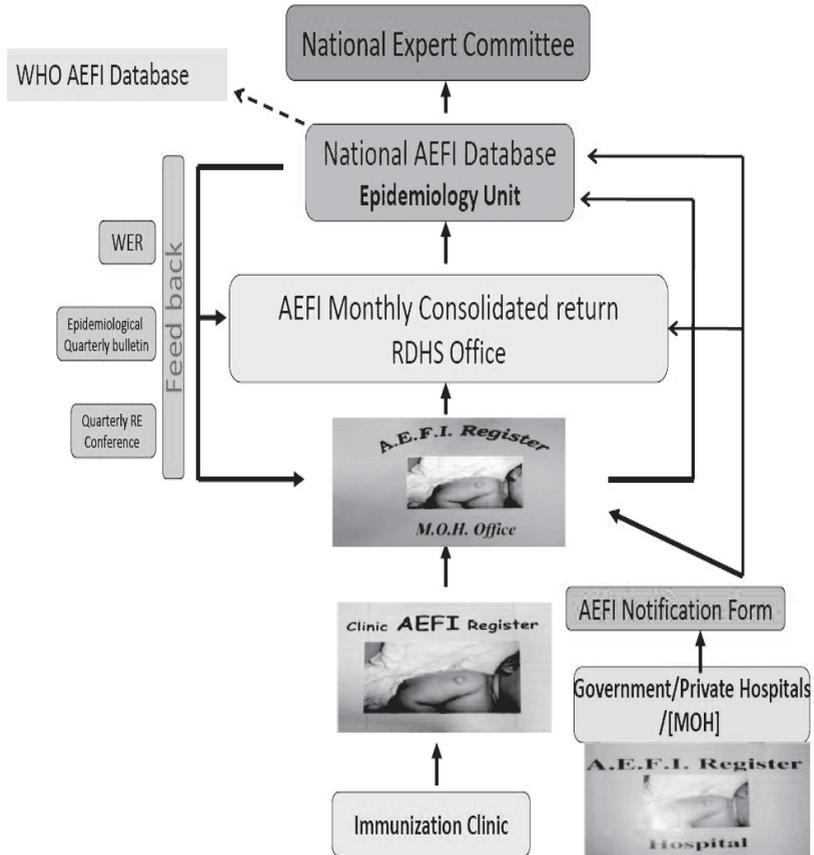
Surveillance of AEFI

All serious and non-serious AEFI should be reported to the Epidemiology Unit, irrespective of its been detected by the public or private sector services⁴. AEFI may be detected in medical institutions at the OPD, and in the wards. Therefore it is important that relevant health workers in hospitals are made aware of AEFI and AEFI surveillance. For the reporting of AEFI, the Epidemiology Unit has developed a Notification Form (Annex IV available at www.epid.gov.lk). The area MOH will investigate all reported serious cases of AEFI, whereas the Epidemiology Unit will investigate all deaths linked to immunization. All deaths suspected to be linked with immunization require a postmortem investigation⁵. Anaphylactic reactions following immunization need to be reported by a separate reporting form (Annex V).

For vaccines used only in the private sector: All AEFIs following administration of these vaccines should be reported to the National Medicinal Drugs Regulatory Authority (NMRA) with a copy to Epidemiology Unit by the healthcare provider and local agent of the relevant vaccine. Any death following administration of any vaccine should be reported to both NMRA and the Epidemiology Unit, within 24 hours.

It is important that all AEFI be recorded in Child Health Development Record (CHRD) by the treating medical officer/medical specialist

Figure: AEFI surveillance system in Sri Lanka



Responsibilities of Medical Officers in AEFI Surveillance:

- Should take a comprehensive immunization history of the child
- Reporting should be done immediately to MOH of the patient’s residential area on suspicion of AEFI using the Notification form for AEFI. Deaths should be notified directly to the Epidemiology Unit.(Telephone 011 269 5112)

- Communication with parents, other members of the community and health staff need to be carried out under all circumstances. They should be kept informed about the investigation, and action being taken or to be taken regarding the AEFI. It is crucial to highlight the benefits of immunization while communicating with the medical staff, public and stakeholders.

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CHAPTER 27

MANAGEMENT OF ANAPHYLAXIS

Introduction

Anaphylaxis following routine vaccination is rare, but can be fatal¹. Hence immunization service providers must be able to recognize the symptoms and signs of anaphylaxis. A fainting attack (vasovagal episode) maybe mistakenly diagnosed as anaphylaxis. The features useful in differentiating a fainting attack from anaphylaxis are given in Table 1².

Table 1. Differences between a fainting attack and anaphylaxis.

Clinical features	Fainting attack	Anaphylaxis
Timing	Immediate, usually within minutes or during vaccine administration	Usually within 15 minutes , but can occur within hours of vaccine administration
Skin and mucous membranes	Generalized pallor, cold clammy skin	Itching (in children especially forehead, hands and ears), tingling around lips, generalised erythema, urticaria, swelling of lips and face
Respiratory system	Normal respiration; may be shallow, but not laboured	Cough, wheeze, hoarseness, stridor or signs of respiratory distress (e.g. tachypnoea, cyanosis, rib recession) upper airway swelling (lip, tongue, throat, uvula or larynx)

Cardiovascular	Bradycardia, weak/absent peripheral pulse, strong carotid pulse Hypotension - usually transient and corrects in supine position Loss of consciousness – improves once supine or in head-down position	Tachycardia, weak/absent carotid pulse. Hypotension – sustained and no improvement without specific treatment (Note: in infants and young children, limpness and pallor are signs of hypotension). Loss of consciousness – no improvement once supine or in head-down position
Gastrointestinal	Nausea, vomiting	Abdominal cramps, diarrhoea, nausea and/or vomiting
Central nervous system	Faintness, light headedness relieved by supine posture	Anxiety and distress, loss of consciousness not relieved by supine posture
<p>In adults and older children, the most common immediate adverse event is a vasovagal episode (fainting), either immediately or soon after vaccination. As a precaution, anyone who complains of giddiness or light-headedness before or after vaccination should be advised to lie down until free of symptoms. Sudden loss of consciousness in young children should be presumed to be anaphylaxis, particularly if a strong central pulse is absent. A strong central pulse (e.g. carotid) persists during a faint or convulsion.</p>		

Diagnosis

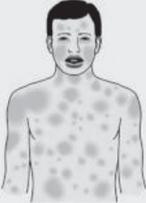
The key to diagnosis involves pattern recognition: *Sudden onset of characteristic symptoms and signs within minutes to hours after exposure to a vaccine.* Clinical criteria for the diagnosis of anaphylaxis are detailed in Figure 1³. In infants, anaphylaxis can be difficult to recognise as they cannot describe their symptoms. Some of the signs of anaphylaxis are normal occurrences in babies; for example, flushing and dysphonia after crying, spitting out after feeding and incontinence. Healthy infants have a lower blood pressure and a higher resting heart rate than older children and adults. Therefore, age-appropriate criteria should be used for documenting hypotension and tachycardia³.

Figure1³: Key criteria to diagnose anaphylaxis

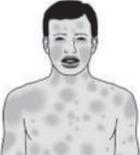
Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

1 Sudden onset of an illness (minutes to several hours), with involvement of the skin, mucosal tissue, or both (e.g. generalized hives, itching or flushing, swollen lips-tongue-uvula)

AND AT LEAST ONE OF THE FOLLOWING:

		
	Sudden respiratory symptoms and signs (e.g. shortness of breath, wheeze, cough, stridor, hypoxemia)	Sudden reduced BP or symptoms of end-organ dysfunction (e.g. hypotonia [collapse], incontinence)

OR 2 Two or more of the following that occur suddenly after exposure to a *likely allergen or other trigger** for that patient (minutes to several hours):

			
Sudden skin or mucosal symptoms and signs (e.g. generalized hives, itch-flush, swollen lips-tongue-uvula)	Sudden respiratory symptoms and signs (e.g. shortness of breath, wheeze, cough, stridor, hypoxemia)	Sudden reduced BP or symptoms of end-organ dysfunction (e.g. hypotonia [collapse], incontinence)	Sudden gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting)

OR 3 Reduced blood pressure (BP) after exposure to a *known allergen*** for that patient (minutes to several hours):

	
Infants and children: low systolic BP (age-specific) or greater than 30% decrease in systolic BP***	Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

* For example, immunologic but IgE-independent, or non-immunologic (direct mast cell activation)

** For example, after an insect sting, reduced blood pressure might be the only manifestation of anaphylaxis; or, after allergen immunotherapy, generalized hives might be the only initial manifestation of anaphylaxis.

*** Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 x age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years. Normal heart rate ranges from 80-140 beats/minute at age 1-2 years; from 80-120 beats/minute at age 3 years; and from 70-115 beats/minute after age 3 years. In infants and children, respiratory compromise is more likely than hypotension or shock, and shock is more likely to be manifest initially by tachycardia than by hypotension.

Systematic approach to treatment of anaphylaxis

If precious minutes are lost early in the treatment of an acute anaphylactic episode subsequent management becomes difficult. The basic initial protocol in any given setting is outlined as steps in Figure 2³. After rapid assessment of the patient's circulation, airway, and breathing, treatment should commence promptly and simultaneously.

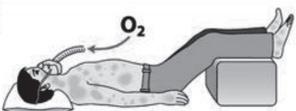
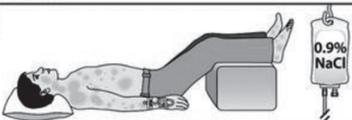
Positioning the Patient

Patients with anaphylaxis should not suddenly sit, stand, walk or be placed in the upright position. Instead, they should be placed on the back with their feet elevated⁴ or, if they are experiencing respiratory distress or vomiting, semi-reclining in a position of comfort with their feet elevated³. This accomplishes 2 therapeutic goals:

- 1) Preservation of fluid in the circulation (the central vascular compartment), an important step in managing distributive shock; and
- 2) Prevention of the empty vena cava/empty ventricle syndrome, which can occur within seconds when patients with anaphylaxis suddenly assume or are placed in an upright position. Patients with this syndrome are at high risk for sudden death and are unlikely to respond to adrenaline regardless of route of administration, because it does not reach the heart and therefore cannot be circulated throughout the body³.

Patients who are breathing and unconscious should be placed on their side (recovery position). Pregnant patients should lie on their left side to prevent caval compression⁵.

Figure 2³: Immediate steps in managing anaphylaxis

1		Have a written emergency protocol for recognition and treatment of anaphylaxis and rehearse it regularly.
2		Remove exposure to the trigger if possible, eg. discontinue an intravenous diagnostic or therapeutic agent that seems to be triggering symptoms.
3		Assess the patient's circulation, airway, breathing, mental status, skin, and body weight (mass).
4		Promptly and simultaneously, perform steps 4, 5 and 6. Call for help: resuscitation team (hospital) or emergency medical services (community) if available.
5		Inject epinephrine (adrenaline) intramuscularly in the mid-antrolateral aspect of the thigh, 0.01 mg/kg of a 1:1,000 (1 mg/mL) solution, maximum of 0.5 mg (adult) or 0.3 mg (child); record the time of the dose and repeat it in 5-15 minutes, if needed. Most patients respond to 1 or 2 doses.
6		Place patient on the back or in a position of comfort if there is respiratory distress and/or vomiting; elevate the lower extremities; fatality can occur within seconds if patient stands or sits suddenly.
7		When indicated, give high-flow supplemental oxygen (6-8 L/minute), by face mask or oropharyngeal airway.
8		Establish intravenous access using needles or catheters with wide-bore cannulae (14 - 16 gauge). When indicated, give 1-2 litres of 0.9% (isotonic) saline rapidly (e.g. 5-10 mL/kg in the first 5-10 minutes to an adult; 10 mL/kg to a child).
9		When indicated at any time, perform cardiopulmonary resuscitation with continuous chest compressions.
10		In addition, At frequent, regular intervals, monitor patient's blood pressure, cardiac rate and function, respiratory status, and oxygenation (monitor continuously, if possible).

Note; Cardiopulmonary resuscitation is initiated with continuous chest compressions only (hands-only) before giving rescue breaths. In adults, chest compression should be performed at a rate of 100-120/minute and at a depth of 5-6 cm. In children, the rate should be at least 100 compressions/minute at a depth of 5 cm (4cm in infants).

Adrenaline (epinephrine)

ADRENALINE, INTRAMUSCULAR is the most important life-saving therapeutic agent in the treatment of anaphylaxis and is the route of choice for most healthcare providers. As initial treatment adrenaline should not be given via the intravenous (IV) route because of the risk of potentially lethal arrhythmias. In Sri Lanka, adrenaline is mostly under-used or has been inappropriately administered as bolus doses via the intravenous route which contributed to pulmonary oedema and death.

Table 2. provides details of adrenaline IM dosing according to age and weight 3-8. There is large inter-individual variability in the response to adrenaline. In clinical practice, it is important to monitor the response and to titrate the dose according to effect. Repeat adrenaline at 5 minute intervals as needed (i.e. if breathing becomes more laboured or level of consciousness decreases). In a field setting to a maximum of three doses. Alternate right and left thigh or arm sites for repeat doses of epinephrine (to maximize absorption of epinephrine). DO NOT inject epinephrine directly into an IM immunization site as it dilates blood vessels and speeds absorption of the vaccine (i.e. the offending allergen)⁹

Many healthcare providers will have given IV adrenaline as part of resuscitating a patient in cardiac arrest. This alone is insufficient experience to use IV adrenaline for the treatment of an anaphylactic reaction. In patients with a spontaneous circulation, intravenous adrenaline can cause life-threatening hypertension, tachycardia, arrhythmias, and myocardial ischaemia⁵.

If not responding adequately, call for help or transport to the nearest hospital to receive expert help, as patients who require repeated IM doses of adrenaline may benefit from an intravenous adrenaline infusion.

The section on IV adrenaline only applies to those experienced in the use and titration of vasopressors in their normal clinical practice (e.g., anaesthetists, emergency physicians, intensive care doctors).

Patients who are given IV adrenaline must be monitored - continuous ECG and pulse oximetry and frequent non-invasive blood pressure measurements as a minimum.

Table 2³⁻⁸: ADRENALINE in the INITIAL management of acute anaphylaxis

Site, and route of administration	Frequency of administration	Dose (ADULT)	Dose (CHILD)
<p>Adrenaline (epinephrine) 1:1000, IM to the midpoint of the anterolateral aspect of the middle third of the thigh immediately</p> <p>Use a 25 mm needle and inject at 90o angle to skin. The skin should be stretched and not bunched (very small infants use a 16 mm needle, very obese adults use 38 mm needle.</p>	<p>Repeat every 5–15 min as needed until there is resolution of the anaphylaxis or appearance of signs of hyperadrenalism</p> <p>Note: Persisting or worsening cough associated with pink frothy sputum (sign of pulmonary oedema) is an important sign of hyperadrenalism</p>	<p>0.3-0.5 mL 0.3 – 0.5 mg (300 - 500 mcg)</p> <p>- 0.3 mL (0.3 mg) for small adults (30 - 50 kg) - 0.5 mL (0.5 mg) if weight >50 kg</p> <p>Maximum 0.5 mg (0.5mL) / dose</p>	<p>0.01 mL/kg 0.01 mg/kg (up to maximum of 0.3 mg (0.3mL) / dose</p> <p>According to age</p> <ul style="list-style-type: none"> • < 1 yr - 0.05 mg • 1– 3 yrs (10-15 kg) – 0.10 - 0.15 mg • 3- 5 yrs (15-20 kg) – 0.15 - 0.20 mg • 5 - 7 yrs (20-25 kg) - 0.20 - 0.25 mg • 7 – 12 yrs (25-30kg) - 0.25 - 0.30 mg
<p>Repeat adrenaline at 5 minute intervals as needed (i.e. if breathing becomes more laboured or level of consciousness decreases). In a field setting to a maximum of three doses. Alternate right and left thigh or arm sites for repeat doses of epinephrine (to maximize absorption of epinephrine). If the offending allergen is a vaccine; DO NOT inject epinephrine directly into an IM immunization site as it dilates blood vessels and speeds absorption of the vaccine⁹.</p>			

The section below on IV adrenaline only applies to those experienced in the use and titration of vasopressors in their normal clinical practice (e.g., anaesthetists, emergency physicians, intensive care doctors). **IV adrenaline by bolus should be used only if cardiac arrest has occurred and not for any other reason.**

FOR SPECIALIST USE ONLY

Table 3³⁻⁸: Intravenous infusion of adrenaline for life-threatening anaphylaxis-induced hypotension who have failed to respond to several IM doses of adrenaline and intravenous volume replacement

For specialist use only	Ensure patient is monitored
Adrenaline IV (1:10,000 contains 100micrograms /ml). <i>Never give the undiluted 1:1000 adrenaline concentration IV.</i>	
<p>With an infusion pump: Mix 1mL of 1:1000 adrenaline in 1000mL of 0.9% saline (1mcg/mL) Start infusion at 0.5 to 1ml /kg/minute (approximately 30 to 100mL/hour in adults) then titrate according to reaction severity</p> <ul style="list-style-type: none"> • Moderate severity Adrenaline 1mg in 100mL sodium chloride 0.9% at 0.5mL/kg/hour (0.08micrograms /kg/minute) • Severe (hypotensive or hypoxic): Adrenaline 1mg in 100mL sodium chloride 0.9% at 1mL/kg/hour (0.17micrograms /kg/minute) <p>Children Since, children with life- threatening anaphylaxis usually have bronchospastic reactions, absorption of adrenaline from intramuscular site is very good and it is difficult to assess blood pressure in small children, it is probably safer to avoid IV adrenaline in small children unless the child is treated in an emergency critical care area under specialist supervision.</p>	
<p>If you do not have an infusion pump, use a standard giving set Adrenaline: 1: 1,000, 1mg in 100 mL sodium chloride 0.9% IV, at approximately 100mL/hour which is ~1 drop per 2 seconds for an adult for most standard drip sets. Titrate rate up and down according to response and side effects</p> <ul style="list-style-type: none"> • Titrate up or down according to response, aiming for lowest effective infusion rate. • Wait for 5 to 10 minutes after a change in the infusion rate to assess the response • Reduce the rate immediately if signs of adrenaline toxicity (tachycardia, tremor and pallor in association with a normal or raised blood pressure) develop. Persisting or worsening cough associated with pulmonary oedema is an important sign of adrenaline overdose and toxicity. • As the reaction resolves, an infusion that was previously therapeutic can quickly start to have toxic effects. Therefore when features of anaphylaxis improve, begin reducing the infusion, aiming for around half the starting rate if possible. • One hour after the resolution of all symptoms and signs, wean the infusion over another 30 minutes and stop. 	

Table 4³: Potential side effects and toxic effects of adrenaline

After the usual recommended therapeutic dose and route for anaphylaxis:

Side effects: Pallor, tremor, anxiety, palpitations, dizziness, headache; these symptoms indicate that a pharmacologic dose has been injected

With adrenaline in the following scenarios.

1. Overly rapid intravenous infusion,
2. Repeated intravenous bolus doses
3. Dosing error (commonest error is using 1:1000 strength meant for IM injection for IV administration)

Toxic effects: Pulmonary oedema, ventricular arrhythmias, hypertension,

Prolonged use can result in severe metabolic acidosis (because of elevated blood concentrations of lactic acid), renal necrosis and tachyphylaxis.

Acute coronary syndromes called “Kounis syndrome” (angina, myocardial infarction, arrhythmias) can also occur in untreated anaphylaxis in patients with known coronary artery disease, in those in whom subclinical coronary artery disease is unmasked, and even in patients (including children) without coronary artery disease in whom the symptoms are due to transient vasospasm

Note: Reasons for apparent lack of response to adrenaline:

Error in diagnosis, patient suddenly stands or sits (or is placed in the upright position) after adrenaline injection; rapid progression of anaphylaxis; patient taking a beta-adrenergic blocker, ACE inhibitor or other medication that interferes with adrenaline effect; adrenaline injected too late; dose too low on mg/kg basis; adrenaline is past expiry date; not enough injection force used; route or injection site not optimal.

Store adrenaline at less than 25 °C and protect from light.

Oxygen (give as soon as possible)

Initially, give the highest concentration of oxygen possible using a mask with an oxygen reservoir. Ensure high flow oxygen (usually

greater than 10 L /min) to prevent collapse of the reservoir during inspiration. If the patient's trachea is intubated, ventilate the lungs with high concentration oxygen using a self-inflating bag. Continuous monitoring of oxygenation by pulse oximetry is desirable.

Supplemental oxygen should be administered by face mask or by oropharyngeal airway at a flow rate of 6–8 L/min to (1) all patients with respiratory distress, (2) those receiving repeated doses of adrenaline or (3) presence of concomitant asthma, other chronic respiratory disease, or cardiovascular disease

Fluids (give as soon as possible)

During anaphylaxis, large volumes of fluids leave the patient's circulation and enter the interstitial tissue; therefore, rapid intravenous infusion of 0.9% isotonic saline (normal saline) should be commenced as soon as the need for it is recognized. Give 1 - 2 litres of 0.9% saline rapidly; 5 - 10mL /kg in the first 5 - 10 minutes to an adult, or 10mL/kg to a child. The rate of administration should be titrated according to the blood pressure, cardiac rate and function and urine output. All patients receiving such treatment should be monitored for volume overload.

Antihistamines

Antihistamines are no longer considered drugs of choice in the initial treatment of anaphylaxis, because they do not relieve life threatening respiratory symptoms or shock. Concerns are about:

- Slow onset of action relative to adrenaline
- Potential harmful effects on the central nervous system such as somnolence and impairment of cognitive function mainly with first generation H1-antihistamines and
- Lack of supporting evidence from randomized controlled trials³⁻⁸

- Although the evidence to support their use is weak, there are pharmacologically logical reasons for them. Antihistamines (H₁-antihistamine) may help counter histamine-mediated vasodilation and bronchoconstriction and have the virtue of safety. It should be used only after patient is stabilised with adrenaline and fluids. H₂-antihistamines are recommended in only a few anaphylaxis guidelines⁴ as the evidence from randomized placebo-controlled trials is not strong. H₂-antihistamine, administered concurrently with an H₁-antihistamine, may potentially contribute to decrease in flushing, headache, and other symptoms, See Table 5 for dosing schedule

Note:

- Sedating antihistamines IV or oral are best avoided as side effects (drowsiness or lethargy) may mimic some signs of anaphylaxis.
- Injectable promethazine should not be used in anaphylaxis as it can worsen hypotension and cause tissue necrosis⁸

Corticosteroids

Benefit of corticosteroids in anaphylaxis is unproven^{3,8}, and there is no evidence that it will reduce duration of reaction and prevent relapse. They may be helpful for asthmatics and could be used as adjuncts⁸. The onset of action takes several hours. It should not be used instead of adrenaline³⁻⁸. It is given only after patient's condition is stabilized with adrenaline and fluids. For dosing schedule see Table 5.

Beta-2 adrenergic agonists

Selective beta-2 adrenergic agonists such as salbutamol or terbutaline are sometimes given in anaphylaxis as additional treatment for wheezing, coughing, and shortness of breath not relieved by epinephrine. But never substitute these medications for adrenaline because they have minimal alpha-1 adrenergic agonist vasoconstrictor effects and do not prevent or relieve laryngeal oedema and upper airway obstruction, hypotension, or shock.

Table 5: Pharmacologic treatment once patient's condition is stabilized with adrenaline and fluids⁵⁻⁸

<i>Drug and route of administration</i>	<i>route and frequency of administration</i>	<i>Dose (adult)</i>	<i>Dose (child)</i>
Cetirizine PO	Single daily dose	10mg	<ul style="list-style-type: none"> • 6 m - 2yrs: 2.5 mg • 2-5 yrs: 2.5-5 mg • >5 yrs: 5-10 mg
Chlorphenamine	IV infusion	10mg	<ul style="list-style-type: none"> • <6m: 250 µg/Kg • >6m to 6 yrs: 2.5 mg • 6-12yrs: 5 mg
Hydrocortisone	Administer IM or IV slowly Repeat every 6 hours as needed	Above >12 years: 200 mg Follow up with prednisolone 50 mg orally daily for 4 days	2 mg/kg every 6 hours <ul style="list-style-type: none"> • <6 m: 25 mg • 6 m- 6 yrs: 50 mg • 6 – 12 yrs: 100 mg Follow up with prednisolone 1 mg/kg up to a maximum of 50 mg orally daily for 4 days
Methyl prednisolone	IV Every 6 h as required	50-100 mg	1 mg/kg IV (maximum 50 mg)
Ranitidine	IV or oral Every 8 h	50mg	1 mg/kg (maximum 50 mg)
Salbutamol via nebulizer or metered dose inhaler (MDI) (for respiratory symptoms)	Every 20 min or continuous	5 mg by nebuliser, driven by oxygen at least 8 L/minute), or continuous actuations of MDI 8 - 12 puffs of 100 mcg of salbutamol	5–10 puffs using MDI or 2.5–5 mg by nebulization
Adrenaline (1:1000) (for upper respiratory tract symptoms such as stridor)	Every 20 minutes to 1 hour Nebulization	Up to 5 mL (5mg)	Upto 5mL (5mg)

Observation and discharge from hospital

Patients who have had a suspected anaphylactic reaction (i.e. an airway, breathing or circulation (ABC) problem) should be treated and then observed for at least 6-8 hours in a hospital with facilities for treating life-threatening ABC problems. They should be reviewed by a consultant and a decision made about the need for further treatment or a longer period of observation. Patients with a good response to initial treatment should be kept under observation for up to 24 hours if they have

- severe reactions with slow onset
- a history of severe asthma or a severe asthmatic component in the current episode
- there is a possibility of continuing absorption of allergen such as vaccines
- a previous history of biphasic reactions
- the anaphylactic episode in the evening or at night
- difficulty in accessing emergency care in case of deterioration

Serum tryptase

The specific test to help confirm a diagnosis of an anaphylactic reaction is measurement of mast cell tryptase. Tryptase is the major protein component of mast cell secretory granules. In anaphylaxis, mast cell degranulation leads to markedly increased blood tryptase concentrations. Tryptase levels are useful in the follow-up of suspected anaphylactic reactions. Tryptase concentrations in the blood may not increase significantly until 30 minutes or more after the onset of symptoms, and peak 1-2 hours after onset. The half-life of tryptase is short (approximately 2 hours), and concentrations may be back to normal within 6-8 hours, so timing of any blood samples is very important. Blood samples for measurement of tryptase levels should be collected and sent to the Medical Research Institute, (MRI).

Sample timing

The time of onset of the anaphylactic reaction is the time when symptoms were first noticed. It is important that this time is accurately recorded.

- Minimum: one sample at 1-2 hours after the start of symptoms.
- Ideally: Two timed samples:
 - 1) First sample at 30 minutes to 3 hours (up to 6 hours acceptable) after the start of symptoms
 - 2) Second sample preferably at 24 hours or in convalescence (for example in a follow up allergy clinic). This provides baseline tryptase levels - some individuals have an elevated baseline level

Serial samples have better specificity and sensitivity than a single measurement in the confirmation of anaphylaxis.

Sample requirements

- *Use a serum or clotted blood sample*
- *Record the timing of each sample accurately on the sample bottle and request form. State on the request form the time of onset of the reaction (symptoms). Record on the sample bottle the number of minutes or hours after the onset of symptoms the sample was taken*
- *As little as 0.5 mL of sample can be enough (children), but 5 mL (adults) is better*
- *Optimally, store the serum from centrifuged samples frozen (-20°C) in the local laboratory, before dispatch to a reference laboratory*
- *Tryptase is very stable. 50% of tryptase is still detectable after 4 days at room temperature so even samples stored at room temperature over a weekend can give useful, though sub-optimal, information*

Notification

It is mandatory that all vaccine associated anaphylaxis be reported to the Epidemiological Unit in the format given as an annex in this book.

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CHAPTER 28

IMMUNIZATION FOR INTERNATIONAL TRAVEL

Introduction

In considering immunization for travellers following information is important.

- Current information on vaccine-preventable diseases at travel
- Activities planned during travel and at travel destination
- Traveller's previous immunization history
- Traveller's general health such as age, allergies, medication, pregnancy and chronic disease conditions
- Time available before departure

Immunization for travellers fall into 3 categories

1. Routine immunization
2. Required immunizations which are required to enter host countries
3. Recommended immunizations

1 Routine immunization - should be up-to-date regardless of travel

2 Required immunizations

Most vaccines take time to become effective and ideally should be given 4 – 6 weeks before travel.

a) Yellow fever vaccine

For persons travelling to endemic countries

Yellow fever vaccination is required for people travelling to endemic countries as per International Health Regulations¹. Currently the

endemicity to yellow fever is confined to certain countries in sub-Saharan Africa, tropical South America and Brazil, more recently. Due to the risk of post vaccination encephalitis, infants less than 9 months should be vaccinated only if the risk of contracting yellow fever is high. Vaccinating people with diseases of the thymus should be avoided as there is a higher risk of adverse reactions. Alternate means of prevention should be recommended to these travellers.

For persons arriving from an endemic country

The International Health Regulations allow countries to require proof of vaccination, International Certificate of Vaccination and Prophylaxis (ICVP), on entry for travellers arriving from endemic countries. Travellers arriving without a completed ICVP may be quarantined or refused entry.

Duration of protection after vaccination

WHO has concluded that a single dose confers adequate life long immunity². However, immunosuppressed groups (chemotherapy, transplant recipients) may need a booster dose to ensure protection.

Certification of vaccination

For purposes of international travel, yellow fever vaccine produced by different manufacturers worldwide, must be approved by WHO and administered at an approved yellow fever vaccination centre. The only authorised place in Sri Lanka for administration of this vaccine is the office of the Assistant Port Health Officer, which is housed in the premises of the Medical Research Institute, Colombo 8. Vaccinees should receive a completed ICVP, signed and validated with the official stamp. This certificate is valid life from 10 days after vaccination.

Contraindications to vaccination

Yellow fever vaccine is contraindicated for immunocompromised group² (e.g. AIDS/ primary immunodeficiencies for those who are on immunosuppressive and immunomodulatory therapies).

If a physician concludes that a particular vaccination should not be administered for medical reasons, the traveller should be given a signed and dated statement of the reasons on the physician's letterhead. Under these conditions, the traveller should obtain specific advice from the embassy or consulate of the country or countries the person plans to visit.

In addition to vaccination all travellers should take adequate measures against exposure to mosquito bites.

(Refer Chapter 21)

b) Meningococcal vaccine

Vaccination against meningococcal disease is required by the government of Saudi Arabia for travellers performing Hajj or arriving for employment. The vaccine should be administered at least 10 days before arrival in Saudi Arabia. It is effective for 3 years.

Children over the age of 2 years and adults should be immunized with the quadrivalent vaccine (serogroups A,C, Y and W135).

Children between 3 months and 2 years of age should receive two doses of the serogroup A conjugate vaccine with a 3-month interval between the two doses. This vaccine is not available in Sri Lanka.

Meningococcal vaccine is also recommended for students who travel to countries that are endemic for meningococcal disease if they plan to live in dormitories or residence halls.

(Refer Chapter 13)

c) Poliomyelitis vaccine

Documented evidence of polio vaccination is not routinely required for travellers under International Health Regulations but may be temporarily recommended in accordance with WHO recommendations in response to new evidence of the spread of wild poliovirus. Some polio-free countries may also require travellers from polio-endemic

countries to be immunized against polio in order to obtain an entry visa, e.g. Saudi Arabia (proof of oral poliovirus vaccination is required 6 weeks before application for an entry visa for visitors arriving from countries reporting poliomyelitis cases).

Travellers to polio-infected areas who have not received any polio vaccine previously should complete a primary schedule of polio vaccination and a single booster dose of OPV or IPV should be given to those who have previously completed the primary course³. An up-to-date list of polio-affected countries is available from the World Health Organization Global Polio Eradication Initiative website (www.polioeradication.org).

(Refer Chapter 15)

(c) Recommended immunizations

These vaccines are administered to protect travellers from illnesses present in other parts of the world and to prevent the importation of infectious diseases across international borders. The vaccinations depend on the travel destination, age, health status, and previous immunization. Most immunization for travel fall into the recommended category.

Varicella vaccine

Varicella infections in adults may result in severe disease with complications. Travellers who are likely to bring them into close contact with children in schools and day care centres, healthcare settings and refugee camps should be immunized before travel if no history of varicella is available. Protection occurs 14 days after the first dose. It is not recommended for pregnant women and immunocompromised persons.

(Refer Chapter 20)

Hepatitis B vaccine

Hepatitis B is endemic in some countries in South America, Africa, Asia and the South Pacific. Immunization is recommended for people who will experience close contact with residents in countries visited. The accelerated schedule of 0, 1, 2 months and a booster at 12 months or 0, 7, 21 days and a booster at 12 months is recommended for travellers. Additionally, hepatitis B vaccination is recommended for persons who travel to endemic countries for medical care as there is a relatively higher risk of acquiring the disease (eg India).

(Refer Chapter 8)

Pneumococcal vaccine

Recommended for adults more than 65 years old and adults with chronic cardio-pulmonary conditions and those with chronic disease. Protection occurs 14 days after vaccination.

(Refer Chapter 14)

Hepatitis A vaccine⁴

All susceptible persons travelling to or working in countries that have high or intermediate hepatitis A endemicity should be vaccinated and age appropriate doses should be administered. The first dose of hepatitis A vaccine should be administered as soon as travel is considered and a second dose should be administered after 6-12 months for long term protection.

One dose of single-antigen hepatitis A vaccine administered at any time before departure can provide adequate protection for most healthy persons. Older adults, immunocompromised persons, and persons with chronic liver disease or other chronic medical conditions planning to depart in <2 weeks should receive the initial dose of vaccine and HNIG (0.02 mL/kg) at the same time at separate anatomical sites.

Travellers aged <12 months or allergic to a vaccine component should receive a single dose of HNIG (0.02 mL/kg), which provides effective protection for up to 3 months.

(Refer Chapter 7)

Typhoid vaccine

Immunity is obtained 2-3 weeks after parenteral (Vi capsular polysaccharide) vaccination. The typhoid vaccines currently available do not offer protection against *Salmonella*. Paratyphi infections

(Refer Chapter 19)

Rabies vaccine

Recommended for travellers to rabies endemic areas. Three doses at 0,7 and 21/28 days are recommended for pre-exposure vaccination. A booster should be given after one year.

If all three doses are not completed, the traveller will not be considered previously vaccinated and will require full post exposure prophylaxis, if an exposure occurs.

Rabies immune globulin (RIG) is not recommended following a rabies exposure in persons who are currently protected by pre-exposure vaccination. When exposed to rabies they only require two boosters of a WHO recommended cell culture rabies vaccine on days 0 and 3.

(Refer Chapter 16)

Japanese encephalitis vaccine

The risk of Japanese encephalitis is highest in pig farming areas of China, Korea and South East Asia. Immunization should be completed 10 days before travel.

(Refer Chapter 11)

Influenza vaccine

The risk for exposure to influenza during international travel depends on the time of year and destination. In the tropics, influenza can occur throughout the year, while in the temperate regions, disease activity occurs during the winter. The vaccine that the traveller receives should be active against the strains of influenza virus prevalent in the country the person visits. Every year, the WHO recommends which strains need to be included. The vaccine should be administered 2 weeks prior to travel. These vaccines are not recommended for children under the age of 6 months.

(Refer Chapter 10)

Long stay travellers

Persons who travel for long term stay such as education and employment should inquire regarding host country vaccine requirements from the respective organisations, e.g. educational institutes or employing organisations, well before travel. This will enable completion of vaccination prior to travel. For example, it is recommended to vaccinate long stay travellers to India, Bangladesh, Nepal, Pakistan and China against hepatitis A, hepatitis B, typhoid fever, meningococcal disease and Japanese encephalitis. Students who travel to UK and Europe may require meningococcal and MMR vaccination.

Additional information

A number of vaccines, both live and inactivated, may be required prior to travel. All commonly used vaccines are relatively safe and can be given simultaneously, at different sites, without impairing antibody responses or increasing rates of adverse reactions. Inactivated vaccines generally do not interfere with the immune response to other inactivated or live-virus vaccines. These could be given at any time before or after a different inactivated vaccine or a live-virus vaccine. If two parenteral live-virus vaccines are not administered on the same day, the second vaccine should be administered at least 4 weeks later.

In the case of immunocompromised travellers vaccination must be considered from the following perspectives:

- safety in the context of the underlying illness and concurrent medication
- the possibility of decreased effectiveness of the vaccine. The doctor should explain to the traveller the risks and benefits of immunization.

Because the situation is evolving, travellers and clinicians can stay updated of new developments by visiting the official U.S. government website for travel (<http://www.cdc.gov/travel>)⁵ and the WHO website www.who.int.

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CHAPTER 29

IMMUNIZATION IN SPECIAL CLINICAL CIRCUMSTANCES

Preterm and low birth weight infants

Preterm infants and infants of low birth weight (lower than 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 hospital¹. All immunizations required at 2 months of age can be administered to preterm or low birth weight infants except for the rotavirus vaccine which should be deferred until the infant is discharged from the hospital to prevent potential spread of this live vaccine virus².

Before pregnancy

Rubella vaccine should be given 1 month and varicella vaccine 3 months prior to pregnancy².

Pregnancy

Immunization during pregnancy poses theoretical risks to the developing fetus. Pregnant women should receive a vaccine when the vaccine is unlikely to cause harm, the risk of disease exposure is high and the infection would pose a significant risk to mother or fetus. When a vaccine is to be given during pregnancy, it should be postponed if possible to the second or third trimester of pregnancy to minimize the theoretical concern about teratogenicity. Routine vaccinations considered safe in pregnancy are inactivated influenza and diphtheria and tetanus toxoid. Hepatitis A and B vaccines could be given if indicated. Inactivated polio virus (IPV) vaccine could be given to pregnant women who have never received polio vaccine or are partially immunized.

Pregnancy is a contraindication to administration of live vaccines. Therefore measles, mumps, rubella, varicella, BCG, live attenuated influenza, oral polio, live Japanese encephalitis and yellow fever vaccinations should be avoided during pregnancy.

Pregnant women at risk of exposure to pathogens liable to cause certain serious illnesses should be considered for immunization. These include pneumococcal and meningococcal infections, Japanese encephalitis and rabies. To prevent such infections the relevant inactivated vaccines are recommended. Human papillomavirus (HPV) vaccine contains no live virus but data on immunization during pregnancy are limited. Therefore, initiation of the vaccine series should be delayed until after completion of the pregnancy.

Pregnant women are at increased risk of complications from influenza. Therefore, inactivated influenza vaccine should be administered to pregnant women during an influenza epidemic, regardless of the trimester. Immunization of pregnant women also protects the infant against influenza². No information is available on the safety of typhoid vaccine in pregnancy. It is therefore advisable to avoid vaccinating pregnant women with typhoid vaccine².

Immunocompromised patients

Safety and effectiveness of vaccines in persons with immune deficiency are determined by the nature and degree of immunosuppression. Such persons will vary in their susceptibility to infection.

Immune deficiency conditions are grouped into primary and secondary (acquired) immune deficiency disorders.

Primary immune deficiencies

These are usually inherited and involve a part of the immune defenses such as B-lymphocyte (humoral) immunity, T-lymphocyte (cell mediated) immunity, complement or phagocytic function.

Live vaccines are contraindicated for severe B-lymphocyte defects but not for selective IgA deficiency and IgG subclass deficiencies.

Live vaccines are contraindicated for all T-lymphocyte mediated immune disorders, leucocyte adhesion deficiency, Chediak-Higashi syndrome and defects of interferon production². Live bacterial vaccines such as BCG and the oral typhoid vaccine are contraindicated in phagocytic function disorders, such as chronic granulomatous disease.

Live virus vaccines are safe to administer to children with disorders of phagocytic function and to children with complement deficiencies. Patients with complement deficiencies should be given Hib, pneumococcal and meningococcal vaccines.

Secondary (acquired) immune deficiencies

Secondary or acquired immune deficiency disorders occur in persons with HIV/AIDS, malignant neoplasms, splenectomy, organ transplantation and in persons on immunosuppressive drugs or radiation therapy. It may also occur in persons with severe malnutrition or protein loss as in nephrotic syndrome.

Live viral vaccines are generally contraindicated because of the increased risk of adverse events. After immunosuppressive therapy for cancer, live virus vaccines are withheld for a minimum of 3 months after discontinuation of therapy and the patient should be in remission. The interval until immune reconstitution varies with the intensity and type of immunosuppressive therapy and the underlying disease. Therefore, it is often not possible to make a definite recommendation when live virus vaccines could be given safely and effectively.

Because patients with congenital or acquired immune deficiencies may not have an adequate response to vaccines, they may remain susceptible despite having been immunized. If there is an available test for a known antibody which relates to protection, specific post-immunization serum antibody titre can be determined 4-6 weeks after immunization, to assess the immune response and as a guide to further immunization².

Persons on corticosteroid therapy

Inactivated vaccines and live virus vaccines should be administered to patients prior to commencement of corticosteroid therapy when possible, as for immunocompetent persons. Inactivated vaccines should be completed ≥ 2 weeks prior and live virus vaccines ≥ 4 weeks prior to commencement of corticosteroid therapy².

Persons on high dose corticosteroid therapy (≥ 2 mg/kg/day of prednisolone or ≥ 20 mg/day in children weighing > 10 kg for 2 weeks or 40 mg/day for > 2 weeks in adults) can become immunosuppressed. They should receive live vaccines only after 4 weeks of cessation of therapy². The interval of 1 month after discontinuation of therapy is based on the assumption that the disease is in remission or under control and that the immune response has been restored.

Persons with asplenia or functional asplenia

These result from the following:

- Surgical removal of the spleen
- Sickle cell disease (functional asplenia)
- Congenital asplenia

All children, adolescents and adults with asplenia, irrespective of the cause, have an increased risk of fulminant bacteremia and need immunization with pneumococcal, Hib and meningococcal vaccines. When surgical splenectomy is planned, immunization status for Hib, pneumococcus and meningococcus should be ascertained and the required vaccines should be administered at least 2 weeks prior to splenectomy. If splenectomy is urgent or vaccination was not done before splenectomy, indicated vaccines should be initiated at 2 weeks after surgery². For booster doses of the vaccines, consultation with a specialist is recommended.

In general, antimicrobial prophylaxis in addition to immunization should be initiated after splenectomy. Some experts continue

prophylaxis throughout childhood and into adulthood for high risk patients with asplenia².

Immunization of HIV infected persons

(Refer Chapter 22)

Immunization of renal dialysis patients and patients with chronic renal disease

Children with chronic renal disease should receive all routine immunizations according to the schedule for healthy children³. An exception being withholding live virus vaccines in children with chronic kidney disease (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. Data from a number of studies suggest that children with CKD might respond suboptimally to immunizations³.

By virtue of their immunosuppressed state, CKD patients are at risk for many infections, particularly hepatitis B, pneumococcus and influenza.

Hepatitis B – Patients should receive 4 doses of hepatitis B vaccine as early in the course of the disease as possible. Dose schedule should be 0, 1, 2 and 6 months. The HBs antibody titre should be assessed 1-2 months after the primary course and annually thereafter. A booster dose should be given if HBs antibody titre falls below 10mIU/mL. Revaccination with a full course is recommended for persons who do not develop protective antibody titre after the primary course⁴.

Pneumococcal vaccine – 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. Because secondary antibody responses are less affected than primary antibody

responses, immunization strategies should be formulated early in the course of progressive renal disease. This approach is particularly important if transplantation and immunosuppressive therapy are being considered.

DTaP, Hib, hepatitis A, Japanese encephalitis, MMR, meningococcal, IPV, typhoid, varicella and inactivated influenza vaccines should be administered prior to commencement of dialysis, if indicated.

Vaccination in kidney transplant recipients

Kidney transplant recipients should receive age-appropriate inactivated vaccines as recommended for the general population. They should not receive live vaccines. If a patient has received a live vaccine, the transplant should be delayed by at least 4 weeks since the time of administration. It is best to wait until the first 3-6 months after kidney transplantation, which is the period of intense immunosuppression, before attempting vaccination. Kidney transplant patients should receive inactivated vaccines based on the risk factors for the respective disease and the likelihood of developing these infections, especially vaccines that are not routinely given to the general population like the pneumococcal, meningococcal and inactivated influenza vaccines⁴.

Patients requiring repeated blood transfusions/blood products

A large number of infections can be transmitted by blood transfusions. These include HIV, hepatitis A, B and C, syphilis, malaria, human T cell lymphotropic virus types 1 and 2, cytomegalovirus, Epstein-Barr virus and parvovirus B19. Since immunization is at present available only for hepatitis A and B, donor blood screening is essential before blood transfusion. Nucleic acid amplification testing (NAT) identifies viral genes in the window period before antibodies develop and is available for identifying infections such as HIV and hepatitis C. At present NAT for hepatitis B virus is available as a donor screening test².

All patients requiring repeated transfusions should be immunized with hepatitis A and B vaccines prior to commencement of transfusion.

Live viral vaccines should be avoided for three months after blood transfusion or infusion of blood products including immunoglobulins

Patients with chronic diseases

Some chronic diseases make persons susceptible to severe manifestations and complications of common infections. In general, immunizations recommended for healthy individuals should be given to such persons with the exception of persons with immunological disorders.

Patients with chronic heart disease, chronic lung disease, CKD, diabetes mellitus, cerebrospinal fluid leak, functional or anatomic asplenia, cochlear implants, should be given the pneumococcal vaccine.

- Children, who have already received a course of pneumococcal conjugate vaccine (PCV), should receive a dose of pneumococcal polysaccharide vaccine (PPSV) on or after the second birthday.
- Children who have not received pneumococcal vaccine previously, should be given a dose of PCV, which should be followed up with a dose of PPSV at least 8 weeks later.
- Adults should also be given one dose of PCV, followed by a dose of PPSV at least 8 weeks later.

All these groups are recommended a single booster dose of PPSV given 5 years after the first dose of PPSV⁵.

Persons with chronic liver disease should receive hepatitis A and hepatitis B vaccines if they have not received them already².

Children with a history of seizures

Infants and children with a history of seizures could be given routine immunizations except Japanese encephalitis vaccine. Japanese encephalitis vaccine should be given one year after the last seizure, provided there is no progressive neurological disorder. If a seizure

follows the first dose of any vaccine, that vaccine should not be repeated. Pertussis immunization in infants with a history of recent seizures should be deferred until a progressive neurological disorder has been excluded or the cause of the earlier seizure has been determined².

A family history of seizures is not a contraindication to pertussis, pneumococcal conjugate, MMR, varicella and influenza vaccines, or a reason to defer immunization².

Healthcare personnel

Healthcare personnel should protect themselves by receiving all appropriate immunizations. All those without evidence of immunity, should receive the MMR, varicella and annual influenza vaccines.

Those without evidence of immunity to varicella should receive two doses of varicella vaccine².

Hepatitis B vaccine should be given to all personnel who are likely to be exposed to blood or blood containing body fluids. A single dose of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) should be given to all those who have not received it earlier².

Adolescents and young adults

Adolescents and young adults may not be protected against all vaccine-preventable diseases because they have escaped natural infection and they have not received all recommended vaccines. Rarely persons who have received immunizations according to the routine schedules may not be immune. To ensure age appropriate immunization, all children should have a routine appointment at 11 to 12 years of age for administration of appropriate vaccines.

At 11 to 12 years the Tdap vaccine should be given to all adolescents and the human papillomavirus (HPV) vaccine should be given to girls and the latter should be repeated 2 and 6 months later².

During adolescent visits, immunization status should be reviewed and deficiencies rectified. Adolescents and young adults intending to travel abroad should have their immunization status reviewed according to their travel plans at least 2-6 months prior to departure, to allow time to administer required vaccines².

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CHAPTER 30

STORAGE AND TRANSPORT OF VACCINES

The control of vaccine-preventable diseases is attributable, in part, to proper storage and handling of vaccines. Vaccines exposed to temperatures outside the recommended ranges can have reduced potency and protection. In addition, there are certain vaccines, which are sensitive to light. Storage and handling errors can cost thousands of rupees in wasted vaccines and need for revaccination. Errors can also result in the loss of patient confidence when repeat doses are required. It is better not to vaccinate than to administer a dose of vaccine that has been stored improperly.

Vaccines are sensitive to heat and freezing and, therefore, should be stored and transported at the correct temperature from the time they are manufactured until they are used. The system used for keeping and distributing vaccines in the recommended condition is called the **cold chain**.

Non-adherence to the recommended cold chain conditions results in reduction of vaccine efficacy leading to vaccine failure. It can also lead to an increased risk of adverse reactions following immunization, particularly after the use of unduly frozen vaccines. Depending on the nature of the product, vaccines can be damaged either by exposure to heat or freezing¹. Tables 1 and 2 illustrate the degree of sensitivity of different vaccines to heat and freezing². With the present distribution system in Sri Lanka, no vaccines should be stored, frozen.

Table 1. Heat sensitivity of different vaccines

<i>Range</i>	<i>Vaccine</i>
most sensitive	OPV
	Measles, MMR
	DTP, DTP-Hep B, DTP-Hib,
	DTP-HepB+Hib, YF
	BCG
Hib, DT	
least	aTd, TT, HepB, JE

Table 2: Freeze sensitivity of different vaccines

<i>Range</i>	<i>Vaccine</i>
most sensitive	HepB
	Hib (liquid)
	DTP, DTP-Hep B, DTP-Hib,
	DTP-HepB+Hib, YF
	DT
	aTd
least sensitive	TT, Hib (lyophilized)

Exposure to heat over time can be monitored using vaccine vial monitors (VVM) and the change in colour will guide decisions on the suitability of vaccines for use. During storage and transportation of freeze-sensitive vaccines (eg. DTP, TT, DT, aTd, hepatitis B and Hib) the risk of freezing is greater than the risk of heat exposure.

This chapter provides general guidelines on storage of vaccines. However, manufacturer’s product information and package inserts should be referred to, for specific and detailed information about storage and handling of specific vaccines.

Storage temperature for vaccines³

All inactivated vaccines require refrigerator storage temperatures between 2°C-8°C, with a desired average temperature of 5°C. An open vial of oral polio vaccine can be kept at 8°C for a maximum period of 3 months. Storage of oral polio vaccine for a longer duration should be in the freezer compartment.

Storage of vaccines in a refrigerator: (Fig. 1)

- The temperature of the refrigerator should be allowed to stabilize prior to storing vaccines. New refrigerators may need 2 or more days of operation to establish a stable operating temperature
- Multi-socket outlets should not be used for connecting the refrigerator to a power supply, because of the danger of being accidentally disconnected

- Combination freezer/refrigerator units with one exterior door are not recommended for storage of vaccines as the risk of freezing of vaccines is high³. 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
- Freeze and store ice-packs in the freezer compartment
- The door of the refrigerator should not be opened frequently
- Arrange the boxes of vaccines in such a way that air can circulate
- The temperature of the main compartment of the refrigerator should range between 2°C -8°C
- Every vaccine-containing refrigerator should have a calibrated thermometer
- 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
- All vaccine storage refrigerators should have generator backup. Ideally, the generator should be automatic
- In case of a power failure, do not open the refrigerator. Take immediate steps to restore power
- If the power failure is likely to last for more than 8 hours, vaccines should be moved to another storage site

Open vial policy⁴

Opened multi-dose vials of liquid vaccines from which one or more doses have been removed, using standard sterile procedures, may be used within **28 days**, *if all of the following conditions are met*:

- 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.

Note:

- Liquid vaccines to which the statement above applies include OPV, DPT, TT, DT, aTd, hepatitis B, and liquid formulations of Hib.
- Freeze-dried vaccines, which include BCG, measles, MMR, yellow fever and freeze dried formulations of Hib, must be discarded six hours after reconstitution or at the end of the immunization session, whichever comes earlier, and therefore opened vials of these vaccines cannot be stored for future use.
- Keep opened multi-dose vials of OPV, DPT, TT, DT, aTd, 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; or
 - If there is evidence of contamination, such as floating particles in the vaccine; or
 - When you suspect that the vaccine has been contaminated.

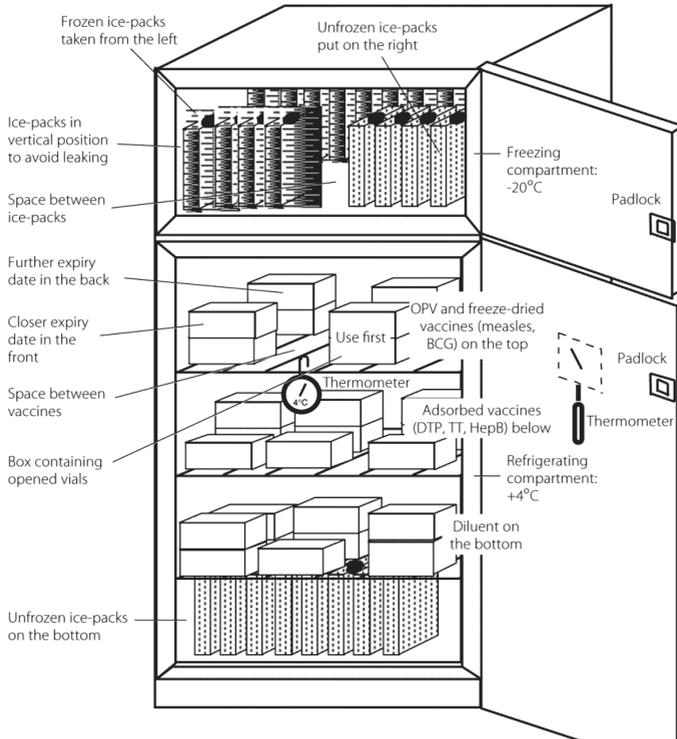


Figure 1. Storage of vaccines in a refrigerator

Diluent

Diluent vials must NEVER be frozen. If the manufacturer supplies a freeze-dried vaccine packed with its diluent, ALWAYS store the product between 2°C-8°C. Only the diluent supplied by the manufacturer should be used for reconstitution of the freeze-dried vaccines⁴.

Temperature monitoring systems

Regular temperature monitoring is vital for proper cold chain management. A calibrated temperature monitoring device, preferably with a buffered probe, should be placed as close as possible to vaccines. If the temperature of the refrigerator is below 2°C or above

8°C, immediate corrective action should be taken.

A) Thermometers (Figure 2)

Temperatures in the refrigerator should be read twice a day, once in the morning and once before leaving at the end of the day. A temperature log should be posted on the door of the refrigerator where the twice daily temperature readings are recorded. Use only calibrated thermometers with a Certificate of Traceability and Calibration. Calibration of thermometers is carried out at the Sri Lanka Standards Institute (SLSI) and the Industrial Technology Institute (ITI) in Colombo. Dial thermometers are no longer recommended by the WHO because they lose their calibration over time, especially if they are dropped.

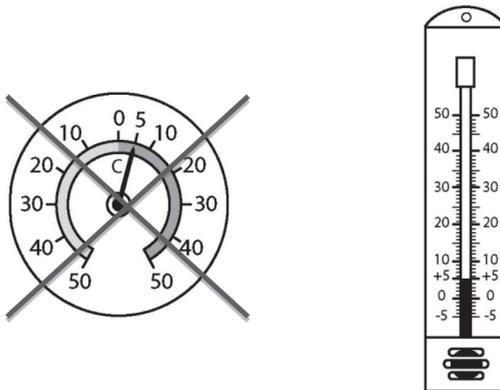


Figure 2. Dial thermometer and stem thermometer

B) 30 day electronic temperature loggers (30 DTR) (Figure 3)

Data loggers (data recorders) are electronic, automatic, continuous, temperature monitoring devices which provide assurance of temperature maintenance during transport and in refrigerators. They are useful when there is no person to monitor temperature, especially when the clinic is closed. One of the primary benefits of using data loggers is the ability to automatically collect data on changes in temperature

on a 24-hour basis. They measure the temperature using sensors and are generally small, battery powered and portable. They are equipped with a microprocessor and an internal memory for data storage. Some data loggers utilize software to access and analyse the stored data using a computer, while others have a local interface device (keypad, LCD) where the data is displayed. In more advanced types, the data can be stored even up to 120 days. However, it is recommended that twice daily manual temperature recording be continued, irrespective of the use of data loggers, due to reported failures in systems that use electronic monitoring.



Figure. 3 30 day temperature loggers (FridgeTag2™ with USB)

These devices are placed with the vaccine load in a vaccine refrigerator. They record the refrigerator temperature at no more than 10-minute intervals and show the temperature history for any day in the last 30 days. As long as the temperature has remained within the recommended range, the device displays “OK” or a tick symbol. Several types of 30 DTR are prequalified by WHO and Figure 3 shows an example. 30 DTRs should not be used in vaccine freezers.

30 DTRs should be placed in an appropriate position where they can be read easily and are unlikely to be damaged. If the refrigerator is used to store vaccines that are not freeze-sensitive, place the device on top of the load, in the warmest part of the refrigerator. If the refrigerator is used to store any freeze-sensitive vaccines, the device should preferably be placed in the coldest part of the refrigerator. This will be the bottom of a basket in chest refrigerators or nearest to the evaporator plate in front-opening models.

Cold chain monitoring systems

A) Vaccine vial monitors (VVM)

VVM is a label fixed to the outer surface of the vaccine vial which contains heat-sensitive material. VVM will measure increases of temperature, but not reductions of temperature. They register cumulative heat exposure over time. The combined effects of time and temperature cause the inner square of the VVM to darken, gradually and irreversibly. A direct relationship exists between the rate of colour change and temperature. The lower the temperature, the slower the colour change and the higher the temperature, the faster the colour change (Figures 4a & 4b).

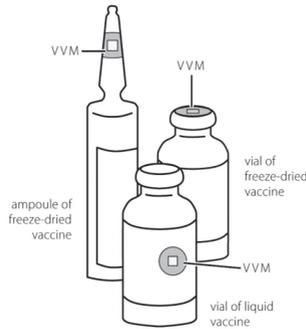


Figure 4a. Location of vaccine vial monitors

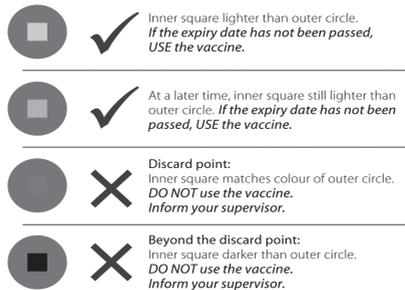


Figure 4b. Interpretation of the vaccine vial monitor²

B) Freeze-tag™ (Figure 5)

The Freeze-tag™ consists of an electronic temperature measuring circuit with an LCD-display and detects exposure to freezing. If the indicator is exposed to a temperature below $0^{\circ}\text{C} \pm 0.3^{\circ}\text{C}$ for more than 60 ± 3 minutes the display will change from the “OK” status into the “alarm” status as indicated in the picture below.



Figure 5 . Indicators used to detect freezing - Freeze-tag™

C) Freeze Watch™ (figure 6)

Freeze Watch™ is an indicator used for detecting freezing and consists of a card embedded with a thin walled glass vial containing a coloured liquid. When exposed to temperatures below 0°C for more than one hour, the vial bursts and releases the coloured liquid, staining the white backing card.

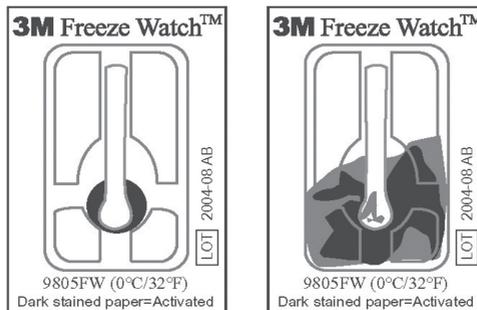


Figure 6. Indicators used to detect freezing - Freeze Watch™

Shake test

When the above freeze indicators show signs of exposure to freezing temperatures or if it is suspected that vaccines have been exposed to freezing, the shake test is carried out. 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: (Figure 7)

- Obtain a vial of vaccine of the same batch from the same manufacturer and freeze it to a solid state for at least 10 hrs at -10°C and let it thaw. This is the control vial
- Choose your test vial from the batch suspected as having been frozen
- Shake vigorously the test and control vials together in one hand for 10 -15 seconds
- Allow to rest on a table
- Compare the sedimentation rates of the deliberately frozen control vial with the suspect vial
- If the test vial has a sedimentation rate similar to or faster than the control vial the batch of vaccines should not be used

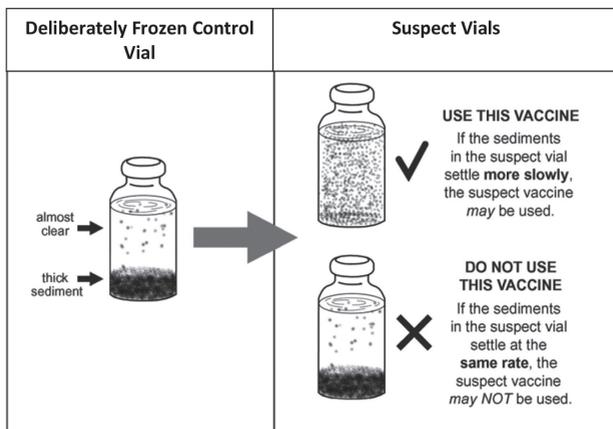


Figure 7. Interpretation of the shake test to determine damage due to freezing of vaccines²

Light sensitivity¹

Some vaccines are very sensitive to strong light and exposure to ultraviolet light (sunlight or fluorescent light) causes loss of potency. BCG, measles, rotavirus, varicella, HPV and MMR vaccines are sensitive to light. Normally, these vaccines are supplied in vials made of dark brown glass, which gives them some protection against damage due to light, but care should be taken to keep them protected from strong light at all times.

Transport of vaccines to outreach health centres

Vaccine carriers (Figure 8) are used for this purpose. They are insulated containers that, when lined with frozen ice-packs (Figure 9), keep vaccines and diluents cold during transportation. These are also used for temporary storage of vaccines when the refrigerator is being defrosted. Vaccine carriers may not be used for storage of vaccine beyond 12 hours.

Placing adsorbed vaccine vials, such as TT, DTP, and liquid vaccines, such as hepatitis B, in direct contact with ice cubes is not recommended as this could damage the potency of vaccines.

The flotation of opened vials on melting ice may also lead to contamination of contents in vials.

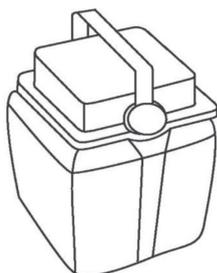


Figure 8. Vaccine carrier

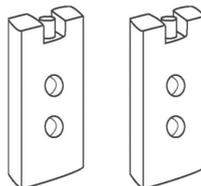


Figure 9. Ice packs

Procedure for packing the vaccine carrier

- Remove the ice packs from the freezer
- Wait for ice packs to be “conditioned” i.e. when the ice core of the pack starts moving (approximately 30-45 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 bag 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)
- Place a layer of frozen ice-packs on top
- Secure the lid tightly
- During immunization the foam pad supplied with the carrier should be used as a temporary lid to securely hold opened vials, while protecting unopened vials in the cool chamber below

Staff training and education

All personnel who handle or administer vaccines should be trained on storage and handling policies and procedures. Continuing education for staff is mandatory when new vaccines are introduced and when there are any changes to the storage and handling guidelines for a particular vaccine.

Emergency plans

Each facility should have a detailed written emergency vaccine retrieval and storage plan in the event of refrigerator and/or freezer malfunctions, during power failures, natural disasters or other emergencies which might compromise appropriate vaccine storage conditions⁵.

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CHAPTER 31

GENERAL INFORMATION ON VACCINES

Vaccines are highly complex biologicals, where batch to batch variation is inevitable even when produced by the same manufacturer. By adhering to good manufacturing practices (GMP), continuous quality control procedures and maintaining cold chain at all times, the manufacturer assures safety, immunogenicity and efficacy of vaccines. As a vaccine non-producing country, Sri Lanka maintains the quality, safety and efficacy of procured vaccines through a stringent process of registration, lot release, monitoring of adverse events following immunization (AEFI) and having an access to a laboratory for quality testing when necessary.

Interchangeability of vaccines

Similar vaccines produced by different manufacturers may differ in their components and formulations and may elicit different immune responses. However, such vaccines have been considered interchangeable when administered according to their licensed indications, although data documenting interchangeability are limited.

Lapsed immunizations

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

Unknown or uncertain immunization status

A physician may encounter some children with uncertain immunization status. Many young adults and some children do not have adequate documentation of immunizations, and recollection by the parent

or guardian may be of questionable validity. In general, these persons should be considered disease susceptible, and appropriate immunizations should be administered. There is evidence that administration of measles, rubella, MMR, varicella, Hib, hepatitis B, or polio vaccine to already immune recipients is not harmful; Tdap, rather than DTP should be given to those 5 years of age or older¹.

Simultaneous administration of vaccines

Most vaccines can 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 visits². When vaccines are administered simultaneously, separate syringes and separate sites should be used. Injections into the same extremity should be separated by at least 1 inch so that any local reactions can be differentiated. Individual vaccines should never be mixed in the same syringe unless they are specifically licensed and labeled for administration in one syringe. If live vaccines are not administered concurrently, a minimum gap of 4 weeks should be kept between immunizations². 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 and HBIG, rabies vaccine and RIG), they should be administered at separate anatomical sites. Live vaccines administered by the oral route (OPV, oral typhoid, rotavirus vaccine) do not interfere with each other if given simultaneously. These vaccines may be given at any time before or after each other. Live vaccines should not be given within three months of receiving immunoglobulin, blood or blood products.

Vaccine safety

Although immunization has successfully reduced the incidence of vaccine-preventable diseases, vaccination can cause both minor and rarely, serious side effects. Public awareness of and controversy

about vaccine safety has increased, primarily because increases in vaccine coverage resulted in an increased number of adverse events that occurred after vaccination. Such adverse events include both true reactions to vaccine and events coincidental to, but not caused by, vaccination. Despite concerns about vaccine safety, vaccination is safer than accepting the risks of the diseases these vaccines would prevent. Unless a disease has been eradicated (e.g. smallpox), failure to vaccinate increases the risks to both the individual and the society³.

Allergy to vaccine components

Vaccine components could cause allergic reactions in some recipients. These reactions could be local or systemic and could include anaphylaxis. The vaccine components responsible could include the vaccine antigen, animal proteins, antibiotics, preservatives (such as thimerosal), or stabilizers (such as gelatin). The most common animal protein allergen is egg protein in vaccines manufactured by using embryonated chicken eggs (influenza and yellow fever vaccines)³.

Allergy to egg protein

Presently, available influenza and yellow fever vaccines contain egg proteins. Yellow fever vaccine is contraindicated in persons who have a history of allergy to egg protein. 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 vaccines. Any such theoretical risk is far outweighed by the risk of such patients remaining unvaccinated. Thus, all patients with egg allergy of any severity, including anaphylaxis, should receive influenza vaccine. Persons with a history of suspected egg allergy should be evaluated by an allergist to determine the status of their egg allergy, but this should not delay their influenza vaccination. Skin testing with the vaccine and dividing the dose are not necessary. The vaccine should be administered in a medical setting where anaphylaxis could be recognized and treated, should it occur⁴.

Contraindications and precautions

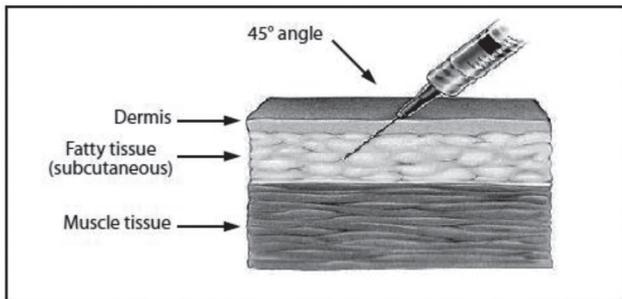
Contraindications and precautions to vaccination are conditions under which vaccines should not or may not be administered.

The only contraindication applicable to all vaccines is a history of a severe allergic reaction (i.e. anaphylaxis) after a previous dose of vaccine or to a vaccine component. In addition, severely immunocompromised persons should not receive live vaccines. Children who experienced encephalopathy within 7 days after administration of a previous dose of diphtheria and tetanus toxoids and whole-cell pertussis vaccine (DTP), 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 foetus, women known to be pregnant should not receive live, attenuated vaccines¹.

Injection techniques

A vaccine recommended to be administered through intramuscular route, should not be administered subcutaneously. All parenteral live vaccines are administered subcutaneously.

1. Subcutaneous (SC) injections



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

Needle size:

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

Sites recommended for subcutaneous injections:

Upper Arm: Deltoid region

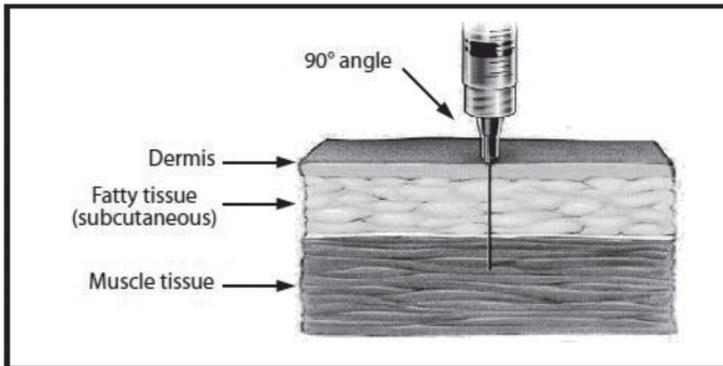
Abdomen: On either sides of the umbilicus

Thigh: Antero-lateral region



Sites on the body where a subcutaneous injection can be given

2. Intramuscular (IM) injections



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

All adjuvanted vaccines should be given IM.

Sites recommended for intramuscular injections:

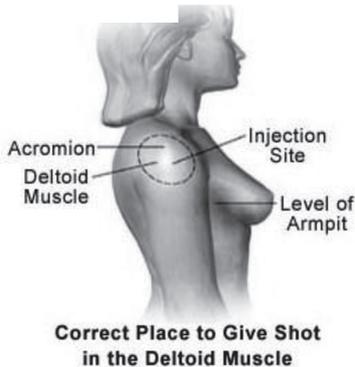
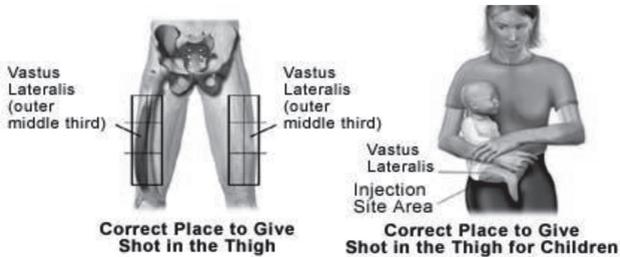
Infants - Antero-lateral thigh

Children over 1 year and adults - deltoid region

Needle size:

Intramuscular injections go into the muscle below the subcutaneous layer. Therefore, the needle must be thicker and longer to ensure that the vaccine is injected into the muscle. Pull back the plunger to make sure that you are not in a blood vessel before injecting the vaccine. 23 -25G needles that are 1 to 1.5 inches long are usually appropriate⁵.

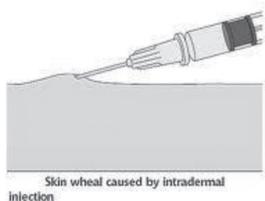
Sites recommended for IM injections:



3. Intradermal (ID) injections

For intradermal injection, a needle of 25 or 27G and 3/8 - 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 can be used for administering intradermal injections.

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CHAPTER 32

FREQUENTLY ASKED QUESTIONS

- In the National Immunization Programme (NIP) of Sri Lanka many vaccines are given routinely and most diseases are well controlled. There are other vaccines available outside the NIP such as rota virus, chickenpox, hepatitis A, human papillomavirus (HPV) and pneumococcal. Who should receive such vaccines?

The decision to vaccinate should be taken in consultation with the health care professional based on the individual's needs.

- Does natural immunity produce better protection than vaccine induced immunity?

Although certain viral diseases such as chickenpox produce natural immunity the disease may be fatal or may cause permanent disability. 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 can be carried out, if necessary.

- Is an interval of 4 weeks mandatory between immunizations?

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.

- Does the interval between vaccinations apply only to live vaccines?

Yes, it is not applicable to killed vaccines.

- If a child has received only one dose of vaccine, is it necessary to restart the schedule?

No. The vaccine schedule could be safely continued as if there has been no delay. The recommended intervals between further doses should be maintained.

- Could children with fever or a common cold be immunized?

The vaccination should only be postponed if a child is seriously ill or has a high fever of $>38^{\circ}\text{C}$ at the time of immunization.

- Sometimes we find that certain vaccines have been administered abroad according to different schedules. What schedule should we follow?

Vaccination schedules are based on the disease prevalence in each country. It would be appropriate to continue with the schedule of the country where the person is going to live. For example, if a person is on holiday, it is not rational to restart or reschedule his future vaccination. On the other hand, for persons who have returned from abroad and are going to live in this country it would be advisable to have their subsequent vaccinations re-scheduled according to the local schedule.

In addition, other vaccines included in the local schedule should be given such as Japanese encephalitis (JE) vaccine.

- Students going for overseas studies are recommended a number of vaccines within a short period. Is it safe to give all of them?

It is advisable to plan an overseas stay well in advance, enabling adequate time intervals for vaccinations. Please refer to the accelerated schedules under each chapter.

Most vaccines could be given as accelerated schedules with the exception of simultaneous administration of cholera and yellow fever vaccines. Two live vaccines such as MMR and varicella could be concurrently administered or with an interval of 4 weeks. Delaying the other vaccines depend on the travel plan. Killed and subunit vaccines can be given at intervals of 1-2 weeks.

- Should vaccination be delayed in low birth weight babies?

Low birth weight babies should receive BCG vaccine when they are fit to be discharged from the hospital. They should also receive their routine vaccinations at the recommended age.

- What precautions should be taken when vaccinating preterm babies?

It is important that preterm infants have their immunizations according to the NIP.

Their age should be calculated from the date of birth. In extremely premature babies (≤ 28 weeks of gestation), the need for monitoring for 48-72 hours should be considered particularly for those with a history of respiratory immaturity due to the risk of developing apnoea. In such situations, the vaccination at 2 months is recommended to be administered in a hospital where a paediatrician can be consulted for further advice.

- What action should be followed if you find any of your liquid vaccines frozen?

The safety and effectiveness of a vaccine is affected by extreme temperature changes and as such should be discarded safely. However, unopened oral polio vaccine can be stored below 0°C.

- What is your advice for a child who has not developed a scar after BCG vaccination?

It depends on the age of the child. If the child is between 6 months to 5 years of age, repeat the BCG. If the child is more than 5 years, do the Mantoux test and if it is negative, administer the BCG.

In general it takes about 10-12 weeks to produce a scar and non-formation of a scar does not mean that BCG has not been taken up. In 10-12 % of vaccinees, scar formation may not take place at all.

- When there is a reaction to DTwP vaccine in the routine EPI schedule, is it better for the patient to go for DTaP vaccine for the next dose or use DT?

As the reactogenicity is less with DTaP vaccine, it can be used when there is a reaction to DTwP vaccine. The DT can also be given, as the DTaP is only available in the private sector.

- Could one interchange different brands of vaccines with regard to children who had begun the vaccination with DTwP or DTaP?

There is no clinical data to support switching from one type of DTwP to another type of DTwP vaccine and DTaP vaccine within the primary vaccination programme, but there is no contraindication to do so. However, it is preferable to continue with the same brand unless it is not available.

- If full DTP vaccinations were completed during childhood vaccination, is it still possible for an adult to get whooping cough?

Yes. The immunity acquired from immunization is not life-long. Epidemiological evidence suggests that routine immunization of adolescents and adults could significantly result in lowering of the incidence and severity of the disease. Pertussis vaccination for adults (TdaP) may be given at intervals of ten years.

- Why is a booster dose of Hib vaccine given during the 2nd year of life?

More than 90% of vaccinees achieve a titre of $>1.0 \mu\text{g/mL}$ after 3 doses with protection lasting up to 15-18 months of age. More than 50% of the time, the titre falls to less than $0.15 \mu\text{g/mL}$ (the minimum protective level), by 18 months. If a booster dose is given at 15-18 months of age, the titre rises by 30-90 fold and reaches levels as high as $40 \mu\text{g/mL}$. Hence a booster dose is recommended at 18 months of age.

- When 2 doses of MMR are to be given to adolescents what should be the minimum interval ?

A minimum of 4 weeks.

- Why is it important to give two doses of MMR vaccine?

Two doses will provide the recipient and the community with better protection.

With the first dose of MMR vaccine, 5-10% children will remain vulnerable to these diseases. However, after the 2nd dose, only 1% will remain susceptible.

- What is the recommended dose of MMR for adults at a high risk of exposure?

Two doses are recommended for adults at a high risk of exposure and transmission (e.g. students attending higher educational institutions, healthcare personnel, international travellers) and 1 dose for adults aged ≥ 18 years.

- Should persons who had been previously diagnosed to have measles, rubella and mumps be excluded from MMR vaccination?

It is not a safe practice to exclude those individuals without reliable confirmatory serological evidence for all 3 diseases.

- 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 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 would cause any harm.

- How long should a female avoid pregnancy, after receiving rubella and chickenpox containing vaccinations?

The minimum interval should be 3 months for chickenpox vaccine and one month for rubella containing vaccines, because of the theoretical risk to the developing foetus.

However, pregnancy within this period is not an indication for termination as no teratogenic effects have been identified.

- Is a history of febrile seizure contraindicated for JE vaccination?

Yes, JE vaccination should be deferred by one year from the last febrile convulsion.

- 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, 80-90% 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, after exposure.

- “Chickenpox in children is usually not serious”. Why not allow children to get the disease?

It is not possible to predict who will have a mild or serious disease. When there is an effective vaccine, it is not worth taking this risk. Even a child with a mild disease could transmit the disease to susceptible persons in the community.

- Is there 100% assurance that a person is protected from chickenpox if 2 doses of vaccine have been administered?

No vaccine is 100% effective in preventing any disease. For chickenpox vaccine, about 90% of people with two doses are completely protected from chickenpox infection and almost 100% from severe disease. On the other hand, if a vaccinated person does get chickenpox, it is usually a mild form with <50 skin lesions.

- What do you give to a child younger than 1 year of age if they were exposed to the chickenpox or zoster virus?

The minimum age for varicella vaccine is 12 months. Vaccination is not recommended for infants younger than 12 months of age even as post-exposure prophylaxis. CDC recommends a healthy infant should receive no specific treatment or vaccination after exposure to VZV. The child can be treated with acyclovir if chickenpox occurs. Immunosuppressed children and neonates should receive VZIG.

- If a child gets breakthrough varicella infection, (less than 50 lesions) could the child go to school?

No. Breakthrough varicella represents replication of wild varicella virus in a vaccinated person. Although most breakthrough disease is mild, the child is infectious and activities should be restricted to the same extent as an unvaccinated person with varicella.

- When a mother has chickenpox at the time of delivery, can the neonate be given the vaccine?

No. The vaccine is only recommended after infancy. To reduce the risk of severe disease in infants, it is recommended that neonates born to mothers who developed varicella within 5 days before to 2 days after delivery should receive VZIG, regardless of whether the mother received VZIG.

- If a person is immunocompromised, is it advisable to vaccinate family members who may be susceptible to chickenpox?

Yes. Because, it is important to protect the immunocompromised who cannot be vaccinated and transmission of vaccine virus from a healthy individual is rare.

- Which live vaccines are recommended for a household of an immunocompromised person?

MMR, varicella and rotavirus vaccines as these rarely transmit diseases. However, OPV is contraindicated as the vaccine virus could be transmitted and could cause vaccine associated paralytic polio (VAPP) in the immunocompromised.

- Can the HPV vaccine be given to women who are already sexually active?

Ideally, HPV immunization should be completed before the onset of sexual activity. However, women who have begun sexual activity will benefit from vaccination if they have not yet become infected with the vaccine preventable HPV serotypes. Vaccination will also prevent re-infection with vaccine specific serotypes.

- Does the HPV vaccine protect against all types of cervical cancers?

No. There are two types of vaccines commercially available - quadrivalent (oncogenic serotypes 16 & 18 and non-oncogenic 6 & 11) and bivalent (oncogenic serotypes 16 & 18). Serotypes 16 and 18 account for nearly 70% of cervical cancers. In addition, there is evidence to suggest that the vaccines provide some cross protection against certain other oncogenic serotypes.

- How long does the HPV vaccine protection last?

Current studies have shown that the HPV vaccine results in a high antibody level not requiring booster doses for up to 10 years. Studies will continue and more data regarding the effectiveness of the vaccine will be available in the future.

- 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.

- If HPV vaccination is administered unintentionally during pregnancy, would that be harmful to the foetus ?

HPV vaccines are not currently recommended for pregnant women due to the fact that vaccines have not been tested in pregnancy during clinical trials, CDC and vaccine manufacturers have monitored and studied safety of HPV vaccine in pregnant women.

Close monitoring has not yet revealed any harmful effects. If a woman receives HPV vaccine and later learns that she is pregnant, there is no reason to be alarmed.

- Is it common to develop chronic arm pain and/or sudden faintness following HPV vaccination ?

Recent data have described two types of syndromes among few young females receiving HPV vaccine ; complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS). Scientific reviews conducted on reports of CRPS and POTS do not support that there is a causative link between HPV vaccination and these 2 syndromes.

- What is the duration of protection of the Hepatitis A vaccine ? Does it provide life long immunity?

One dose of Hepatitis A vaccine will protect the recipient for at least 1 year. A second dose given after 6 to 12 months will usually confer lifelong protection.

- “I did not continue with the 2nd dose of hepatitis A vaccination for my children as I was informed that hepatitis A is not a public health problem in Sri Lanka . What is your advice ?”

Hepatitis A is endemic in Sri Lanka with occasional outbreaks. Therefore, it is recommended to complete the vaccination for your children.

- 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, fingerstick devices or other diabetes-care equipments 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 younger than 60 years of age.

- If I do not belong into any risk group, would it be necessary for me to take hepatitis B vaccine ?

Studies have demonstrated that nearly 15% of people who get infected with hepatitis B are unable to identify a risk factor that explains how they got the disease. Therefore, when there is an effective vaccine available it is advisable to use it rather than being unprotected. It also prevents primary hepatocellular carcinoma.

- “PCV is not a priority vaccine in my practice as there is no sufficient local data to show the importance of recommending it to the below 5 year age group “.

There is sufficient global and regional data justifying the use of PCV vaccination in this age group, although there is a lack of local disease burden data.

Therefore, having not enough data should not be a barrier for recommending PCV with regard to decision-making. Moreover, reasonable estimates of invasive pneumococcal disease (IPD) based on the incidence of clinical syndromes particularly those associated with pneumococcal disease may help to make informed decisions on the introduction of PCV conjugate vaccine for vulnerable groups.

Furthermore, preventing pneumococcal disease is a priority for many countries at present and some of them have already met their targets of decreased incidence such as the US. Furthermore, introduction of PCV has also shown decreased incidence of pneumonia among the older adult population.

- Do I have to take flu vaccine every year ?

Yes. Unlike other vaccines the flu vaccine is only effective for a year. Annually, the composition of the influenza vaccine is reviewed by WHO, based on recent virus surveillance studies, epidemiological trends and post vaccination studies, in order to

decide which type of influenza viruses strains should be included in the flu vaccine. Therefore, a new vaccine is needed each year due to changes occurring in the antigenic structure of the virus, making the pre-existing antibodies ineffective in binding and neutralizing the virus.

- Would the seasonal flu vaccine provide any protection against H5N1 Influenza (Avian/bird flu)?

No. H5N1 Influenza strain is not included in the vaccine.

- A nine month old baby was inadvertently given pentavalent and OPV vaccines instead of MMR vaccine. What should be done ?

Administration of an additional dose of pentavalent vaccine with OPV is not harmful but the healthcare provider who administered the vaccine should be more responsible and careful before administering the vaccine. However, it is important to give the missed MMR vaccine after one month.

- If a baby develops high fever after pentavalent vaccine at the age of 2 or 4 months what options would be available, instead of using pentavalent vaccine at the age of 6 months?

As most probably the high fever could be due to the presence of whole cell pertussis component of the pentavalent vaccine, a vaccine consists of acellular pertussis could be used (e.g. hexavalent vaccine).

- What follow up action should be taken if a 12 year old child was given a tetanus toxoid instead of aTd ?

A dose of aTd is recommended after 6 months.

- 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

- What is the immunization plan for an eight year old child awaiting elective splenectomy?

At least 2 weeks before surgery child should be given one dose of meningococcal, Hib and pneumococcal conjugate vaccines. Two months after surgery, one dose of pneumococcal conjugate and pneumococcal polysaccharide vaccines should be administered. After 5 years, one lifetime booster of pneumococcal polysaccharide vaccine should be given. In addition, in every five years, a booster vaccine of meningococcal vaccine should be given. Furthermore, annual influenza vaccination should also be considered.

- What is the role of pneumococcal vaccination during an influenza epidemic ?

Individuals who are at high risk would be predisposed to secondary bacterial infections such as streptococcal pneumonia following influenza which may be fatal.

Studies have identified that nearly 50% bacterial pneumonia in those individuals affected by influenza were due to *Streptococcus pneumoniae* and responsible for up to 20% deaths.

Therefore, pneumococcal vaccination becomes life saving in some individuals during flu epidemics.

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NATIONAL IMMUNIZATION PROGRAMME OF SRI LANKA 2017

Annex I

VACCINE	AGE										COMMENTS	
	Birth	Month 2	Month 4	Month 6	Month 9	Month 12	Month 18	3 years	School entry	10 – 15 years		Pregnancy
BCG	•											Before leaving hospital within 24 hours of birth. To be given to children between 6 months and 5 years of age, with no evident BCG scar.
Polio oral		•	•	•		•		•				
IPV		•	•									
DTP-Hep B-Hib		•	•	•								
DTP		•	•	•		•						
MMR					•		•			•		*Females only (one dose at 15-44 years for all females who have not been fully immunized earlier)
Live JE vaccine						•						
DT								•				
aTd (adult tetanus & diphtheria)										•		
HPV										•		Females year six at school two doses six months apart
Tetanus										•		First pregnancy – 1 st dose after the 12 th week of pregnancy. 2 nd dose: 6 – 8 weeks after the first dose. One dose of tetanus toxoid should be administered during every subsequent pregnancy, upto a maximum of five doses.

VACCINES OUTSIDE THE NATIONAL IMMUNIZATION PROGRAMME OF SRI LANKA 2017

Annex II

VACCINE	COMMENTS								
	Birth	Month 2	Month 4	Month 6	Month 12	Month 18	2nd year of life	School entry	Over 10 years
DTap-Hep B- IPV-Hib	■	■	■	■	■	■	■		DTP-Hep B and Hib when provided by the same manufacturer can be mixed together and administered as one dose.
DTP-Hib					■				
Hib		■	■	■					
Pneumococcal conjugate		■	■	■					
Rotavirus		■	■	■					To infants from 6 weeks to 24 weeks of age, 2 doses at 2 and 4 months, 3 doses at 2,4, 6 months
Varicella									1 yr to 12 yrs of age 1st dose at 12-15 months & 2nd dose 4-6 yrs or > 13 yrs 2 doses 4-8 weeks apart.
Tdap (reduced antigen DTP)								■	Adolescents and adults
Human papillomavirus									Bivalent - females > 9 years of age, 3 doses at 0, 1, 6 months Quadrivalent - males and females 3 doses at 0, 2, 6 months

INDIVIDUAL

Hepatitis A	For those who have not previously received Hep A vaccination - 2 doses at 0 & 6 to 12 months later (over 2 years)		
Hepatitis B	For those who have not previously received Hep B vaccination - 3 doses at 0, 1 & 6 months		
Hepatitis A + B	For those who have not previously received Hep A & B vaccination - 3 doses at 0, 1 & 6 months later (over 2 years)		
Typhoid	Injectable: 1 dose every 3 years		

SPECIAL CIRCUMSTANCES

Influenza	Meningococcal	Pneumococcal polysaccharide	Cholera	Rabies	Yellow fever
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RECOMMENDATIONS FOR ROUTE AND SITE OF IMMUNIZATION

VACCINE	TYPE	ROUTE	SITE
Adult Tetanus & Diphtheria (aTd) toxoid	Toxoids	IM	Deltoid
BCG	Live attenuated bacteria	ID	Deltoid of left arm
Cholera	Live attenuated bacteria	Oral	-
Diphtheria - Tetanus Toxoid & Pertussis (DTP)	Toxoid & inactivated bacteria	IM	Anterolateral aspect of the thigh
Diphtheria - Tetanus Toxoid - Pertussis - Hepatitis B & H. influenzae type b (DTP-HepB - Hib) (Pentavalent)	Toxoid & inactivated bacteria, recombinant viral antigen and polysaccharide protein conjugate	IM	Anterolateral aspect of the thigh
Diphtheria - Tetanus Toxoids - 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 and inactivated viruses.	IM	Anterolateral aspect of the thigh
Diphtheria reduced antigen - Tetanus Toxoid - Pertussis reduced antigen (Tdap)	Toxoid & inactivated bacterial antigen	IM	Deltoid
Diphtheria & Tetanus toxoid (DT)	Toxoids	IM	Deltoid
<i>H. influenzae type b</i> (Hib)*	Polysaccharide protein conjugate	IM	< 2 years - anterolateral aspect of thigh > 2 years - 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 seasonal	Inactivated viruses	IM	Deltoid
Human papillomavirus	Recombinant viral antigen	IM	Deltoid
Japanese encephalitis live	Live attenuated virus	SC	Deltoid
Measles, Mumps & Rubella (MMR)	Live attenuated viruses	SC	Deltoid
Meningococcal conjugate	Polysaccharide compound conjugate	IM	Deltoid
Pneumococcal conjugate	Polysaccharide compound conjugate	IM	< 2 years - anterolateral aspect of the thigh >2 years - deltoid
Pneumococcal polysaccharide	Polysaccharide	IM or SC	>2 years - deltoid >2 years - deltoid
Oral Polio Vaccine (OPV) Inactivated Polio Vaccinate (IPV) (iIPV)	Live attenuated virus Inactivated virus Fractional dose	Oral IM ID	< 2 years - anterolateral aspect of the thigh >2 years - deltoid
Rotavirus	Live virus	Oral	
Rabies	Inactivated virus	IM/SC/ID	Deltoid
Tetanus	Toxoid	IM	Deltoid
Typhoid	Capsular polysaccharide	IM	Deltoid
Varicella	Live virus	SC	Deltoid
Yellow Fever	Live virus	SC	Deltoid

ID - Intradermal

IM – Intramuscular

SC - Subcutaneous

Notification Form for Adverse Events Following Immunization (AEFI)

Patient Information						
Name:			MOH Division:			
Age: <input type="checkbox"/> <input type="checkbox"/> months/years		Sex: Male <input type="checkbox"/> Female <input type="checkbox"/>		Telephone:		
Name & address of the Parent/Guardian:						
Information on the vaccine (primary suspected and other)						
Vaccine (Generic Name)	Vaccine (Trade name)*	Route	Dose (1 st , 2 nd , 3 rd , 4 th)	Batch/Lot Number	Expiry date	VVM Status (I, II, III, IV)
Diluent used: Yes <input type="checkbox"/> No <input type="checkbox"/> If "yes", Diluent batch/lot number						
					Expiry date of Diluent	
<i>*Trade name is necessary only in private sector immunization</i>						
Place vaccine administered:					Date:	
Person vaccine administered: Doctor <input type="checkbox"/> PHNS/Nurse <input type="checkbox"/> PHM <input type="checkbox"/> PHI <input type="checkbox"/>					Time: am/pm	
Adverse Events						
Local Adverse Events	Injection site abscess <input type="checkbox"/> BCG Lymphadenitis <input type="checkbox"/>					
Requiring investigation	Severe local reaction <input type="checkbox"/>					
CNS Adverse Events	Vaccine associated paralytic poliomyelitis <input type="checkbox"/> GBS <input type="checkbox"/>					
Requiring Investigation	Encephalopathy <input type="checkbox"/> Encephalitis <input type="checkbox"/> Meningitis <input type="checkbox"/>					
	Seizures Febrile <input type="checkbox"/> Seizures Afebrile <input type="checkbox"/>					
Other Adverse Events	Anaphylaxis <input type="checkbox"/> Persistent screaming <input type="checkbox"/> Osteitis / Osteomyelitis <input type="checkbox"/>					
Requiring Investigation	Hypotonic Hyporesponsive Episode <input type="checkbox"/> Toxic Shock Syndrome <input type="checkbox"/>					
Adverse Events Not	Allergic reaction <input type="checkbox"/> Arthralgia <input type="checkbox"/>					
Requiring Investigation	High fever (>39°C / 102°F) <input type="checkbox"/> Nodule at the injection site <input type="checkbox"/>					
Other Adverse Events	a) b)					
<i>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</i>						
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 <input type="checkbox"/> Discharged <input type="checkbox"/>			
			Outcome: Recovered completely <input type="checkbox"/> Partially recovered <input type="checkbox"/> Death <input type="checkbox"/>			
Reporting source						
Date of the notification:		Institution & Designation:			Telephone:	
Name & Signature of the notifying officer/General Practitioner:						

(Medical Officers who attend any patient suffering from Adverse Effects Following Immunization shall notify in this form to the Medical Officer of Health the area of the patients residence)

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? <input type="checkbox"/> Yes <input type="checkbox"/> No If 'Yes', Allergen (Drug/Vaccine/Food/Other) - <i>specify</i> ?						
Part I: Clinical features						
Date & time of clinical examination: Date(dd/mm/yy)				Time : am/pm		
Skin &	<input type="checkbox"/> Urticaria <input type="checkbox"/> Erythema <input type="checkbox"/> Pruritus <input type="checkbox"/> Prickle sensation			Specify the site of reaction:		
	Eye	<input type="checkbox"/> Red bilateral <input type="checkbox"/> Red unilateral <input type="checkbox"/> Itchy				
Mucosa	Angioedema	<input type="checkbox"/> Tongue <input type="checkbox"/> Throat <input type="checkbox"/> Uvula <input type="checkbox"/> Larynx <input type="checkbox"/> Lip <input type="checkbox"/> Face <input type="checkbox"/> Limbs <input type="checkbox"/> Other				
Respiratory system	<input type="checkbox"/> Sneezing <input type="checkbox"/> Rhinorrhoea <input type="checkbox"/> Sore throat	<input type="checkbox"/> Hoarse voice <input type="checkbox"/> Stridor	<input type="checkbox"/> Sensation of throat closure <input type="checkbox"/> Cough	<input type="checkbox"/> Tachypnoea <input type="checkbox"/> Difficulty in swallowing <input type="checkbox"/> Rhonchi	<input type="checkbox"/> Wheezing <input type="checkbox"/> Indrawing / retractions <input type="checkbox"/> Chest tightness	<input type="checkbox"/> Grunting <input type="checkbox"/> Cyanosis <input type="checkbox"/> Difficulty in breathing
	Circulatory system	BP (mmHg)	<input type="checkbox"/> Measured hypotension	<input type="checkbox"/> Decreased central venous pulse	<input type="checkbox"/> Capillary refill time >3secs	Heart rate (m) <input type="checkbox"/> Tachycardia
CNS	<input type="checkbox"/> Loss of consciousness		<input type="checkbox"/> Distress	<input type="checkbox"/> Other(<i>specify</i>):		
GIT	<input type="checkbox"/> Diarrhoea	<input type="checkbox"/> Nausea	<input type="checkbox"/> Abdominal pain/cramp	<input type="checkbox"/> Vomiting		
Diagnostic Criteria	<input type="checkbox"/> Rapid onset of occurrence of above sign & symptoms			<input type="checkbox"/> 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	<input type="checkbox"/> Oral <input type="checkbox"/> Parenteral	<input type="checkbox"/> Vaccine	<input type="checkbox"/> Serum	<input type="checkbox"/> Other (<i>specify</i>).		
Generic name :			Trade name :			
Batch number :		Expiry date :		<i>For vaccine:</i> VVM status <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV <input type="checkbox"/> 1 st dose <input type="checkbox"/> 2 nd dose <input type="checkbox"/> 3 rd dose <input type="checkbox"/> 4 th dose		
If diluent used, specify batch number & expiry date:						
If parenteral medicine/vaccine:			<input type="checkbox"/> Single dose <input type="checkbox"/> Multi dose	<input type="checkbox"/> Liquid <input type="checkbox"/> Lyophilised		
Route of administration: <input type="checkbox"/> Oral <input type="checkbox"/> IV <input type="checkbox"/> IM <input type="checkbox"/> SC <input type="checkbox"/> ID <input type="checkbox"/> Other(<i>specify</i>)						
Site of Administration: <input type="checkbox"/> Deltoid <input type="checkbox"/> Thigh <input type="checkbox"/> Buttock <input type="checkbox"/> Other (<i>specify</i>)						
Person who administered: <input type="checkbox"/> Doctor <input type="checkbox"/> Nurse <input type="checkbox"/> PHI <input type="checkbox"/> PHM <input type="checkbox"/> Other (<i>specify</i>)						
Place of administration/reaction: <input type="checkbox"/> Hospital <input type="checkbox"/> MOH <input type="checkbox"/> Clinic <input type="checkbox"/> Private Hospital <input type="checkbox"/> GP <input type="checkbox"/> Other(<i>specify</i>)						

Part 3: Management		
Was Adrenaline administered? <input type="checkbox"/> Yes <input type="checkbox"/> No		
If 'Yes', Route : <input type="checkbox"/> IM <input type="checkbox"/> SC <input type="checkbox"/> IV <input type="checkbox"/> Other (<i>specify</i>) Dose:.....ml		
Place: <input type="checkbox"/> Clinic <input type="checkbox"/> MOH <input type="checkbox"/> Hospital <input type="checkbox"/> Other (<i>specify</i>) Time (of 1 st dose):.....am/pm		
Person who administered adrenaline: <input type="checkbox"/> Doctor <input type="checkbox"/> Sister/Nurse <input type="checkbox"/> PHI/PHM <input type="checkbox"/> Other		
Was a repeat dose of adrenaline given? <input type="checkbox"/> Yes <input type="checkbox"/> No	If 'Yes', describe (<i>including the time</i>)	
What other medicines were administered? <input type="checkbox"/> Yes <input type="checkbox"/> No	If 'Yes', describe (<i>including the time</i>)	
Any other details concerning medicines/management (<i>including CPR</i>)?		
Investigation	Blood taken for mast cell Tryptase: <input type="checkbox"/> Yes <input type="checkbox"/> No If 'Yes' specify the time interval after event: <i>(Note: Serum Tryptase levels peak 60-90 min after the onset of anaphylaxis and persist to 6 h. Therefore It is recommended that blood should be taken between 1 and 2 h after the initiation of symptoms.)</i>	
Part 4: Outcome		
Onset of first symptom: Date (dd/mm/yy) Time: am/pm		
Outcome: <input type="checkbox"/> Full recovery <input type="checkbox"/> Not fully recovered <input type="checkbox"/> Recovered with sequelae <input type="checkbox"/> Death		
Specify details:		
Time at outcome (recovery/death) Date (dd/mm/yy) Time: am/pm <input type="checkbox"/> Unknown		
Highest impact of Adverse drug event/Adverse Event Following Immunization:		
<input type="checkbox"/> Did not interfere with daily activities <input type="checkbox"/> Interfered, but did not prevent daily activities <input type="checkbox"/> 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.

SLMA Guidelines and Information on Vaccines - Fifth edition 2014

First published in 2001 the SLMA Guidelines and Information on Vaccines filled a vacuum that cannot be filled easily in Sri Lanka. It gained instant popularity from the first publication. The book gained wider acceptance as the reference standard for almost all vaccine related questions in day to day practice for general practitioners, specialists in the field as well as academia. I carried a copy of the pocket guide all the time during my practice for the last 14 years.

The fifth edition published in 2014 by the same group of experts as in the fourth edition is a highly commendable achievement. The new edition gives a lot of practical information to all the practitioners at the office and it takes away the need to browse the internet.

The latest edition has added two more chapters; one on Immunological basis for vaccination and more importantly immunization in the elderly. The chapter on immunological basis of vaccination takes us through the old theories of immunology and scientific basis for vaccination. The science has discovered fine details about how T cells, B cells, cytokines interact with microbes and antigens in producing immunological reactions. This chapter gives new information in these areas for busy practitioners to read at leisure while working in the office set up. It also gives us different approaches to vaccine production based on this advanced knowledge. Readers are fully informed about the trajectories of the vaccine industry in the future.

It is well known that developed countries recommend vaccination of their elderly populations with co morbidities against certain vaccine preventable diseases. However this is not the routine practice in Sri Lanka. In those countries the mortality and morbidity in elderly due to these infectious disease have come down. The life expectancy has gone up to eighties in these countries and one contributory factor is vaccination against influenza and pneumococcus with polysaccharide vaccine. It is well known that diabetics benefit with these vaccinations after 60 years of age. Even the otherwise healthy elderly populations do get benefits with this approach. It does reduce the long term hospitalization costs of this category of population. This chapter is an eye opener and I believe it will promote a dialogue on the subject.

The chapter on surveillance and prevention of Adverse Events Following Immunization (AEFI) had been modified and renamed as Adverse Events Following Immunization. It has a better approach to describe the problem and explains the detail surveillance system. The need for post exposure passive immunization for protection against specific diseases in the relevant chapters with minimal repetition is encountered. Many other chapters have been revised with new information. Current status of the meningococcal vaccine especially on vaccination against type B antigen and vaccine derived polio and early diagnosis of HIV with DNA-PCR are examples. Despite these updates, it retains the same size to be a pocket guide or an office guide.

SLMA Committee on Communicable Diseases and Dr. Lucian Jayasuriya who spearheads this activity should be highly commended for the job well done.

Amarasena S. SLMA Guidelines and Information on Vaccines. *Ceylon Medical Journal* 2016; **60**(4):166

Published by the Sri Lanka Medical Association,
6, Wijerama Mawatha, Colombo 7, Sri Lanka

The preparation and printing of this book is sponsored by
GlaxoSmithKline Pharmaceuticals, Sri Lanka, as a contribution to
medical education.

ISBN-978-955-9386-41-4

