

Immunization Handbook

Third Edition

**National Expanded
Programme on
Immunization,
Sri Lanka**

**Epidemiology Unit
Ministry of Health
Sri Lanka
2012**



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Funded by the UNICEF

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FOREWORD

Sri Lanka's national immunization programme is frequently quoted as one of the strongest performers, not only in the region, but also in the world. The National EPI programme has an excellent record, with extremely low incidence of EPI diseases and high coverage of all EPI vaccines.

The provision of routine immunization services in Sri Lanka constitutes a major preventive health activity of the Ministry of Health. The first manual for Medical Officers on technical and implementation information on the Expanded Programme on Immunization was published by the Epidemiology Unit of the Ministry of Health in 1979 with the assistance of UNICEF and WHO. The updated 2nd edition of the Immunization Handbook was published in 2002 with the assistance of WHO.

As the epidemiological pattern of the EPI diseases changed over the years and more cost effective vaccines are available, the Ministry of Health revised the immunization schedule on a few occasions since 2002. Objectives of the EPI programme were also changed accordingly as coverage of immunization has improved. Hence improvement of quality of services provided and changing of target age groups were considered.

As the immunization schedule and the objectives of the immunization programme changed, Epidemiology Unit of the Ministry of Health decided to update the Immunization Handbook accordingly. I am pleased with this new edition of the Immunization Handbook, published by the Epidemiology Unit and hope this edition, will help health professionals to provide quality immunization services.

Producing such a publication was possible through the dedication and voluntary time commitment on the part of those involved. I would like to extend my sincere thanks to all the contributors for completing this very important and timely task.

Appreciation is extended to UNICEF for providing necessary funds for its publication.



Dr U. Ajith Mendis
Director General of Health Services,
Ministry of Health
Sri Lanka

June 2012.

PREFACE

Immunization is one of the most successful and cost-effective public health interventions in the constant struggle of the human being against the diseases that affect its well-being.

The National EPI programme has an excellent record, with extremely low incidence of EPI diseases and high coverage of all EPI vaccines. However, unless the country pays attention to key issues of programme quality it could lose the advantages it has gained in disease control over the last 30 years.

Due to the rapidly expanding environment in the immunization field, some information published in the previous edition of the Immunization handbook is already outdated. This continues to be a challenge for the National EPI as more new vaccines are approved for use, new vaccine combinations are developed and additional data are available on the immunogenicity and efficacy of vaccines.

The objective of the Immunization Handbook 2012 is to provide updated clinical guidelines for health professionals in Sri Lanka on the safest and most effective use of vaccines in their practice. This new Immunization Handbook provides information on vaccine preventable diseases, the vaccines available, and the updated National Immunization Schedule, as well as practical advice and strategies for health professionals immunizing children and adults.

These guidelines are based on the best available scientific evidence at the time of writing, from published and unpublished literature. The guidelines will be reviewed periodically when new evidence becomes available.

All chapters have been updated and revised since the 2002 edition. In addition , 10 new chapters for Human Papillomavirus, live Japanese Encephalitis, Rabies, Typhoid , Influenza, Varicella, Hepatitis A, Yellow Fever, Cholera and rotavirus vaccines are included in the new edition.

I would like to thank all the authors who updated the handbook - and all those who acted as peer reviewers. I am grateful to Dr Samitha Ginige consultant Epidemiologist for his untiring efforts as the editor in making this manual a reality. Appreciation is extended to the UNICEF for their assistance in providing funds for this publication.

I trust this edition, like its previous editions, will prove a valuable resource for health professionals.

Dr Paba Palihawadana
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Ministry of Health
Sri Lanka.

June 2012

ABBREVIATIONS

AD syringe	auto-disable syringe
AEFI	adverse events following immunization
AFP	acute flaccid paralysis
AIDS	acquired immunodeficiency syndrome
ARV	anti-rabies vaccine
aTd	adult diphtheria and tetanus toxoid vaccine
BCG	Bacillus Calmette-Guérin vaccine
BP	blood pressure
CHDR	child health development record
CFR	case fatality rate
CCID50	cell culture infective dose 50
CRS	congenital rubella syndrome
CSF	cerebrospinal fluid
DNA	deoxyribonucleic acid
DTP	diphtheria, tetanus and pertussis vaccine
DT	diphtheria and tetanus vaccine
DTwP	diphtheria, tetanus and whole cell pertussis vaccine
DTaP	diphtheria, tetanus and acellular pertussis vaccine
DTaP-HepB	diphtheria, tetanus and acellular pertussis and hepatitis B vaccine
DTwP/Hib	diphtheria, tetanus, whole cell pertussis and <i>Haemophilus influenzae</i> type b vaccine
DTwP-HepB-Hib	diphtheria, tetanus and whole cell pertussis, hepatitis B and <i>Haemophilus influenzae</i> type b vaccine
DTaP-HepB-IPV -Hib	diphtheria, tetanus, acellular pertussis , hepatitis B and inactivated polio vaccine
dTpa	Reduced antigen diphtheria, tetanus and acellular pertussis vaccine
ELISA	enzyme linked immunosorbent assay

EPI	Expanded Programme on Immunization
ERIG	equine rabies immunoglobulin
GBS	Guillain-Barré Syndrome
HAV	hepatitis A virus
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
Hep B	hepatitis B
HBIG	hepatitis B immunoglobulin
HBsAg	hepatitis B surface antigen
HDC	human diploid cell
HDCV	human diploid cell vaccine (for rabies)
HHE	hypotonic, hyporesponsive episode
Hib	<i>Haemophilus influenzae</i> type b
HIV	human immunodeficiency virus
HPV	human papilloma virus
HRIG	human rabies immunoglobulin
HTIG	human tetanus immunoglobulin
ICNO	Infection Control Nursing Officer
ID	Intradermal
IG	immunoglobulin
IgA	immunoglobulin A
ILI	Influenza Like Illness
IM	intramuscular
IPD	Invasive pneumococcal disease
IPV	injectable polio vaccine

IU	international units
JE	Japanese encephalitis
LJEV	live JE vaccine
mIU	milli international units
mL	millilitre
MMR	measles, mumps and rubella vaccine
MNT	maternal and neonatal tetanus
MOH	Medical Officer of Health
MR	Measles and rubella vaccine
MRI	Medical Research Institute
MVHRV	Monovalent Human Rotavirus Vaccine
NNT	Neo-natal Tetanus
NIDs	National Immunization Days
OCV	oral cholera vaccine
OPD	Out Patient's Department
OPV	oral polio vaccine
PCEC	purified chick embryo cell vaccine (for rabies)
PCV	pneumococcal conjugate vaccine
PHI	Public Health Inspector
PVBHRV	Pentavalent Bovine Human Reassortant Vaccines
PET	post exposure treatment (for rabies)
PVRV	purified vero cell rabies vaccine

RDHS	Regional Director of health services
RE	Regional Epidemiologist
RIG	rabies immunoglobulin
RMSD	Regional Medical Supplies Division
RNA	ribonucleic acid
SC	subcutaneous
SMI	School Medical Inspection
TB	tuberculosis
TCV	tissue culture vaccine
TIG	tetanus immunoglobulin
TOPV	Trivalent Oral Polio Vaccine
TT	tetanus toxoid
UNICEF	United Nations Childrens Fund
VAPP	vaccination associated paralytic poliomyelitis
VLPs	virus-like particles
VPD	Vaccine Preventable Disease
VVM	Vaccine Vial Monitor
WER	Weekly Epidemiological Report
WHO	World Health Organization
WRCD	Weekly Return of Communicable Diseases

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IgA	immunoglobulin A
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IPD	Invasive pneumococcal disease
IPV	injectable polio vaccine

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VLPs	virus-like particles
VPD	Vaccine Preventable Disease
VVM	Vaccine Vial Monitor
WER	Weekly Epidemiological Report
WHO	World Health Organization
WRCD	Weekly Return of Communicable Diseases

PRINCIPLES OF VACCINATION

Introduction

Vaccines

“With the exception of safe water, no other modality, not even antibiotics, has had such a major effect on mortality reduction...” (Plotkin)

Immunization is the process whereby a person is made immune or resistant to an infection, typically by the administration of a vaccine. Vaccines are highly regulated, complex biologic products designed to induce a protective immune response both effectively and safely.

Vaccination is the administration of a vaccine to stimulate a protective immune response that will prevent disease in the vaccinated person if contact with the corresponding infectious agent occurs subsequently. Thus vaccination, if successful, results in immunization: the vaccinated person has been immunized. In practice, the terms “vaccination” and “immunization” are often used interchangeably. Immunization is a proven tool for controlling and eliminating and eradicating life-threatening infectious diseases and is estimated to avert over 2 million deaths each year. It is considered as one of the most cost-effective health investments.

The word “vaccine” comes from the Latin word *vaccinus*, which means “pertaining to cows.” What do cows have to do with vaccines? The first vaccine was based on the relatively mild cowpox virus, which infected cows as well as people. This vaccine protected people against the related, but much more dangerous, smallpox virus. More than 200 years ago, Edward Jenner, a country physician practicing in England, noticed that milkmaids rarely suffered from smallpox. The milkmaids often did get cowpox, a related but far less serious disease, and they never became ill with smallpox. In an experiment that laid the foundation for modern vaccines, Jenner took a few drops of fluid from a skin sore of a woman who had cowpox and injected the fluid into the arm of a healthy young boy who had never had cowpox or smallpox. Six weeks later, Jenner injected the boy with fluid from a smallpox sore, but the boy remained free of smallpox. Dr. Jenner had discovered one of the fundamental principles of immunization. He had used a relatively harmless foreign substance to evoke an immune response that protected someone from an infectious disease. His discovery eased the suffering of people around the world and eventually led to eradication of small pox, a disease that killed a million people, mostly children. By the beginning of the 20th century, vaccines were in use for diseases that had nothing to do with cows [rabies, diphtheria, typhoid fever, and plague] but the name stuck.

Today, there are many vaccines available to prevent nearly 30 communicable diseases. Indeed, vaccination has become one of the most important preventive health care interventions of all time. Every year millions of children and adults receive vaccinations that protect them from a host of infectious diseases; meanwhile, the arsenal of vaccines is growing rapidly through bio-medical research.

Today all countries have national immunization programmes, and in most developing countries, children under five years are immunized with the standard WHO recommended vaccines that protect against eight diseases – tuberculosis, diphtheria, tetanus (including neonatal tetanus through immunization of mothers), pertussis, polio, measles, hepatitis B, and Hib. These vaccines are preventing more than 2.5 million child deaths globally each year.

A large number of new vaccine products are currently in the pipeline and are expected to become available in coming years. According to recent unpublished data, more than 80 candidate vaccines are in the late stages of clinical testing. About 30 of these candidate vaccines aim to protect against major diseases for which no licensed vaccines exist, such as malaria. If successful, malaria vaccine would be the first vaccine against a parasite that causes disease in humans.

About 50 candidate vaccines target diseases for which vaccines already exist, such as pneumococcal disease, Japanese encephalitis, hepatitis A, and cholera: however, these candidates hold the promise of being more effective, more easily administered, and more affordable than the existing vaccines.

Immunization

Immunity

Immunity is the ability of the human body to tolerate the presence of material indigenous to the body (“self”), and to eliminate foreign (“non-self”) material. This discriminatory ability provides protection from infectious disease, since most microbes are identified as foreign by the immune system. Immunity to a microbe is usually indicated by the presence of antibody to that organism. Immunity is generally very specific to a single organism or group of closely related organisms. There are two basic mechanisms for acquiring immunity - active and passive.

Active Immunity

Active immunity is stimulation of the immune system to produce antigen-specific humoral (antibody) and cellular immunity. Unlike passive immunity, which is temporary, active immunity usually lasts for many years, often for a lifetime. One way to acquire active immunity is to survive infection with the disease-causing form of the organism. In general, once persons recover from infectious diseases, they will have lifelong immunity to that disease. Following exposure of the immune system to an antigen, certain cells (memory B cells) continue to circulate in the blood (and also reside in the bone marrow) for many years. Upon re-exposure to the same antigen, these memory cells begin to replicate and produce antibody very rapidly to re-establish protection.

Another way to produce active immunity is by vaccination. Vaccines interact with the immune system and often produce an immune response similar to that produced by the natural infection, but they do not subject the recipient to the

disease and its potential complications. Many vaccines also produce immunologic memory similar to that acquired by having the natural disease.

Many factors may influence the immune response to vaccination. These include the presence of maternal antibody, nature and dose of antigen, route of administration, and the presence of an adjuvant (e.g. aluminum-containing material) added to improve the immunogenicity of the vaccine. Host factors such as age, nutritional factors, genetics, and coexisting disease, may also affect the response.

Passive Immunity

Passive immunity is the transfer of antibody produced by one human or other animal to another. Passive immunity provides protection against some infections, but this protection is temporary. The antibodies will degrade over the time. The most common form of passive immunity is that which an infant receives from its mother. Antibodies are transported across the placenta during the last 1–2 months of pregnancy. As a result, a full-term infant will have the same antibodies as its mother. These antibodies will protect the infant from certain diseases for up to one year. This type of protection is better against some diseases (e.g. measles, rubella, tetanus) than others (e.g. polio, pertussis).

How does immunization work

There are many types of vaccines, but they all work in the same general way, by preparing the immune system to attack the infection. Basically vaccine contains components that are more or less similar to the infecting organism, and so the immune system responds as it would to an infection with that organism. The most important consequence of successful vaccination is that long lived memory lymphocytes are produced. These respond more quickly and in a more co-ordinated way to subsequent infections so that the infectious microbe is destroyed more quickly. Protection is not always complete, infection may not be prevented but the severity of the illness is usually reduced.

The first exposure to a vaccine stimulates the immune response (known as priming). The immune system takes time to respond to the antigen by producing antibodies and immune cells. Initially immunoglobulin M (IgM) antibody is produced but this is in small amounts and does not bind very strongly to the antigen. After a few days the immune response begins to make immunoglobulin G (IgG) antibody, which is more specific to the microbe. Priming may need more than one dose.

Subsequent administration of the same vaccine stimulates the secondary response. The secondary response is much faster than the primary response and produces predominantly IgG rather than IgM. The aim is to generate enough immune cells

and antibodies, specific to the infectious microbe, to provide long lasting protection against the disease.

Classification of vaccines

There are two basic types of vaccines: live attenuated and inactivated. The characteristics of live and inactivated vaccines are different, and these characteristics determine how the vaccine is used.

Live attenuated vaccines

Live vaccines are derived from “wild,” or disease-causing, virus or bacteria. These wild viruses or bacteria are attenuated, or weakened, in a laboratory, usually by repeated culturing. The resulting vaccine organism retains the ability to replicate (grow) in the vaccinated person and produce immunity, but usually does not cause illness. The immune response to a live attenuated vaccine is virtually identical to that produced by a natural infection.

For live vaccines, the first dose usually provides protection. An additional dose is given to ensure seroconversion. For instance, 95% to 98% of recipients will respond to a single dose of measles vaccine. The second dose is given to assure that nearly 100% of persons are immune (*i.e.*, the second dose is “insurance”). Immunity following live vaccines is long-lasting, and booster doses are not necessary, with the exception of oral polio vaccine, which requires multiple doses.

Live attenuated vaccines may cause severe or fatal reactions as a result of uncontrolled replication (growth) of the vaccine virus. This only occurs in persons with immunodeficiency (e.g. from leukemia, treatment with certain drugs, or HIV infection).

Live attenuated vaccines are labile, and can be damaged or destroyed by heat and light. They must be handled and stored carefully.

Currently available live attenuated viral vaccines include measles, mumps, rubella, varicella, yellow fever, oral polio and influenza (intranasal). Live attenuated bacterial vaccines include BCG and oral typhoid vaccine.

Inactivated vaccines

Inactivated vaccines are produced by growing viruses or bacteria in culture media and then inactivating them with heat or chemicals (usually formalin). Because they are not alive, they cannot grow in a vaccinated individual and therefore cannot cause the disease, even in an immunodeficient person. Unlike live antigens, inactivated antigens are usually not affected by circulating antibody.

Whole cell, toxoid, subunit, recombinant and conjugate vaccines all come under the category of inactivated vaccines, in that they are non-infectious but retain the ability to stimulate the immune system.

Whole cell vaccines

Growing whole bacteria or viruses (e. g. inactivated influenza or inactivated polio vaccine) in culture media, then treating them with heat and/or chemicals, produces an inactivated, non-viable vaccine.

Toxoid vaccines

In some bacterial infections (e.g. diphtheria, tetanus) the clinical manifestations of disease are caused not by the bacteria themselves but by the toxins they secrete. Toxoid vaccines are produced by purifying the toxin and altering it chemically (usually with formaldehyde). While no longer toxic, the toxoid is still capable of inducing a specific immune response protective against the effects of the toxin.

Subunit vaccines

The whole organism is grown in culture media and then the organism is further treated to purify only those components to be included in the vaccine (e.g. acellular pertussis and the meningococcal B vaccine).

Recombinant vaccines

For example, the hepatitis B vaccine is made by inserting a segment of the hepatitis B virus gene into a yeast cell. The modified yeast cell produces large amounts of hepatitis B surface antigen, which is purified and harvested and used to produce the vaccine. The recombinant hepatitis B vaccine is identical to the natural hepatitis B surface antigen, but does not contain virus DNA, and is therefore unable to produce infection.

Conjugated vaccines

Children under two years of age do not respond well to antigens such as polysaccharides, which produce antibodies via a T-cell independent mechanism. If these polysaccharide antigens are chemically linked (conjugated) to a protein that T-cells recognize, then these conjugate vaccines can elicit strong immune responses and immune memory in young children.

Inactivated vaccines always require multiple doses. In general, the first dose does not produce protective immunity, but only “primes” the immune system. A protective immune response develops after subsequent multiple doses.

In contrast to live vaccines, in which the immune response closely resembles natural infection, the immune response to an inactivated vaccine is mostly humoral. Little or no cellular immunity results. Antibody titers against inactivated antigens diminish with time. As a result, some inactivated vaccines may require periodic supplemental doses to increase, or “boost,” antibody titres.

Currently available inactivated vaccines are limited to inactivated whole viral vaccines (influenza, polio, rabies, and hepatitis A), inactivated whole bacterial vaccines (pertussis, typhoid, cholera, and plague), “Fractional” vaccines include subunit, (influenza, acellular pertussis), recombinant (hepatitis B) and toxoids (diphtheria, tetanus).

Other components in vaccines - Excipients

Adjuvant

A substance added to a vaccine to enhance the immune response by degree and/or duration, making it possible to reduce the amount of immunogen per dose or the total number of doses needed to achieve immunity. The commonly used adjuvant are aluminum salts (aluminum hydroxide, aluminum phosphate or potassium aluminum sulfate), which primarily enhance the immune response to proteins. They have been shown to be safe over seven decades of use. Rarely, they may cause injection site reactions, including subcutaneous nodules, sterile abscess, granulomatous inflammation or contact hypersensitivity.

Preservatives

Chemicals (e.g. thimerosal, phenol, 2 phenoxy ethanol) are added to multidose, killed or subunit vaccines in order to prevent serious secondary infections as a result of bacterial or fungal contamination.

Additives

Substances other than those already mentioned may be added to vaccines for different purposes such as:

- ◆ to support the growth and purification of specific immunogens and/or the inactivation of toxins. These include antibiotics added to prevent contamination during viral cell culture; substances needed for the growth of viruses, such as egg or yeast proteins, glycerol, serum, amino acids and enzymes; and formaldehyde used to inactivate viruses and protein toxins. Most of these reagents are removed in subsequent manufacturing steps, but minute “trace” amounts may remain in the final product. The amounts present are only of consequence for individuals who are allergic to them.

- ◆ to confirm product quality or stability, compounds may be added to vaccines for a variety of manufacture-related issues: controlling acidity (pH); stabilizing immunogens through necessary steps in the manufacturing process, such as freeze drying; and preventing immunogens from adhering to the sides of glass vials with a resultant loss in immunogenicity. Examples of such additives include potassium or sodium salts, lactose, polysorbate 20 or 80, human serum albumin and a variety of animal proteins, such as gelatin and bovine serum albumin.

Timing and Spacing of Vaccines

Optimal response to a vaccine depends on multiple factors, including the nature of the vaccine and the age and immune status of the recipient. Recommendations for the age at which vaccines are administered are influenced by age-specific risks for disease, age-specific risks for complications, ability of persons of a certain age to respond to the vaccine, and potential interference with the immune response by passively transferred maternal antibody.

Certain products, including inactivated vaccines, toxoids, recombinant subunit, and polysaccharide conjugate vaccines, require administration of 2 or more doses for development of an adequate and persisting antibody response. Tetanus and diphtheria toxoids require periodic reinforcement or booster doses to maintain protective antibody concentrations.

The simultaneous administration of the most widely used live and inactivated vaccines does not result in decreased antibody responses or increased rates of adverse reaction. Simultaneous administration of all vaccines for which a child is eligible can be very important in childhood vaccination programmes because it increases the probability that a child will be fully immunized at the appropriate age.

Live parenteral (injected) vaccines (measles, rubella, MMR, varicella, and yellow fever) that are not administered simultaneously should be separated by at least 4 weeks. This precaution is intended to reduce or eliminate interference from the vaccine given first on the vaccine given later.

Live vaccines administered by a nonparenteral route (OPV, oral typhoid, live attenuated influenza) are not believed to interfere with each other if not given simultaneously. These vaccines may be given at any time before or after each other.

All other combinations of two inactivated vaccines or live and inactivated vaccines may be given at any time before or after each other.

Most vaccines in the childhood immunization schedule require two or more doses for stimulation of an adequate and persisting antibody response. Studies have

demonstrated that recommended ages and intervals between doses of the same antigen(s) provide optimal protection or have the best evidence of efficacy. Administering doses of a multidose vaccine at shorter than the recommended intervals may interfere with optimal antibody response and protection. Vaccine doses should not be administered at intervals less than the recommended minimal intervals or earlier than the minimal ages.

However, available data indicate that intervals between doses longer than those routinely recommended do not affect seroconversion rate or titre when the schedule was completed. Consequently, it is not necessary to restart the series or add doses of any vaccine due to an extended interval between doses.

Herd immunity

Herd immunity (or community immunity) describes a type of immunity that occurs when the vaccination of a portion of the population (or herd) provides protection to unprotected individuals. Herd immunity theory proposes that, in diseases passed from individual to individual, it is more difficult to maintain a chain of infection when large numbers of a population are immune. The higher the proportion of individuals who are immune, the lower the likelihood that a susceptible person will come into contact with an infectious agent. From both theoretical and practical perspectives, disease usually disappears before immunization levels reach 100%, as has been seen with smallpox and poliomyelitis.

The proportion of immune individuals in a population above which a disease may no longer persist is the *herd immunity threshold*. Its value varies with the virulence of the disease, the efficacy of the vaccine, and the contact parameter for the population.

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Introduction

Vaccination is one of the most effective and safe health interventions provided the vaccines are of known good quality, appropriately stored and handled, and given safely.

A safe injection is defined by the World Health Organization as an injection that:

- ◆ Does not harm the **recipient**,
- ◆ Does not expose the **health care worker** to any avoidable risks,
- ◆ Does not result in waste that is dangerous to **the community**.

Unsafe injections can result in transmission of a wide variety of pathogens, including viruses, bacteria, fungi and parasites. They can also cause non-infectious adverse events such as abscesses and toxic reactions. In addition, wrong selection of recipients and vaccines too can cause harm to the recipients.

This chapter explains the standard set of immunization procedures, which health workers should follow during the implementation of immunization programme activities.

Educate vaccine recipients in general terms about immunization.

Health workers should educate people in a culturally sensitive way, preferably in their own language, about the importance of vaccination, the diseases that vaccines prevent, the recommended immunization schedules, the need to receive vaccines at recommended ages and the importance of bringing their or their child's vaccination record to every health care visit. Parents and adult recipients should be encouraged to take the responsibility for ensuring that they or their child complete the full series. Providers should answer all questions recipients may have and provide appropriate educational materials at suitable reading levels, preferably in the patient's preferred language. Providers should familiarize themselves with information on immunization provided by the health department as well as by other sources.

As long as the diseases that vaccines prevent are rarely seen by the general public today, vaccine safety concerns will continue to have a high profile. Careful and timely counselling can help people to weigh the benefits of vaccines and the risks of the disease that the vaccine will prevent, as well as the small risk posed by the vaccine itself. By providing vaccines in a climate of appropriate informed consent, including discussion of commonly held misconceptions, health care providers can help ensure that immunization will maintain its status as one of the most effective preventive measures in the history of medicine.

Consent

Prior to vaccination, parents/guardian should be given adequate information including the type of vaccine, disease/s protected, number of doses needed for protection, contraindications, possible adverse events and what to do if adverse events occur to make an informed decision.

Consent in special programmes/mass vaccination/school programmes

In large scale school programmes a informed consent from the parent or guardian should be obtained before administration of vaccine. If a child's health status or suitability for vaccination cannot be established, vaccination should be postponed.

Pre-vaccination screening

Before vaccination, the Medical Officer, RMO, the Nurse/Public health nurse, the Public Health Inspector or the Public Health Midwife should make sure that the individual to be vaccinated does not have a contraindication to the indicated vaccine or a condition which could increase the risk of a severe reaction. One way to do this is to routinely inquire about the presence of such conditions.

A reliable decision to vaccinate an adult or a child can be based exclusively on the information elicited from the recipient or from the child's parent, and on the provider's observations and judgment about the health of the potential vaccine recipient at the time. At a minimum, this includes questioning the recipient or the child's parent about:

- ◆ the recipient's current state of health,
- ◆ potential contraindications,
- ◆ reactions to previous vaccinations.

The following information is needed to assess the fitness of a person for vaccination. Inform the parents, that the conditions listed below do not necessarily mean that their child cannot be vaccinated today. But they should inform the provider if any of the following conditions are present:

Vaccine recipient:

- ◆ is unwell today,
- ◆ has had a reaction to previous vaccinations or any other drugs,
- ◆ has had any allergies to vaccines or vaccine components (e.g. neomycin),
- ◆ is having treatment which lowers immunity (e.g. steroids such as cortisone and prednisolone, radiotherapy, or chemotherapy),
- ◆ has a disease which lowers immunity (e.g. leukaemia, cancer,HIV),

- ◆ has had a vaccine containing live viruses within the last month (e.g. measles, poliomyelitis, yellow fever or rubella vaccines), or an injection of immunoglobulin or a blood transfusion within the last three months,
- ◆ has a chronic illness,
- ◆ has a disease of the brain or the spinal cord.

False contraindications to vaccination

Conditions listed below are not contraindications to vaccination. Children with these conditions should be vaccinated with all recommended vaccines:

- ◆ mild illness without fever ($T < 38.5^{\circ}\text{C}$),
- ◆ family history of any adverse events following immunization,
- ◆ past history of convulsions,
- ◆ treatment with antibiotics,
- ◆ treatment with locally acting (inhaled or low-dose topical) steroids,
- ◆ asthma, eczema, atopy,
- ◆ previous pertussis-like illness, measles, rubella, mumps or meningococcal disease,
- ◆ prematurity (vaccination should not be postponed),
- ◆ history of neonatal jaundice,
- ◆ low weight in an otherwise healthy child,
- ◆ any stable neurological conditions including cerebral palsy and Down syndrome,
- ◆ contact with an infectious disease,
- ◆ child's mother is pregnant,
- ◆ child to be vaccinated is being breastfed,
- ◆ poorly documented vaccination history.

Standard vaccination procedure

Before administering vaccines, the following procedures should be followed:

- ◆ provide details to parents on benefits and possible risks of vaccination to support informed decision making ,
- ◆ check whether preparations have been made to respond to possible emergencies,
- ◆ read the product information,
- ◆ check whether there are any contraindications to vaccination from the pre-vaccination assessment,

- ◆ adverse events following previous immunizations (AEFI). If present, record it on the CHDR and Clinic AEFI Register,
- ◆ check the identity of the recipient,
- ◆ check the identity of the vaccine to be administered,
- ◆ ensure that cold chain of the vaccines is maintained,
- ◆ check the vaccine to be administered for obvious signs of deterioration (check expiry date and note any particular matter or colour change that may indicate damage to the vaccine),
- ◆ ensure that the correct vaccines are being administered according to the schedule,
- ◆ check the needle and syringe (AD Syringe) to make sure it is sterile,
- ◆ administer the vaccine, using the correct technique (see details below on needle selection, needle angle, Injection location, and position of the subject).

Storage

Vaccines that are not stored and transported correctly will lose potency. Vaccines must be handled and stored as recommended in the manufacturers' package inserts. The temperatures at which vaccines are transported and stored should be monitored according to national guidelines. Vaccines must not be administered after their expiry date, and vaccines that have undergone a breach in the cold chain should not be used without appropriate consultation.

The general rule for most vaccines is that they should be refrigerated at +2°C to +8°C and NOT FROZEN. Vaccines such as DTP, DT, aTd, TT Hib, hepatitis B and Hib containing liquid Pentavalent vaccines are inactivated by freezing. Detailed guidelines on correct storage and transport are given under Chapter VI; i.e. Maintenance of cold chain of EPI vaccines.

Open vial policy

After considering all the relevant factors the National Advisory Committee on Communicable Diseases decided to introduce the open vial policy in Sri Lanka from year 2005. Therefore open multi dose vials of all liquid vaccines (OPV, DPT, TT, DT, aTd, Hep B, and DTP-Hib-Hep B) could be reused in subsequent sessions.

After using one or more doses of vaccines from these multi dose vaccine vials during an immunization session, remaining doses could be reused in subsequent immunization sessions within 4 weeks of their opening. However all the following conditions must be fulfilled before reusing the vaccines so that the potency of vaccines and the safety of their administration could be guaranteed.

- ◆ The expiry date has not been reached
- ◆ The vaccines should be stored and transported under appropriate cold chain conditions. All conditions which apply for the maintenance of cold chain for the unopened vials should apply for the opened vials as well.
- ◆ The opened vials that are returned to the MOH office should be kept in a separate container when they are stored in the refrigerator (+2°C to +8°C) after the clinic session.
- ◆ In every clinic session previously opened vaccine vials should be used first, before opening any new vaccine vials.

Approximate number of doses in the opened vials should also be included in the vaccine movement register before sending vaccines to the clinics and after receiving from the clinic.

Vaccine inspection:

The vaccine identification label and expiry date on the vaccine vial or package should be checked by the vaccine provider before administration. Vaccines should not be used beyond their expiry date. If only the month and year are provided for the expiry date, the vaccine can be used to the end of that month. Before use, vaccine vials should be inspected for any irregularities, e.g., particulate matter, damage or contamination, any colour change.

Reconstitution

Freeze-dried vaccines such as BCG, Measles, Measles-Mumps -Rubella , live JE and Rubella which are used in the National EPI programme in Sri Lanka should be reconstituted with the correct diluent only (the diluent supplied with the specific vaccine) using a sterile syringe and needle. After six hours or at the end of a session, whichever comes first, reconstituted vaccines must be discarded. With gentle shaking the dried cake/powder is easily dissolved. They should be kept under proper cold chain conditions and protected from heat and sunlight. Note that reconstituted vaccines deteriorates rapidly at room temperature. A sterile 21 gauge needle should be used for reconstitution and a separate 23 gauge needle 25 mm in length should be used for administration of the vaccine. After reconstitution that needle should be removed from the vial. Same syringe should be used to withdraw and administer the vaccine.

Cleaning of skin

It is not necessary to disinfect the skin before and after administration of vaccines. However, the cleaning of the skin may be done by using dry or wet (with boiled cold water) swab. Do not use cotton balls stored wet in a multi-use container.

Route of administration

Majority of the EPI vaccines are given by deep intra-muscular or subcutaneous route. The two major exceptions are Oral Polio Vaccine (OPV), which is given by mouth and BCG, which is given by intra-dermal injection. In general, all aluminium salt containing adsorbed vaccines should be administered intra-muscularly.

Injection techniques

◆ Intra muscular injections

The needle should be inserted at an angle of 60 to 90 degrees into the vastus lateralis or deltoid muscle. For the vastus lateralis, the needle should point towards the knee and for the deltoid, the needle should point towards the shoulder. For intramuscular injections (IM) a 23-25 gauge, 2.5 cm (1”) long needle is recommended.



Figure 1 : Intramuscular injection technique (IM)

◆ Subcutaneous injection technique

Subcutaneous injections (SC) are usually administered at a 45° angle to the skin. The standard needle for administering vaccines by SC injection is a 25 gauge needle, 1.6 cm (5/8”) in length.



Figure 2 : Subcutaneous injection technique

◆ Intradermal injection technique

For intradermal injection of BCG vaccine, a 26 or 27 gauge, 10 mm needle is recommended. The intradermal injection technique requires special training, and should be performed only by a trained provider.



Figure 3: Intradermal injection technique (IM)

Syringe selection

Preferably a sterile auto-disable (AD) syringe and needle should be used for each single immunization. In the absence of sterile AD syringe and a needle a sterile reusable syringe and needle could be used. All used needles and syringes should be discarded into a safety box.

Recommended injection sites

The choice of injection sites depends primarily upon the age of the individual being vaccinated. The anatomical sites recommended as routine injection sites are the anterolateral thigh and the deltoid muscle.

1. For IM injections:

IM injections are administered into the vastus lateralis muscle (anterolateral thigh) in infants < 1 year of age and the deltoid muscle if \geq 1 year of age. Appropriate site selection is important to avoid inadvertent injection into a blood vessel or injury to a nerve.

The buttock should not be used for active immunization, immunogenicity is lower to hepatitis B and rabies vaccines if given in the buttock, probably because of injection into adipose tissue where the vaccine is not well mobilized. The buttock is an acceptable site for administration of immunoglobulin when large volumes are administered.

Vaccines containing adjuvants are to be injected intramuscularly. If inadvertently injected subcutaneously or intradermally, increased inflammation, induration or granuloma formation may occur.

◆ The anterolateral thigh (vastus lateralis) site

- The infant's nappy must be undone to ensure the injection site is completely exposed and the anatomical markers easily identified.
- Position the leg so that the hip and knee are flexed and the vastus lateralis is relaxed (Figure 4).
- The upper anatomical marker is the midpoint between the anterior superior iliac spine and the pubic tubercle, and the lower marker is the upper part of the patella.
- Draw an imaginary line between the 2 markers down the front of the thigh. The correct site for IM vaccination is lateral to the midpoint of this line, in the outer (anterolateral) aspect (see Figure 4).
- Do not inject into the anterior aspect of the thigh where neurovascular structures can be damaged.



Figure 4: Thigh showing the recommended (vastus lateralis) injection site (X)

◆ **The deltoid site**

It is essential to expose the arm completely from the top of the shoulder to the elbow when locating the deltoid site. The injection site is halfway between the shoulder tip (acromion) and the muscle insertion at the middle of the humerus (deltoid tuberosity).



Figure 5 : Upper arm showing the recommended (deltoid) injection site (X)

2. Subcutaneous injection sites

Subcutaneous injections should be administered over the deltoid muscle.

After administering the vaccine, do the following:

- ◆ Give instructions, to the parent or guardian regarding what to do in the event of Common reactions or serious adverse reactions,
- ◆ Record the vaccination in the child health development record CHDR and in the clinic immunization register.

In situations where large groups of individuals are vaccinated, the detailed arrangements might vary from those recommended above, but the principles of hygiene, valid consent, and thorough pre immunization assessment must still be adhered to.

Recording of vaccination details

Each vaccination provider should record all relevant vaccination data on the child health development card or other immunization card. Parents and guardians should be encouraged to present the record every time their child is seen by a health professional. The following should be recorded:

- ◆ the date of vaccination,
- ◆ details of the vaccine given, including batch number,
- ◆ the name/signature of the person providing the vaccination,
- ◆ any severe or moderate adverse event,
- ◆ date the next vaccination is due.

The health staff conducting the immunization clinic (health unit, other clinics or hospital clinics) should enter the necessary information in the relevant clinic registers too, according to the instructions given by the Department of Health Services.

Adverse Events Following Immunization (AEFI)

Recipients of vaccine should remain under observation until they are seen to be in good health and not be experiencing an immediate adverse reaction. It is not possible to specify an exact length of time for post-vaccination observations but it is recommended that recipients should remain in the clinic/hospital for about 15 minutes. Parents or guardian should be provided with the necessary information before leaving the clinic on how to act if the child develops an adverse event following immunization.

Children who have had serious adverse events following vaccination may be subsequently vaccinated (in the event of absence of absolute contraindications) under close medical supervision at a MOH Office or in a hospital.

Anaphylaxis

The most serious immediate reaction to vaccination, though it is rare, is anaphylaxis. The incidence of anaphylaxis reactions vary with the type of vaccine. But the incidence of true anaphylaxis is only 1-3 cases per million vaccinations. Any member of the health staff carrying out vaccination must be able to distinguish between anaphylaxis, convulsions, fainting and attend to the initial management. [Refer to Chapter on Anaphylaxis]

Reporting of Adverse Events Following Immunization (AEFI)

Adverse events following immunization should be reported to the respective MOH. In the case of **very severe adverse events** the Epidemiology Unit should be informed promptly (telephone 0112681548 or fax 0112696583). The MOOH should investigate all the severe AEFIs. The Monthly Surveillance Report on AEFIs which is sent to the Epidemiology Unit should include all the AEFIs reported to the MOH during the given month.

Administration of two or more vaccines on the same day

Different antigens/vaccines could be given on the same day, if necessary. Inactivated vaccines and live attenuated virus vaccines, particularly those in the national EPI schedule (childhood schedule) can generally be given during the same visit. Vaccines that should be administered by injections should be given at different sites (e.g. DPT, MR, MMR and hepatitis B). More than one live attenuated virus vaccine may be given on the same day; but if only one is given, a second live attenuated vaccine should not be given within 4 weeks of the first vaccine because the response to the second vaccine may be diminished. In addition there is a specific interaction between some vaccines (e.g. yellow fever and cholera vaccines) and they should not be given within 4 weeks of each other.

Different vaccines should not be mixed in the same syringe unless it is clearly stated in the instructions of the manufacturer (given in the information schedule supplied by the vaccine supplier). Different vaccines given to a person on the same day should be injected at different sites using different syringes.

Safe injection practices

It is well known that giving injections using nonsterile procedures can cause abscesses and transmit life-threatening infectious diseases, including hepatitis B, hepatitis C and HIV.

Not only do unsafe injection practices pose a direct danger to the recipient and health worker, but improper disposal of used injection equipment presents a continued risk of infection and an environmental hazard to individuals and local communities. The safety of injections, including the proper disposal of used injection equipment, is therefore a concern for the entire healthcare sector. Health workers are supposed to follow the following basic steps while conducting immunization sessions.

- ◆ Use a new sterile AD syringe and needle for every injection and a new sterile syringe and needle each time a lyophilized vaccine is reconstituted.
- ◆ Discard an AD syringe that has touched any nonsterile surface (e.g. hands, environment surfaces) before injection or sterility is breached.
- ◆ Prepare the injection materials on a designated surface (table or tray) that is clean, and where blood and body fluid contamination is unlikely.
- ◆ Protect fingers with a small gauze pad before opening glass ampoules.
- ◆ For multi-dose vials, always pierce the septum with a sterile needle. Never leave a needle in place in the stopper of the vial.
- ◆ Never re-cap the AD syringe, but dispose of it immediately into the safety box after use.

Sources

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Public Health Agency of Canada, 2006. *Canadian Immunization Guide*, 7th ed. Ottawa, p.21 – 37.

World Health Organization, 1999. *Immunization Safety Surveillance Guidelines for Managers of Immunization Programmes on Reporting and Investigating Adverse Events Following Immunization*. Manila. WHO/WPRO/EPI/99.01.

Introduction

Introducing a small amount of smallpox virus by inhaling through the nose or by making a number of small pricks through the skin (variolation) to create resistance to the disease appears to have begun in the 10th or 11th century in Central Asia. The practice spread; in Asia and Africa, the method was nasal, while in Europe it involved skin punctures. Variolation was introduced into England in 1721. There, in 1798, Edward Jenner, having studied the success of variolation with cowpox — a mild illness — in protecting against smallpox, began to carry out inoculations against smallpox, the first systematic effort to control a disease through immunization.

For the last 200 years, the use of vaccines has continued to reduce the burden of many bacterial and viral diseases globally.

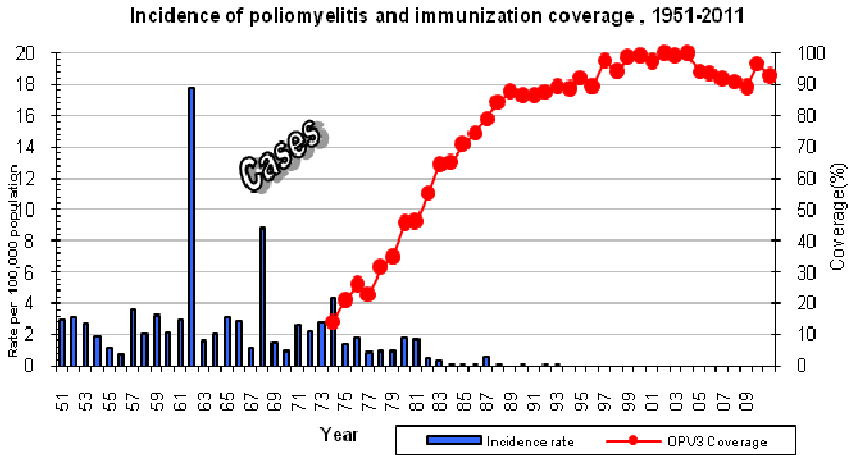
National immunization Programme in Sri Lanka is a major success story. According to the routine immunization coverage as well as periodical surveys conducted, virtually all eligible children and women throughout the country are receiving all their scheduled vaccine at the appropriate time.

Objectives of any immunization programme are to bring down the morbidity and mortality of vaccine preventable diseases. With the high levels of immunization coverage achieved, not surprisingly the target diseases have declined to low levels or are not being detected at all, in spite of acceptable surveillance. Both Polio and diphtheria cases have not been reported since 1993 and 1995 respectively. Poliovirus transmission has probably ceased, neonatal tetanus has reached elimination levels; pertussis is reported at very low levels. After the introduction of measles immunization to the EPI in 1984/85, 2nd dose of measles containing vaccine in 2003 and conduct of measles catchup immunization programmes in 2003 and 2005, the incidence of measles has gradually decreased and already reached elimination levels. It also seems probable that, with the outstanding success of introducing rubella vaccine, cases of the congenital rubella syndrome has already declined to near zero. In the same manner Hepatitis B and Hib diseases also will reach elimination levels in time to come.

Immunizing a child not only protects that child but also other children by increasing the general level of immunity in population and minimising the spread of infection.

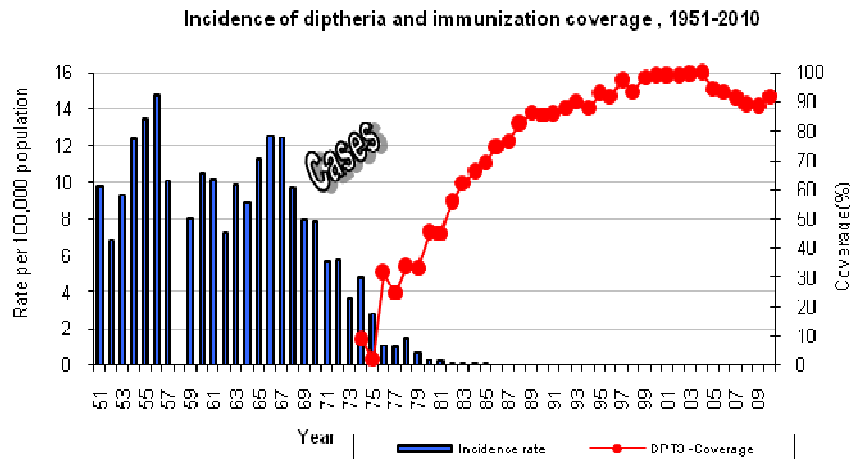
Figure 6: Disease incidence and immunization coverage, Sri Lanka, 1951 -2010

Incidence of Poliomyelitis and OPV3 coverage

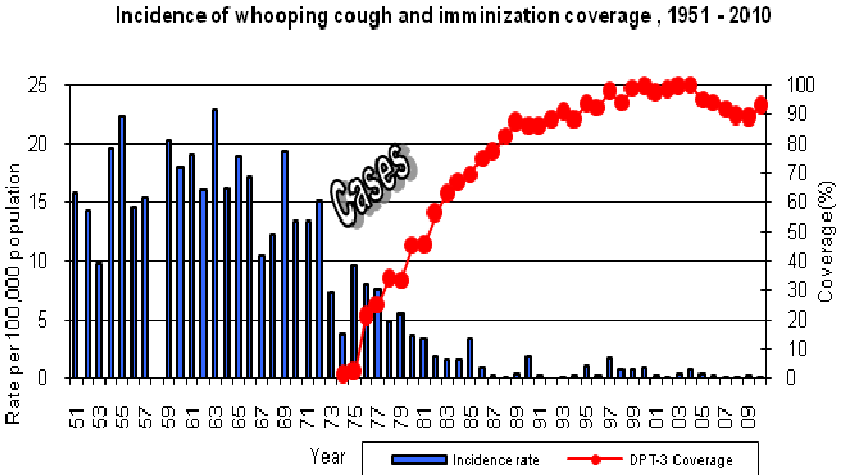


EPI

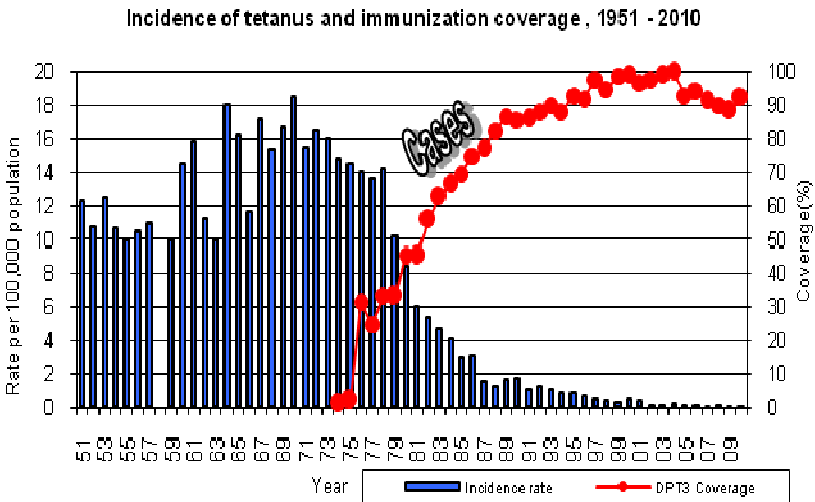
Incidence of Diphtheria and DPT 3 coverage



Incidence of Pertussis and DPT3 coverage

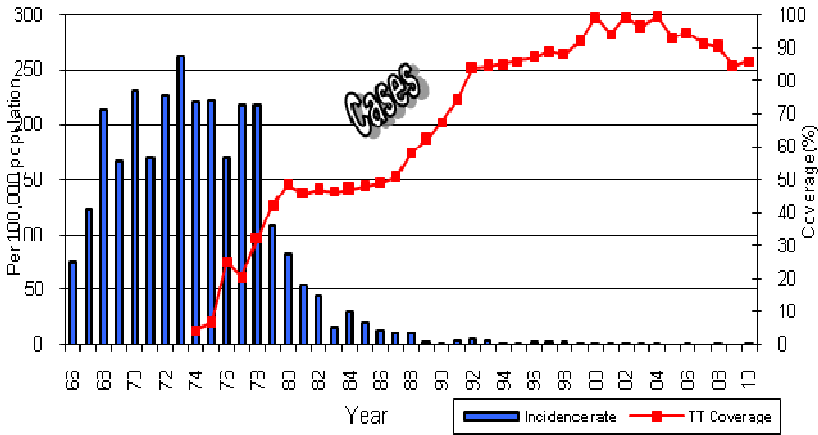


Incidence of Tetanus and DPT 3 coverage



Incidence of Neonatal tetanus and pregnant mothers' tetanus toxoid coverage

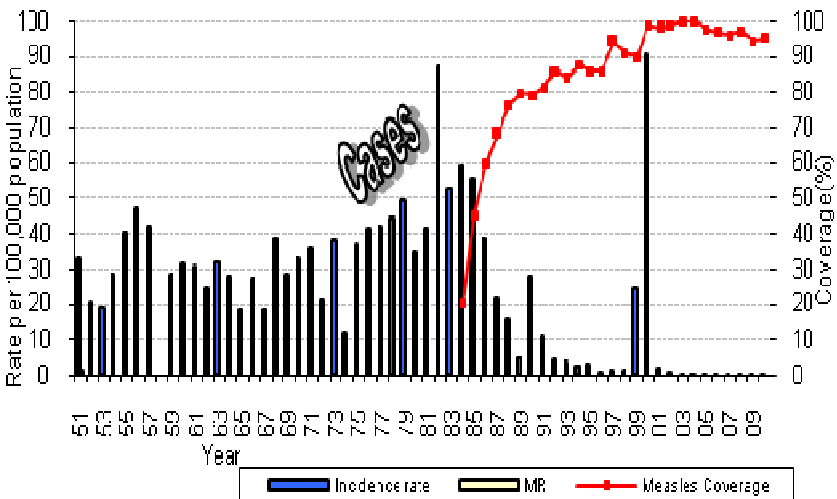
Incidence of neonatal-tetanus and TT coverage , 1966 - 2010



EPI

Incidence of Measles and Measles vaccine coverage

Incidence of Measles and Measles vaccine coverage , 1951-2010



History of Immunization in Sri Lanka

The history of immunization in Sri Lanka goes back to the 19th century. The law relating to compulsory vaccination (against smallpox) is referred to in the Vaccination Ordinance of 1886.

The milestones of immunization in Sri Lanka

- 1886 Vaccination against smallpox introduced under the Vaccination Ordinance
- 1949 BCG Vaccination introduced against tuberculosis
- 1961 “Triple” vaccination introduced against diphtheria whooping cough and Tetanus
- 1962 Oral polio vaccine introduced
- 1963 BCG vaccination of newborn introduced
- 1969 Tetanus Toxoid administration to pregnant mothers introduced
- 1978 Launching of the Expanded Programme on Immunization
- 1981 Revision of the immunization schedule and the introduction of a modified list of contraindications
- 1984 Introduction of Measles vaccine to the EPI
- 1985 Strengthening of cold chain and logistics in EPI
- 1988 Introduction of Killed JE vaccine to the EPI
- 1989 Universal Childhood Immunization (UCI) achieved with over 80% coverage among infant immunizations
- 1991 Revision of Tetanus Toxoid schedule
- 1995 Conduct of first Polio National Immunization Days
- 1996 Introduction of Rubella vaccine
- 1996 Conduct of the second Polio National Immunization Days

- 1997 Conduct of the third Polio National Immunization Days
- 1998 Conduct of the fourth Polio National Immunization Days
- 1999 Conduct of the Polio National Immunization Days
- 2000 Consultative meeting held to review the National Immunization Schedule
- 2001 Introduction of the new National Immunization Schedule;
- ◆ DTP at 2, 4 and 6 months of age
 - ◆ Introduced MR vaccine at 3 years
 - ◆ Introduced aTd at 10 years
- 2003 Introduction of HBV vaccine and AD syringes to the EPI
- 2003 Measles catch-up immunization programme
- 2005 MR catch-up immunization programme
- 2008 Introduction of Hib containing Pentavalent Vaccine
- 2009 Introduction of live JE vaccine to the EPI
- 2011 Revision of the National Immunization Schedule;
- ◆ Introduction of MMR vaccine 1st dose at 1 year of age
 - ◆ Introduction of MMR vaccine 2nd dose at 3 years of age
 - ◆ live JE vaccine at 9 months of age

The first manual for Medical Officers, giving technical information on the Expanded Programme on Immunization was published in 1979 by the Ministry of Health with the assistance of UNICEF and WHO.

Updated version of this manual was published as National Immunization Hand Book in 2002 and this is the 2012 update of that hand book.

The purpose of this immunization handbook is to give health professionals a clear clinical guidance on safest and most effective use of both EPI and non EPI vaccines in their practice.

Objectives of the National Programme on Immunization

The objectives of the country's EPI are as follows,

- ◆ Eradication of Poliomyelitis.
- ◆ Elimination of measles, Neonatal Tetanus and Diphtheria.
- ◆ Reduction of morbidity and mortality due to Whooping cough, Hepatitis B, Haemophilus influenza, Mumps, Tetanus, tuberculosis and Japanese encephalitis.
- ◆ Reduction of morbidity and mortality due to, CRS and Rubella and prevention of outbreaks.
- ◆ Prevention and control of burden of selected diseases through introduction of new vaccines.

By addressing the above objectives, Sri Lanka is expected to eradicate or reduce morbidity and mortality associated with vaccine-preventable diseases to levels that are no longer public health concerns.

National Immunization Schedule

National immunization schedule which was approved by the National Advisory Committee on Communicable Diseases on 3rd June 2011 comes into effect from October 2011.

According to the current EPI schedule, all children during their first year of life should be immunized with BCG (at birth), OPV (on completion of 2,4,6 months), DTP- Hep B- Hib (on completion of 2,4,6 months), JE (on completion of 9 months) and 1st dose of MMR (on completion of 1 year) to complete the primary series of vaccination before reaching the age of one year. Other than that, older children should be immunized with OPV (on completion of 18 months), DTP (on completion of 18 months), 2nd dose of MMR (on completion of 3 years), DT (at 5 years), aTd (at 12 years), and pregnant women with tetanus toxoid (TT).

National Immunization Schedule for EPI Vaccines – Sri Lanka

**Approved at the National Advisory Committee on Communicable Diseases
on 03rd June 2011**

Age	Vaccine	Remarks
DURING FIRST YEAR OF LIFE (INFANCY)		
0-4 weeks	BCG	Before leaving hospital, preferably within 24 hours of birth. If a scar is not present 2nd dose could be offered after 6months, up to 5 years.
On completion of		
2 nd Month	OPV & Pentavalent (DTP-HepB-Hib) (1st dose)	For a defaulter or for an unimmunized child minimum of 6-8 weeks gap between doses is adequate
4 th Month	OPV & Pentavalent (DTP-HepB-Hib) (2nd dose)	Preferably 6-8 weeks after 1st dose
6 th Month	OPV & Pentavalent (DTP-HepB-Hib) (3rd dose)	Preferably 6-8 weeks after 2nd dose
9 th Month	A dose of Live JE Vaccine	On completion of 9 months

IN SECOND YEAR OF LIFE		
At 12 months	MMR (1 st Dose)	On completion of 1 st year
At 18 months	OPV & DTP (4 th dose)	On completion of 18 th month
PRE SCHOOL GOING AGE		
At 3 years	MMR (2 nd Dose)	On completion of 3 rd year
SCHOOL GOING AGE		
At 5 years	OPV & DT (5 th dose)	On completion of 5 th year
In School		
At 12 years	aTd (adult Tetanus diphtheria)	On completion of 12 th year
PREGNANT WOMEN		
1 st Dose	Tetanus Toxoid	During 1 st pregnancy, after 12 weeks of POA
2 nd Dose	Tetanus Toxoid	During 1 st pregnancy, 6-8 weeks after the 1 st dose
3 rd Dose	Tetanus Toxoid	During 2 nd pregnancy, after 12 weeks of POA
4 th Dose	Tetanus Toxoid	During 3 rd pregnancy, after 12 weeks of POA
5 th Dose	Tetanus Toxoid	During 4 th pregnancy, after 12 weeks of POA

One booster dose of Tetanus Toxoid (TT)	Tetanus Toxoid	During 1st pregnancy with a written evidence of previously being immunized with 6 doses of Tetanus Toxoid as per National EPI schedule (3 doses of DTP in infancy + DTP at 18 months + DT at 5 years + aTd at 12 years) during childhood and adolescent and a gap of 10 years or more after the last Tetanus Toxoid containing Immunization.
Tetanus Toxoid immunization not indicated	<ul style="list-style-type: none"> ◆ 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. ◆ Mothers who have received 6 doses of Tetanus Toxoid according to the National EPI schedule during childhood and adolescence and if the gap between the last Tetanus Toxoid containing immunization and the present pregnancy is less than 10 years, are protected and do not need further Tetanus Toxoid immunization for the present pregnancy. 	

- ◆ Mothers who have received 6 doses of Tetanus Toxoid according to the National EPI schedule 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 immunization for the present pregnancy.

FEMALES IN THE CHILD-BEARING AGE GROUP

15-44 years	Rubella containing vaccine (MMR)	One dose of MMR vaccine should be given to all females between 15 and 44 years of age, who have not been immunized with rubella containing vaccines earlier.
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Sources

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Introduction

Mycobacterium tuberculosis, the aetiological agent of tuberculosis (TB), is a leading cause of human disease and death worldwide, particularly in the developing countries. Human TB has existed for thousands of years. No country is free of TB, and the disease is endemic in most poor countries of the world. It is estimated that about one-third of the current global population is infected asymptotically with *Mycobacterium tuberculosis*, of which 5–10% will develop clinical disease during their lifetime.

Mycobacterium tuberculosis usually attacks the lungs, but can also affect other parts of the body, including the bones, joints, and brain.

HIV and TB form a lethal combination, each speeding the other's progress. HIV weakens the immune system. Someone who is HIV-positive and infected with TB bacilli is many times more likely to become sick with TB than someone who is HIV-negative infected with TB bacilli. TB is a leading cause of death among people who are HIV-positive. Emerging mycobacterial drug resistance is further complicating the situation.

Bacteriology

M. tuberculosis accounts for 98–99% of all pulmonary and for 80–90% of all types of TB. The genus *Mycobacterium* is characterized by slender, nonmotile rods with complex, lipid-rich cell walls resisting destaining by acid alcohol (hence “acid fast”). *Mycobacteria* are strictly aerobic and grow on fairly simple solid or fluid media.

Mode of transmission

The most important source of human infection is an already infected person who spreads the highly infectious bacilli via respiratory droplets. The risk of developing disease is highest in children under 3 years of age, lowest in later childhood, and high again among adolescents, young adults, the very old and the immunosuppressed. Reactivation of long-latent infections accounts for a large proportion of cases of clinical disease in older people. Susceptibility to disease is markedly increased in the following groups:

- ◆ those with HIV infection and other forms of immunosuppression,
- ◆ underweight and under-nourished people,
- ◆ people with debilitating diseases such as chronic renal failure, cancer, silicosis,
- ◆ diabetics or postgastrectomy,
- ◆ substance abusers.

Incubation period

The period from infection to demonstrable primary lesion, or significant tuberculin reaction, is about 4 -12 weeks. While the subsequent risk of progressive pulmonary or extrapulmonary tuberculosis is greatest within the first year or two after infection, latent infection may persist for a lifetime. HIV infection appears to increase the risk significantly and shortens the interval for development of clinical tuberculosis.

Clinical Features

Primary infections can occur at any age, but children are most often affected in areas of TB high incidence and high population density. The symptoms and signs of TB vary significantly with the age and immune status of the patient and with the stage of the disease.

Primary infection may be asymptomatic and often resolves spontaneously. However, it may progress by local spread in the lungs to cause Pulmonary Tuberculosis, pleurisy or bronchopneumonia.

However, *Mycobacterium tuberculosis* may spread from the site of the primary infection by lymph and blood to other parts of the body. In some instances, especially in young children, haematogenous spread may result in severe primary disease, including miliary TB and TB meningitis. It may affect any organ or tissue including lymph nodes, pleura, pericardium, kidneys, bones and joints, larynx, skin, intestines, peritoneum and eyes. Extrapulmonary tuberculosis is less common than pulmonary tuberculosis. Extrapulmonary tuberculosis occurs more frequently among persons who are infected with HIV, but pulmonary tuberculosis remains the most common type of tuberculosis among this group too.

Classic clinical symptoms of TB include chronic cough, moderate fever and night sweat, fatigue, reduced appetite and weight loss. These symptoms occur as the involved tubercles expand and form caseous centers that may subsequently undergo liquefaction and become cavities.

Epidemiology

Global Situation

Globally, 9.2 million new TB cases and 1.7 million deaths from TB occurred in year 2006, of which 0.7 million cases and 0.2 million deaths were among HIV-positive people. The World Health Organization (WHO) estimates that the largest number of new TB cases in 2005 occurred in the South-East Asian Region, which accounted for 34% of incident cases globally. However, the estimated incidence rate in sub-Saharan Africa is nearly twice that of the South-East Asian Region, at nearly 350 cases per 100 000 population.

Situation in Sri Lanka

As a result of the control measures adopted, the number of Tuberculosis (TB) cases detected each year declined gradually up to 1986. However, there has not been a significant decline in the incidence since then. Around 9000 new cases of TB are detected annually and tuberculosis still continues to pose a major public health challenge in Sri Lanka.

In the year 2009, nine thousand one hundred and eighteen (9118) new TB cases have been detected and among them 4764 were smear positive. There were 2357 extra pulmonary TB cases, 196 relapses and 89 treatment failures. Further 124 defaulters were registered by the national TB control programme.

BCG vaccine

The BCG vaccine was first derived in France from an attenuated strain of *M. bovis* in 1921. Originally the vaccine was given orally, but this was found to be ineffective and the intradermal route was introduced in Sweden in 1927. The letters B, C, G stand for Bacillus, Calmette-Guérin. Bacille describes the shape of a bacterium; Calmette and Guérin are the names of the people who developed the vaccine.

BCG, which is currently the only available TB vaccine, providing protection against TB meningitis and the disseminated form of the disease in infants and young children. However, it does not prevent the establishment of primary infection or reactivation of latent TB, the latter condition being the main source of *mycobacterium* spread in the community.

Thousands of lives have been saved through BCG vaccination over the years. The vaccine is relatively safe, inexpensive and requires only one injection. Despite its shortcomings, BCG vaccination is considered a life-saving and important part of standard TB control measure in most endemic countries.

Most high-burden countries practice BCG vaccination of infants as part of the national childhood immunization programme, but in industrialized countries, where the disease has become rare, vaccination of defined high-risk groups is increasingly becoming the preferred strategy.

Following its introduction into the WHO's Expanded Programme on Immunization in 1974, the vaccine soon reached global coverage rates exceeding 80% in countries endemic for TB.

BCG Vaccine has been used in Sri Lanka since 1949 to combat TB and complications associated with TB and has been included in the Expanded Programme on Immunization (EPI) since its inception in 1978.

Characteristics of the BCG Vaccine

The current BCG vaccine contains a live attenuated strain of *M. bovis*. It is presented as freeze dried substance with a diluent in a separate ampoule.

Each 0.1 ml of live attenuated BCG vaccine (Bacillus Calmette Gueri strain) contains between 1×10^5 and 33×10^5 C.F.U. Reconstitute with sodium chloride injection.

BCG vaccine is available in the form of 10 dose vials with 0.5 ml diluents and 20 dose vial with 1ml diluents.

Indications

A single dose of BCG vaccine should be given to all infants as soon as possible after birth. This protects the young children against developing complications of primary infection, such as TB meningitis and miliary TB.

If children are brought without a BCG scar (after 6 months of the initial dose) despite BCG vaccination could be re-vaccinated with a 2nd dose of BCG after 6 months up to 5 years of age even without doing a mantoux test. Even in the absence of BCG scar following the second dose a further dose is not recommended.

BCG vaccination of adults is not normally recommended but may be considered for tuberculin-negative persons in unavoidable and close contact with cases of multidrug-resistant *Mycobacterium tuberculosis*.

Efficacy

The efficacy of BCG vaccine is estimated from prospective clinical trials and retrospective case-control studies. Although clinical trials have demonstrated conflicting results with regard to estimating BCG vaccine efficacy, meta-analytic reviews have estimated the vaccine efficacy to be 51% in preventing any TB disease. In newborns the protective effect of BCG vaccine against TB compared with that in unvaccinated children is estimated at 74% for any form of TB and 64% for meningitis, and up to 78% for disseminated disease.

The duration of protection after neonatal BCG vaccination is not well known but commonly believed to decline gradually to non-significant levels after 10–20 years.

Immunization Schedule

National policy is to give BCG vaccination to all new born babies routinely; before leaving the hospital preferably within 24 hours of birth.

Dosage & Administration

Lyophilized reconstituted BCG vaccine recommended dose for children less than one year is 0.05 ml. and others (more than one year) 0.1 ml. BCG vaccine is given as a single intradermal injection.

BCG vaccine is supplied as freeze-dried vaccine with diluent in a separate ampoule. Special care is needed in opening the ampoule and reconstituting the vaccine so that the vaccine is not blown out of the ampoule. Because of sensitivity to daylight, the vaccine must be kept in the dark. If not used immediately after reconstitution, the vaccine should be kept cool (+2°C to +8°C) and protected from light, and any opened vaccine vial remaining at the end of a session (maximum 6 hours) should be discarded.

Site

The site of inoculation should be in the deltoid region (i.e. half way down the deltoid muscle) in the left upper arm as sites higher on the arm are more likely to lead to keloid formation; the tip of the shoulder should be avoided.

Correct intradermal BCG vaccination almost invariably results in minor local reactions (erythema, induration, tenderness) often followed by a small ulceration at the site of injection. The age and immune status of the vaccinee, the skills of the vaccinator, as well as the strain and dose of the BCG vaccine, may influence the extent of these responses. Within a few months, the local reaction is followed by a small scar. Presence of a typical scar is used as a marker of previous BCG vaccination.

Storage

Both BCG vaccine and diluent should be stored and transported between +2°C to +8°C. The diluent should not be frozen but kept cool (+2°C to +8°C). BCG vaccine deteriorates when exposed even for short period to direct sun light and therefore advised to be stored in dark. The expiry date is specified on the BCG ampoule label.

Contraindications

The following conditions are considered as contraindications for the use of BCG Vaccine:

- ◆ presence of one of the general contraindications for any vaccine,
- ◆ history of an allergy to any of the vaccine components,
- ◆ children with symptomatic or documented human immunodeficiency virus (HIV) infection,
- ◆ for patients under high dose of immunosuppressive treatment (corticosteroids, alkylating agents, antimetabolites, Radiation),
- ◆ those with cell-mediated immune deficiency (known or suspected congenital immunodeficiency, leukaemia, lymphoma or generalized malignant disease),
- ◆ history of Keloid and lupoid reactions at the site of injection following BCG vaccination (such children should not be revaccinated),
- ◆ Pregnancy.

Precautions

BCG vaccine may be given concurrently with another live vaccine, but if they are not given at the same time, an interval of at least 4 weeks should be allowed between the administration of BCG vaccine and any other live vaccine, whichever is given first.

Further immunization to the same arm used for BCG vaccination may be avoided for at least three months because of the risk of regional lymphadenitis.

BCG vaccine should be injected by a person with proper training to administer intradermal vaccines.

Adverse Events

A local reaction is commonly seen after BCG vaccination. A small tender red swelling appears at the site of the injection. The swelling will gradually change to a small vesicle and then an ulcer in 2-4 weeks. The reaction usually subsides in 2 – 5 months and practically in every child it leaves a superficial scar 2-10 mm in diameter.

Complications following BCG vaccination are rare: the incidence of fatal dissemination of BCG is estimated to be 0.19–1.56 per million vaccinees and has almost exclusively occurred in inadvertently immunized persons with severely compromised cellular immunity.

Most reactions are generally mild and do not require treatment. Adverse reactions are more common in young vaccinees and are frequently related to improper technique in administration and improper dilution. Reactions may include persistent or spreading skin ulceration at the immunization site, regional (axillary) lymphadenopathy and keloid formation.

Moderately severe reactions, such as marked lymphadenitis or suppurative adenitis, occur in 0.2 to 4.0 per 1,000 vaccinees.

Rates of adverse reactions appear to vary with the strain of vaccine, dose and method of immunization, and the age of the recipient.

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POLIOMYELITIS VACCINE

Introduction

Poliomyelitis is a highly infectious disease caused by the poliovirus. It causes paralysis and mainly affects children under three years of age although it can strike at any age. One in 200 infected cases end up with irreversible paralysis. Among those, 5% to 10% will die from respiratory paralysis. The disease has no cure although it can be successfully prevented on which the global poliomyelitis eradication initiative had been based.

Virology

Polio virus (wild) is a human enterovirus and a member of the family of Picornaviridae. It is a RNA virus and was first isolated in 1909 by Karl Landsteiner and Erwin Popper. There are three antigenic types (type 1, type 2, and type 3) and all three types can cause paralysis. Most cases of paralysis are due to type 1, while paralysis caused by type 3 and 2 are less frequent.

Mode of transmission

The mode of transmission is primarily from person to person through faeco-oral route and after entry the virus multiplies in throat and intestines. It then spreads to the regional lymph nodes. Once established, the virus can enter the blood stream and invade the central nervous system spreading along the nerve fibres. As it multiplies, the virus destroys the motor neurons that activate muscles. Paralysis of the muscles of respiration and/or swallowing is life-threatening. The time between the infection and onset of paralysis is 10 to 21 days.

Following exposure, the virus is excreted with faeces intermittently for one month or more after infection. Heavy shedding of the virus occurs just prior to the onset of paralysis and during the first two weeks after initial symptoms occur. There is no long term carrier state following infection although immunosuppressed persons are known to excrete the virus for longer periods.

Poliovirus is demonstrable in throat secretions as early as 36 hours and in faeces 72 hours after exposure to infection in both clinical and inapparent cases. Virus is more easily detectable for a longer period in faeces than in throat secretions.

Poliovirus infects only humans and does not survive long in the environment outside the human body. It is rapidly inactivated by heat, formaldehyde, chlorine and ultra violet light.

Clinical Features

Greater than 90% of polio infections are silent or presents as non-specific fever. Aseptic meningitis occurs in about 1% of infections. An additional 4-8% of

infections will result in a minor illness known as abortive poliomyelitis. A minor illness presents with symptoms of fever, malaise, headache, nausea and vomiting. Flaccid paralysis occurs in less than 1% of poliovirus infections. In paralytic cases, muscle pain with spasms and fever are associated with the rapid onset of acute flaccid paralysis. Paralysis of poliomyelitis is characteristically asymmetrical with fever present at the onset. The legs are affected more often than the arms. The maximum extent of paralysis is reached in a short period, usually within 3-4 days. Paralysis due to poliomyelitis is considered to be irreversible. Paralysis of respiratory muscles can result in death.

Epidemiology

Global Situation

Poliomyelitis case load in the world have declined from an estimated 350,000 cases in more than 125 endemic countries in 1988 to 650 cases in 16 countries by the end of 2011. This is mainly attributed to the efforts of the global poliomyelitis eradication initiative and especially the success of the effective vaccine against the disease. By end of 2011 only 3 countries remain polio-endemic which are Afghanistan, Pakistan and Nigeria and they are the current focus of the global programme.

Situation in Sri Lanka

The disease was known to cause outbreaks in Sri Lanka and was made a notifiable disease in 1944 for its public health impact. The yearly average number of cases then was 277. The first reported major outbreak occurred in 1962, with 1810 cases and 180 deaths. Since then, epidemics occurred in six yearly cycles till 1987, but the number of reported cases during each epidemic, gradually decreased over the time.

In 1961, administration of Trivalent Oral Polio Vaccine (TOPV) first commenced as a pilot project and thereafter in 1963 mass immunization with TOPV was initiated island wide. The Expanded Programme on Immunization (EPI) commenced in 1978 and within this programme immunization coverage of OPV vastly improved. The number of poliomyelitis cases reported showed a clear downward trend along with a steady increase in the immunization coverage of infants and children with TOPV over the years. The last virologically confirmed case of polio was detected in Sri Lanka in 1993.

Sri Lanka adopted the preventive strategies of the global eradication initiative to eradicate polio from the country. These strategies included, attaining high immunization coverage, enhanced surveillance of cases of Acute Flaccid Paralysis (AFP) and conducting supplementary immunization activities. However, recent outbreaks of polio had been reported from most of the neighbouring countries in the South East Asian Region [SEAR] and Sri Lanka carries a risk of importing the disease from these countries.

Oral Polio Vaccine (OPV)

The first vaccine for polio was developed by Jonas Salk in 1952 in the United States. This was an inactivated polio vaccine based on poliovirus grown in monkey kidney tissue culture. An oral vaccine was developed by Albert Sabin some years later and was introduced globally in 1962. This is a stabilized preparation of live attenuated polio viruses, of the Sabin strains type 1, type 2 and type 3 (Leon) propagated in MRC5 human diploid cells. OPV is widely used in many countries and the success of the Global Polio Eradication Initiative was mostly attributed to the effectiveness of this vaccine.

Oral Polio Vaccine (OPV) has been used in Sri Lanka since 1963 to successfully combat the polio outbreaks and has been included in the Expanded Programme on Immunization (EPI) since its inception in 1978.

Characteristics of the Vaccine

The attenuated poliovirus in the Sabin vaccine replicates very efficiently in the intestines, the primary site of virus infection and produces excellent intestinal immunity which prevents infection with wild virus in areas where the virus is endemic. It replicates less efficiently in the nervous tissue. However OPV is easy to administer and provides a longer lasting immunity than the inactivated vaccine. The live virus used in the vaccine is shed in stools and can spread to others within a community, resulting in protection against poliomyelitis even in individuals who have not been directly vaccinated. This phenomenon is termed herd immunity.

OPV is commercially available in trivalent and monovalent forms. Trivalent vaccine provides protection against all 3 sub types in a single vaccine and individual monovalent vaccines against sub types PV1, PV2 and PV3 offers selective immunity to the relevant sub type. The vaccine contains small traces of antibiotics i.e. neomycin and streptomycin but does not contain preservatives.

A single dose of the live attenuated trivalent OPV produces immunity to all 3 virus sub types in approximately 50% of recipients. Three doses of the vaccine produce protective antibodies to all 3 virus serotypes in more than 95% of recipients. As with other live virus vaccines, immunity produced by OPV is life long.

Indications

- ◆ Primary and booster immunization of infants and children.
- ◆ Immunization of infants and children in Supplementary Immunization Activities (SIA) e.g. National Immunization Days (NIDs), Sub National Immunization Days (SNIDs).

- ◆ Immunization of children in “Mopping up” immunization campaigns.
- ◆ Outbreak response immunization following detection of AFP case.
- ◆ OPV can also be given in adult life when a person is likely to be exposed to a high risk of infection, such as travelling to endemic areas.
- ◆

OPV can be safely and effectively given simultaneously with BCG, DPT, DT, TT, BCG, Measles, Rubella, Hepatitis B, Hib and Yellow Fever Vaccines and with Vit A. Unlike other live vaccines OPV need not have a minimum interval of 4 weeks with any other live vaccine.

Immunization Schedule

The present schedule of oral polio vaccine recommended for routine immunization of children through the EPI has been decided on the epidemiology of the disease, objectives of the Polio Eradication Initiative and the feasibility of implementation of the programme in Sri Lanka.

On completion of two months of age every infant should receive the first dose of OPV, followed by two more doses on completion of 4 months and 6 months of age respectively. Even if there is a delay between doses the child should be given the scheduled doses as/when he/she presents for immunization with the minimum of 6 to 8 weeks interval . It is very important to ensure that every child receives three doses of OPV before completion of one year of age. The interval between any two consecutive doses should not be less than 6 weeks for routine immunization. The 4th dose of OPV should be given at or on completion of 18 months of age. The 5th dose of OPV should be given at 5 years of age or at school entry.

It is not necessary to start the schedule again if any dose is missed by the recipient. The subsequent doses should be continued at appropriate intervals. In this situation the child will receive all the scheduled doses late and will have adequate levels of immunity late.

Dosage & Administration

OPV is usually provided in vials containing 10 or 20 doses of vaccine. OPV is to be administered exclusively by the oral route. One immunizing dose is contained in two drops of the vaccine (0.1ml). The container must first be shaken well to obtain a homogenous mixture of contents but foaming should be avoided. The drops are delivered directly into the mouth from a special dropper supplied with the multi-dose glass vials or directly from the multi-dose plastic tubes. Care

If a child vomits within half an hour of administration of OPV a repeat dose is recommended. Mild diarrhoea is not a contraindication for OPV. These children should be given an additional dose when the child recovers from that diarrhoea episode.

Storage

Oral Polio Vaccine is thermolabile and requires maintenance of an effective cold chain. The vaccine can be stored at minus 20°C (-20°C) in the freezer compartment of the refrigerator or freezer room for up to two years and + 2 °C to + 8 °C in the refrigerator compartment up to 6 months .

According to the Open Vial Policy practised within the EPI, opened OPV vials with vaccine doses remaining by the end of an immunization session can be re-used in the next immunization session. These vials should be kept at +2°C to +8°C with other such vaccine vials in the main compartment of the refrigerator for up to 28 days. OPV vials/tubes are supplied with Vaccine Vial Monitors (VVM) as part of its label.

Cautions and contraindications

OPV vaccination is contraindicated for persons with:

- ◆ primary abnormalities in the immune system (e.g. agammaglobulinemia, hypogammaglobulinemia),
- ◆ secondary immunosuppression due to medication, leukaemia, lymphoma or advanced malignancy,
- ◆ children with known hypersensitivity to any component of the vaccine, e.g : neomycin, streptomycin and polymyxin B.

According to the recommendations of the WHO, symptomatic and asymptomatic HIV infection is not a contraindication for immunization with OPV unless they are severely immunocompromised.

Adverse Events

Live, oral poliomyelitis vaccine does not normally induce general or local reactions and the risk of complications is low. However, the oral polio vaccine (OPV) rarely can cause Vaccine Associated Paralytic Poliomyelitis (VAPP).

The overall risk of VAPP is approximately one case for 2.4 million doses administered and appears to be higher following the first dose. These cases occur

within 4 to 30 days following immunization in vaccine recipients and 7-60 in contacts of vaccine recipients. In Sri Lanka only one probable case of VAPP had been reported during the 45 years of commencing immunization with OPV.

Inactivated Polio Vaccine (IPV)

An injectable preparation of the inactivated polio vaccine is used in some of the industrialized countries which have already been certified polio free and this vaccine is also considered as the vaccine of choice for immuno suppressed individuals.

IPV protects the vaccinee by producing sufficient serum antibody levels to prevent the virus from entering the nervous system via the blood stream. IPV produces less gastrointestinal immunity than does OPV, so persons who receive IPV may be infected with wild poliovirus but the immunity conferred by the vaccine will prevent the infection from progressing to viraemia and will protect the motor neurons but they are likely to transmit the wild poliovirus to the community.

Dosage and administration

The dosage of IPV is 0.5 ml and it is administered either subcutaneously or intramuscularly. When given in combination with other vaccines such as DPT or Hepatitis B it should be given intramuscularly. The immunization schedule of IPV is similar to that of OPV and the minimum interval between 2 consecutive doses is 4 weeks.

Contraindications

Moderate to severe illness and severe allergy to vaccine components are the contraindications.

Adverse events

Adverse events following IPV are rare and uncommon.

Storage

IPV should be stored at 2°C – 8°C and freezing should be avoided as it affects the potency of the vaccine.

OPV Vs IPV

OPV, which induces excellent mucosal immunity in the intestinal wall and provides protection from ingested wild polio viruses by preventing them from entering the blood stream, is considered the vaccine of choice for countries where personal and community hygiene is poor and where the wild polio virus may still circulate although clinical paralytic disease incidence is very low or absent.

In comparison the more expensive IPV produces significantly less intestinal immunity to the polio virus. Although IPV suppresses pharyngeal excretion of wild poliovirus, this vaccine has only limited effects on intestinal excretion of poliovirus. As a result a child immunized with IPV may not develop the disease if infected with wild poliovirus, but is likely to spread the wild poliovirus to other children.

Therefore OPV remains the vaccine of choice in Sri Lanka which has been free from polio for 17 years but is yet to achieve the polio free certification since the disease is still prevalent in the region.

The major advantage of IPV is that there is no risk of Vaccine Associated Paralytic Poliomyelitis (VAPP).

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PERTUSSIS (WHOOING COUGH) VACCINE

Introduction

Pertussis is an acute bacterial disease involving the respiratory tract. Pertussis is an important public health concern even in countries with high vaccination coverage.

Thomas Sydenham first used the term 'infantum pertussis' in 1670, 'pertussis' meaning a violent cough of any kind. Bordet and Gengou identified the causative organism in 1906 (hence the name *Bordetella pertussis*), and the first crude vaccine was developed soon after from killed bacteria. An improved understanding of the organism resulted in a standardized whole cell vaccine. During the 1980s and 1990s knowledge of the components of *B. pertussis* and their biological roles led to the development of acellular pertussis vaccines.

Before vaccines became widely available, pertussis was among the most common childhood diseases. In industrialized countries, the average annual incidence was in the order of 150–200/100 000. Following large-scale pertussis vaccination during the 1950s–1960s, a dramatic reduction (>90%) in pertussis incidence and mortality was observed in the industrialized world. Pertussis vaccine (combined with diphtheria and tetanus toxoids) has been part of the WHO Expanded Programme on Immunization since its inception in 1974.

Despite it being very effective in preventing clinical disease, the vaccine has limited impact on the circulation of *B. pertussis* even in countries with high vaccination coverage. Remaining non-immunized children and older individuals with waning immunity may serve as reservoirs of the infection and they occasionally transmit *B. pertussis* to unimmunized young infants. Furthermore, the considerable numbers of susceptible adolescents and adults allow the occurrence of pertussis outbreaks, although high vaccination coverage may prolong the interepidemic intervals.

Bacteriology

B. pertussis, the causative agent of pertussis, is a small, fastidious Gram-negative coccobacillus with exclusive affinity for the mucosal layers of the human respiratory tract. Occasionally, other infectious agents, in particular *B. parapertussis*, may cause pertussis-like disease. Hence, laboratory confirmation of clinically suspected cases is important, particularly for the diagnosis of index cases.

Mode of transmission

Pertussis is a highly infectious bacterial disease transmitted from infected to susceptible individuals through droplets. It is highly communicable in the early catarrhal and at the beginning of the paroxysmal cough stages (i.e. in the first 2 weeks)

Thereafter, communicability gradually decreases and becomes negligible in about 3 weeks for non-household contacts.

Susceptibility of non-immunized individuals is universal. Secondary attack rates of up to 90% in non-immune household contacts can occur. Transplacental immunity in infants has not been demonstrated. One episode of pertussis usually confers prolonged immunity although second episodes (some of which may actually be due to *B. parapertussis*) can occasionally occur.

Clinical Features

Following an incubation period of 7–10 days, patients develop catarrhal symptoms including cough. In the course of 1–2 weeks, coughing paroxysms ending in the classical whoop may occur. In typical cases, cough is particularly severe at night and frequently followed by vomiting. In young infants, pertussis may cause only apnoea and cyanosis, whereas in adolescents and adults, uncharacteristic, persistent cough may be the only manifestation of the disease. The catarrhal, paroxysmal and convalescent stages of the disease may last for more than a month, sometimes several months.

Complications occur in 5–6% of pertussis cases, most frequently in infants aged <6 months. Bronchopneumonia (5.2%) is the most prominent problem, with relatively high mortality. The incidence of pertussis-associated encephalopathy is 0.9/100 000.

Epidemiology

Global Situation

Recent estimates from WHO suggest that, in 2003, about 17.6 million cases of pertussis occurred worldwide, 90% of which were in developing countries, and that about 279 000 patients died from this disease. It is further estimated that, in 2003, global vaccination against pertussis averted about 38.3 million cases and 607 000 deaths.

Situation in Sri Lanka

Whooping cough is a notifiable disease in Sri Lanka. According to hospital inward statistics, over 1000 cases per year of the disease were reported until the late 1970s; a gradual decline has been observed from the 1990s and < 100 cases have been reported annually from 2001 onwards. For the year 2010, a total of 24 clinically suspected cases of pertussis were reported from all over the country. Not a single death related to pertussis has been reported in the recent past.

Pertussis vaccines

The primary aim of pertussis vaccination is to reduce the incidence and severity of the disease among young children. It has been postulated that given high and sustained coverage, vaccination could eliminate pertussis as a public health problem.

The vaccine is usually administered in the national childhood immunization programme as combined diphtheria-tetanus-whole cell pertussis vaccine (DTwP) or diphtheria-tetanus-acellular pertussis vaccine (DTaP). DTP vaccines can be presented in combination with one or more additional vaccines such as *Haemophilus influenzae* type b (Hib), hepatitis B (HepB) and poliovirus vaccine (IPV).

Diphtheria-tetanus-whole cell pertussis vaccine (DTwP) has been part of the National Immunization Programme of Sri Lanka since 1961. Currently the EPI programme uses pentavalent vaccine (DTwP-Hep B-Hib) to immunize infants against five diseases including pertussis.

Characteristics of the Vaccine

Whole cell pertussis vaccines

The whole cell pertussis vaccine is a suspension of *B. pertussis* organisms that have been inactivated, usually by formalin. Most whole cell pertussis vaccines are available only in combination with diphtheria and tetanus toxoids. All whole cell pertussis (or DTwP) vaccines contain aluminium salt as adjuvant and, in most cases, thiomersal as preservative.

Reactogenicity, particularly local reactions due to whole cell pertussis vaccine tend to increase with age and the number of injections; whole cell pertussis vaccines are therefore not recommended for immunization of adolescents and adults.

Acellular pertussis vaccines

Acellular pertussis vaccines contain inactivated pertussis toxin either alone or in combination with other *B. pertussis* components such as filamentous haemagglutinin (FHA), fimbrial antigens and pertactin (PRN).

The acellular pertussis vaccines have shown similar protective efficacy to the whole cell pertussis vaccines (>85%). It is still debated whether monovalent or bivalent acellular pertussis vaccines (containing inactivated pertussis toxin only or in combination with FHA) are as effective as the polyvalent acellular pertussis vaccines (containing three to five components). In order to reduce the reactogenicity of booster injections, acellular pertussis vaccines with reduced antigen concentration have been formulated for use in adolescents and adults.

Types of pertussis containing vaccine preparations

◆ Diphtheria-tetanus-whole cell pertussis vaccine (DTwP)

Diphtheria-tetanus-whole cell pertussis vaccine (DTwP) is prepared by combining purified diphtheria toxoid, purified tetanus toxoid and killed *B. pertussis* bacilli. The antigens are adsorbed on to aluminium phosphate as adjuvant.

Each 0.5 ml dose of DTwP contains diphtheria toxoid ≤ 25 Lf (≥ 30 IU), tetanus toxoid ≥ 5 Lf (≥ 40 IU) and *B. pertussis* ≤ 16 OU (≥ 40 PU) adsorbed on aluminium phosphate (Al P₀₄) ≥ 1.5 mg.

◆ Diphtheria-tetanus-acellular pertussis vaccine (DTaP)

Diphtheria-tetanus-acellular pertussis vaccine (DTaP) contains purified diphtheria toxoid, purified tetanus toxoid and inactivated pertussis toxin either alone or in combination with other *B. pertussis* components such as FHA, fimbrial antigens and PRN.

Each 0.5 ml dose of DTaP contains diphtheria toxoid ≥ 30 IU, tetanus toxoid ≥ 40 IU and *B. pertussis* toxoid 25 mcg, FHA 25 mcg and PRN 8 mcg. The antigens are adsorbed on to aluminium salt as adjuvant.

◆ DTaP-HepB vaccine

Each 0.5 ml dose of DTaP-HepB also contains 10 mcg of hepatitis B surface antigen (HBsAg) with diphtheria toxoid ≥ 30 IU, tetanus toxoid ≥ 40 IU and *B. pertussis* toxoid 25 mcg, FHA 25mcg and pertactin 8mcg. HBsAg is produced in genetically-engineered yeast cells (*Hansenula polymorpha*) carrying the relevant gene of the HBsAg. The antigen is purified and inactivated by several physicochemical steps.

◆ DTwP-Hib vaccine

Each single dose of 0.5 ml contain 12.5 Lf of diphtheria toxoid, 5 Lf of tetanus toxoid, 10 ug of purified Haemophilus b saccharide and approximately 25 ug of CRM197 protein and than 16 OPU of inactivated pertussis cells

◆ DTwP-Hep B-Hib vaccine

Each 0.5 ml dose of vaccine contains 30 IU purified diphtheria toxoid, 60 IU purified tetanus toxoid, 4 IU inactivated *B. pertussis*, Hib oligosaccharide 10 μ g conjugated to approx. 25 μ g of CRM 197, purified Hepatitis B surface antigen 10 μ g and Aluminium phosphate (adjuvant) 0.3 mg. Liquid preparation of this presentation is currently used in the National Immunization programme.

◆ DTaP-HepB-IPV-Hib

Each 0.5 ml dose of DTaP-HepB-IPV-Hib also contains more than or equal to 30 IU (25LfU) of diphtheria toxoid, more than or equal to 40 IU (10Lf U) of tetanus toxoid, 25mcg of pertussis toxoid, 25mcg of filamentous haemagglutinin and 8mcg of pertactin, 10mcg of recombinant HBsAg protein, 40 D-antigen units of poliovirus Type 1, 8 D-antigen units of poliovirus Type 2 and 32 D-antigen units of poliovirus Type 3 and 10mcg of purified capsular polysaccharide of Hib covalently bound to approximately 20-40mcg of tetanus toxoid.

The inactive ingredients in the vaccine are: aluminium hydroxide, aluminium phosphate, 2-henoxyethanol, lactose, Medium 199, neomycin (traces), polymyxin (traces), polysorbate 80, polysorbate 20, sodium chloride (salt) and water

◆ Reduced-antigen diphtheria-tetanus-acellular pertussis vaccine (dTpa)

Each 0.5 ml dose of dTpa contains diphtheria toxoid ≥ 2 IU, tetanus toxoid ≥ 20 IU and *B. pertussis* toxoid 8 mcg, FHA 8mcg and PRN 2.5 mcg.

Indications

1. Diphtheria-tetanus-whole cell pertussis containing vaccine (DTwP) preparations

- ◆ Primary course of immunization against diphtheria, tetanus and pertussis is recommended for all infants on completion of 2, 4 and 6 months of age, with a booster dose at 18 months of age; if the primary course is interrupted, it should be resumed but not repeated, allowing appropriate intervals (minimum interval of 6 weeks) between the remaining doses.
- ◆ Vaccination of unimmunized children less than 5 years of age against diphtheria, tetanus and pertussis.

2. Diphtheria-tetanus-acellular pertussis containing vaccine (DTaP) preparations

- ◆ Primary course of immunization against diphtheria, tetanus and pertussis is recommended for all infants at 2, 4 and 6 months of age, with a booster dose at 18 months of age, unless there is an absolute or temporary contraindication; if the primary course is interrupted, it should be resumed but not repeated, allowing appropriate intervals (minimum interval of 6 weeks) between the remaining doses.
- ◆ Vaccination of unimmunized children up to 5 years of age against diphtheria, tetanus and pertussis.

Efficacy

Despite major differences in the composition, modes of preparation and reactivity among both wP and aP vaccines, comprehensive clinical trials have demonstrated that most efficacious vaccines of either category will protect 85% of the recipients from clinical disease. The duration of protection following the primary 3-dose course in infants and one booster dose at least 1 year later is believed to be on average 6–12 years for both wP and aP vaccines. This is similar to, or somewhat shorter than, immunity following natural infection.

It is important to note that both DTwP and DTaP vaccines have similar immunogenicity, and therefore can achieve high vaccine effectiveness. The major advantage of the acellular vaccines is reduced reactogenicity leading to comparatively less local and systemic adverse reactions than whole cell pertussis vaccines.

On principle, the same type of wP containing or aP containing vaccines should be given throughout the primary course of vaccination. However, the limited data available do not suggest that changing between an aP containing and a wP containing vaccine interferes with safety or immunogenicity. Therefore, if the previous type of vaccine is unknown or unavailable, any wP vaccine or aP vaccine may be used for subsequent doses.

Dosage & Administration

The dose of both DTwP and DTaP containing vaccine is 0.5 mL, administered intramuscularly in the anterolateral aspect of mid thigh in infants and in the deltoid muscle in those 12 months of age and older. The vaccine should be shaken well before use.

Storage

All DTP vaccines should be stored in a dry place at a temperature between +2°C to +8°C. Transportation should also be at +2°C to +8°C.

DTP vaccines can be irreversibly damaged by inadvertent freezing. Pertussis vaccine can be damaged by heat.

DTP vaccine should never be frozen. The “shake test” (Refer to chapter on Cold Chain of vaccines) will determine if the vaccine has been damaged by freezing. If the vaccine fails the shake test it must be discarded.

Cautions and contraindications

The following conditions are considered as either contraindications or cautions for the use of DPT vaccines.

1. Presence of one of the general contraindications for any vaccine
2. History of severe local or general adverse events following a preceding dose of DTP vaccine, as explained below:

Severe local adverse events: an extensive area of redness and swelling at the injection site, 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.

Severe general adverse events:

- ◆ fever equal to or more than 39.5°C within 48 hours of vaccination,
- ◆ anaphylaxis,
- ◆ prolonged inconsolable screaming lasting more than 3 hours,
- ◆ convulsions occurring within 72 hours.

A personal or family history of allergy is not a contraindication to immunization against pertussis, nor is stable neurological conditions such as cerebral palsy or spina bifida.

In those with history of severe adverse events which contraindicate further doses of DTP, DT should be used for subsequent vaccinations.

3. Presence of progressive neurological disorder

Progressive neurological disorder (e.g. infantile spasms) is a contraindication. Certain groups of children (children with a documented history of cerebral damage in the neonatal period, children with a history of convulsions, in whom the advisability of pertussis immunization requires special considerations because of their medical histories. For them, the risk of a severe adverse event following pertussis vaccination may be higher (than in children without such histories), but the effects of pertussis could be even more severe. Decisions regarding further administration of pertussis vaccine should be guided by an individualized evaluation of benefits and risks. Where there is a doubt, appropriate advice should be obtained from a consultant paediatrician before a decision is made to withhold vaccination.

Adverse Events

Serious adverse events are rare following DTP immunization.

Local reactions such as pain, redness and swelling around 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.

General adverse events, which are uncommon, include headache, lethargy, malaise, myalgia and pyrexia. As mentioned, severe general adverse events, such as anaphylaxis, are rare.

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TETANUS VACCINE

Introduction

Tetanus is an infectious bacterial disease caused by toxigenic strains of *Clostridium tetani*. Tetanus has long been known as the scourge of parturient women, newborn babies and wounded soldiers. In the 18th century one out of every six infants born at the Rotunda Hospital in Dublin died from neonatal tetanus. Hippocrates described tetanus, but the cause was not recognized until 1884 and the toxin not purified until 1890. The toxoid (chemically inactivated toxin) was first prepared in 1924.

The disease may affect any age group, and case-fatality rates are high even where modern intensive care is available. The overwhelming majority of tetanus cases is birth-associated and occurs in developing countries among newborn babies or in mothers following unclean deliveries and poor postnatal hygiene. Tetanus in children and adults following injuries may also constitute a considerable public health problem. In Sri Lanka both Tetanus and Neonatal Tetanus ((NNT) has reached elimination levels because of the successful immunization programme.

Bacteriology

C. tetani is a Gram positive, spore-forming, motile strictly anaerobic bacillus. Spores are prevalent in the environment, particularly in the soil of warm and moist areas, and may be carried in the intestinal tracts of humans and animals. When introduced into dirty necrotic wounds (favourable anaerobic conditions), the spores may convert to toxin producing tetanus bacilli.

Mode of transmission

Cl. tetani is not an invasive organism; infection with *Cl. tetani* remains localized. The disease usually occurs through infection of a skin injury with tetanus spores. Tetanus spores introduced into an area of injury convert to tetanus bacilli in the presence of necrotic tissue with reduced oxygen potential. Tetanus spores are usually introduced into the body through a puncture wound contaminated with soil, street dust, animal or human faeces; through lacerations, burns and trivial or unnoticed wounds. Tetanus occasionally follows surgical procedures performed under unhygienic conditions. Maternal tetanus is a consequence of unclean delivery and unsafe abortion practices.

The incubation period for tetanus is usually 3-21 days with an average of about 10 days. It may range from 1 day to several months, depending on the character, extent and location of the wound.

Neonatal tetanus

Neonatal tetanus occurs when unclean instruments are used to cut the umbilical cord or when contaminated material is used to cover the umbilical stump in babies without protective concentrations of tetanus-specific antibody.

Tetanus and NNT are not directly transmitted from person to person. The average incubation period for NNT is about 6 days, with a range from 3 to 28 days. Overall, neonatal tetanus case-fatality rates are very high, exceeding 80% among cases with a short incubation period.

Clinical Features

Tetanus is an acute, often fatal, disease caused by the toxin produced by *C. tetani*. The most important toxin of *C. tetani* is the highly potent tetanospasmin. This toxin blocks inhibitory neurotransmitters in the central nervous system and causes muscular stiffness and spasms typical of generalized tetanus.

Generally, a shorter incubation period is associated with a more heavily contaminated wound, more severe disease and a worse prognosis. Generalized tetanus, the most common form of the disease, is characterized by increased muscle tone and generalized spasms. Early symptoms and signs include increased tone in the masseter muscles (trismus, or lockjaw), dysphagia, stiffness or pain in the neck, shoulder and back muscles. Some patients develop paroxysmal, violent, painful, generalized muscle spasms. A constant threat during generalized spasms is reduced ventilation or apnoea or laryngospasm. The patient may be febrile, although many have no fever; mental state is unimpaired. Sudden cardiac arrest sometimes occurs, but its basis is unknown. Other complications include pneumonia, fractures, muscle rupture, deep vein thrombophlebitis, pulmonary emboli, decubitus ulcers and rhabdomyolysis. Death results from respiratory failure, hypertension, hypotension or cardiac arrhythmia .

The overall tetanus case-fatality rate varies between 10% and 70%, depending on treatment, age and general health of the patient. Without hospitalization and intensive care, fatality is almost 100% among the oldest and the youngest patients. In settings with optimal care, it may be reduced to 10–20%.

Tetanus Neonatorum (NNT)

Inability to suck is the most common presenting symptom in the neonates. Tetanus neonatorum is typified by a new born infant who sucks and cries well for the first few days after birth and subsequently develops progressive difficulty and inability to feed because of trismus, generalized stiffness with spasms or convulsions and opisthotonus.

The WHO definition of neonatal tetanus is an illness occurring in a child who has the normal ability to suck and cry in the first 2 days of life but who loses this ability between days 3 and 28 of life and becomes rigid and has spasms.

Epidemiology

Global Situation

Tetanus remains an important public health problem in many parts of the world, particularly in the poorest districts of tropical developing countries, where tetanus morbidity and mortality are dominated by maternal and neonatal tetanus (MNT). Estimates from WHO suggest that in 2002, the total number of deaths caused by tetanus worldwide was 213,000, of which neonatal tetanus was estimated to represent about 180,000 and maternal tetanus possibly as many as 15,000–30,000 deaths.

Situation in Sri Lanka

Tetanus and neonatal tetanus are notifiable diseases in Sri Lanka. According to hospital in-ward statistics, around 2000 cases of tetanus per year were reported until the late 1970s; a gradual decline has been observed from the 1980s and < 50 cases have been reported annually from 1997 onwards. For the year 2009, only a total of 18 clinically confirmed cases of tetanus have been reported from all over the country.

Immunization to prevent tetanus in the newborn during the neonatal period commenced in Sri Lanka in 1969. According to hospital in-ward statistics, around 500 - 1000 cases of neonatal tetanus per year were reported until the late 1970s; a sharp decline has been observed from the 1980s onwards and < 5 cases have been reported annually from 1997 onwards. For the year 2009, not a single case of clinically suspected neonatal tetanus has been reported from all over the country.

Tetanus vaccines

Tetanus is readily preventable through immunization with tetanus toxoid-containing vaccines, which are included in childhood immunization programmes all over the world. To obtain long-lasting immunity, however, booster doses are required. Where National Immunization Programmes have maintained high coverage with TT-containing vaccines for several decades, tetanus has become very rare, but occurs occasionally in the elderly and other non or insufficiently immunized people.

The goals of tetanus control are primarily to eliminate MNT globally; and to achieve and sustain high coverage of 3 doses of DTP and of appropriate booster doses in order to prevent tetanus in all age groups.

Diphtheria-tetanus-whole cell pertussis vaccine (DTwP) has been part of the National Immunization Programme of Sri Lanka since 1961. Immunization of pregnant mothers with TT to prevent MNT commenced in Sri Lanka in 1969.

Characteristics of the Vaccine

Tetanus vaccines are based on tetanus toxoid, a modified neurotoxin that induces protective antitoxin. Tetanus toxoid adsorbed is prepared by detoxification of the sterile filtrate of broth cultures of *Clostridium tetani* with formalin and heat. The toxoid is purified by chemical method and is adsorbed onto aluminium phosphate as adjuvant. Thiomersal is added as preservative.

Tetanus toxoid vaccines are available as single toxoid (TT), combined with diphtheria toxoid (DT) or low-dose diphtheria toxoid (aTd) and in combination with diphtheria and pertussis vaccines (DTwP, DTaP or dTaP). The DTP combination (primarily for children aged less than 1 year) has been part of WHO's Expanded Programme on Immunization since its inception in 1978.

Immunity to tetanus is antibody-mediated and depends upon the ability of anti-toxins to neutralize tetanospasmin. Immunity to tetanus toxin is induced only by immunization; recovery from clinical tetanus does not result in protection against further attacks. A small amount of tetanus toxin, although enough to cause the disease, is insufficient to stimulate antibody production. Therefore, all patients with clinical tetanus should be immunized with tetanus toxoid, either at the time of diagnosis or during convalescence.

Maternal tetanus antitoxin passes via the placenta to the foetus. Hence, when pregnant women receive a booster dose or the second dose of a primary series at least 2 weeks before delivery, both mother and child are protected against birth-associated tetanus. If this last dose is given within 2 weeks of delivery, the time for a booster response to occur may be insufficient to guarantee protection of the newborn. Nonetheless, the opportunity should still be taken to give the dose that is due in order to provide protection during future pregnancies.

The magnitude of the response to a booster dose of tetanus toxoid can depend on the time since last vaccination, and circulating antibody level. It has been widely reported that the higher the pre-booster antibody titre, the lower the relative increase in antitoxin response to immunization. The clinical relevance of this observation is that boosting an individual with high antitoxin levels does not provide additional short-term or long-term protection. **Therefore, immunization schedules need to be appropriately spaced to provide the optimal regime for booster vaccinations.** Furthermore, if the schedule of primary or booster immunizations is interrupted, there is no requirement to re-start the primary series as it is likely that response to the next dose in the series will sufficiently boost the levels of antitoxin.

Types of Tetanus containing vaccine preparations

- ◆ DTwP-Hep B-Hib vaccine - Refer to chapter on Pertussis

- ◆ **Diphtheria-tetanus toxoids vaccine (adsorbed) DT** – Refer to chapter on diphtheria
- ◆ **Adolescent/adult formulation diphtheria and tetanus toxoids vaccine (adsorbed) aTd** - Refer to chapter on diphtheria
- ◆ **Monovalent Tetanus toxoid (TT)**
- ◆ **Diphtheria-tetanus-whole cell pertussis vaccine (DTwP)** - Refer to chapter on pertussis
- ◆ **Diphtheria-tetanus-acellular pertussis vaccine (DTaP)** - Refer to chapter on pertussis
- ◆ **DTaP-HepB vaccine** - Refer to chapter on pertussis
- ◆ **DTwP-Hib vaccine** - Refer to chapter on pertussis
- ◆ **DTaP-HepB-IPV-Hib** - Refer chapter on Pertussis
- ◆ **(Adolescent/adult formulation) dTpa** - Refer to chapter on pertussis

Indications

1. Diphtheria-tetanus-pertussis containing vaccine (DTwP/DTaP) preparations

- ◆ Primary course of immunization against diphtheria, tetanus and pertussis is recommended for all infants at 2, 4 and 6 months of age, with a booster dose at 18 months of age, unless there is a genuine contraindication; if the primary course is interrupted, it should be resumed but not repeated, allowing appropriate intervals between the remaining doses i.e. minimum 6 -8 weeks interval between 1st and 2nd dose and 2nd and 3rd dose, minimum 1 year period between the 3rd and 4th dose.
- ◆ Vaccination of unimmunized older children against diphtheria, tetanus and pertussis up to 5 years of age.

2. Adsorbed diphtheria and tetanus vaccine (DT)

- ◆ This vaccine is used for primary immunization against diphtheria and tetanus in place of DTwP- or DTaP- vaccine when immunization against pertussis is contraindicated.

- ◆ It is recommended for booster vaccination of children against diphtheria and tetanus at the age of 5 years (immediately before school entry). It should be given at least 3 years after the most recent dose of DTwP or DTaP vaccine.
Vaccines containing DT are used for children aged less than 7 years and dT containing vaccines for individuals aged more than 7 years.

3. Adolescent/adult formulation diphtheria and tetanus vaccine (aTd)

- ◆ This vaccine is for booster immunization against diphtheria and tetanus of children aged 12 years (Grade 7 in school) who have already received a primary course of DTP/ DT (4 DTP & 1DT doses) . It should be given at least 7 years after the dose of DT vaccine.

4. Tetanus toxoid (TT)

Monovalent Tetanus toxoid vaccine is recommended for:

- ◆ vaccination of pregnant women with an inadequate or unknown immunization history against tetanus/neonatal tetanus,
- ◆ immunization of non immune persons against tetanus,
- ◆ treatment of patients with tetanus prone wounds.

Both TT and aTd can be used at any time during pregnancy.

Efficacy

Both the efficacy and the effectiveness of tetanus toxoid are well documented. In most clinical trials, efficacy has ranged from 80% to 100%. Serological data from the United Kingdom (UK) and United States of America (USA) illustrate antibody profiles after two different vaccination approaches. In the UK, three doses are given at 2, 3 and 4 months of age, and then again at school entry. Although antibody levels decline after the primary series in infancy, there is an excellent response to the booster at school entry and antibody levels persist at least until age 15, when another booster results in rapid and high increase in antibody. In the USA, the primary series is 2, 4 and 6 months and an additional booster is given at 18 months of age [similar to Sri Lankan schedule], resulting in another antibody peak. However, by school entry, levels have fallen close to those seen in the UK without the booster in the second year of life. Again, the response to a further booster in later childhood (e.g. 4–8 years) is excellent, and by the adolescent years the antibody profiles in both countries are similar.

While the booster at age 18 months may give higher protection to the toddler and preschool age group, both schedules give good protection to school children and lay the foundation for long-lasting protection after a booster in adolescence.

In summary, three DTP doses in infancy will give three to five years of protection and there are limited data suggesting that this may persist up to seven years; a further dose/booster (e.g. in early childhood) will provide protection into adolescence, and one or two more boosters will induce immunity well through adulthood - a duration of 20–30 years has been suggested. Booster responses can still be elicited after intervals of 25–30 years, demonstrating the persistence of immunological memory.

Immunization Schedule

The present National immunization schedule recommended for routine immunization of children, adolescents and pregnant mothers has been decided on the epidemiology of the disease, feasibility of implementation of the EPI in the country and the objectives of the National Elimination Programme of tetanus and neonatal tetanus.

1. Pre exposure immunization against tetanus

1.1 Immunization from infancy up to adolescence

On completion of two months of age every infant should receive the first dose of tetanus toxoid in the form of Pentavalent vaccine (DTwP-Hep B-Hib) followed by two more doses on completion of 4 months and 6 months of age respectively. Even if there is a delay between doses the child should be given the scheduled doses as/when he/she presents for immunization. It is very important to ensure that every child receives three doses of DTP containing vaccine before completion of one year of age. The interval between any two consecutive doses should not be less than 6–8 weeks for routine immunization. The 4th dose of tetanus toxoid is given as DTP at or on completion of 18 months of age. The 5th dose of tetanus toxoid should be given in the form of DT on completion of 5 years of age or at school entry. Sixth booster dose of tetanus toxoid should be given in the form of the aTd at 12 years (Grade 7 in school) of age.

It is not necessary to start the schedule again if any dose is missed by the recipient. Subsequent doses should be continued at appropriate intervals. In this situation the child will receive all the scheduled doses late and will have adequate levels of immunity late.

1.2 Immunization during pregnancy

The number of TT doses required and timing of boosters during pregnancy will

depend on the past immunization history of the pregnant mother with tetanus containing vaccines.

1.2.1 Immunization of pregnant mothers who have not received tetanus containing vaccines in infancy and childhood as per the EPI schedule

Pregnant mothers who have not received tetanus containing vaccine according to the EPI schedule during infancy and childhood i.e. six doses of tetanus containing vaccines -3 doses of DTP/ penta in infancy + DTP at 18 months + DT at 5 years + aTd at 12 years, should be immunized according to the following schedule.

Pregnant women with an incomplete or unknown immunization history should always receive 2 doses of tetanus toxoid vaccine during her first pregnancy: the first dose after 12 weeks of gestation and the second dose 6 -8 weeks after the first dose (minimum 2 weeks before delivery).

A pregnant mother with the history of having received two doses of TT during her 1st pregnancy needs to be given one booster dose of TT during her 2nd pregnancy, after 12 weeks of gestation.

A pregnant mother with a history of receiving three doses of TT during her 1st & 2nd pregnancies needs to be given one booster dose of TT during her 3rd pregnancy, after 12 weeks of gestation.

A pregnant mother with a history of having received four doses of TT during her 1st, 2nd and 3rd, pregnancies needs to be given one booster dose of TT during her 4th pregnancy, after 12 weeks of gestation.

A pregnant mother who has received 5 doses of tetanus toxoid during her previous pregnancies as mentioned above does not need further booster doses of tetanus toxoid during subsequent pregnancies.

1.2.2 Immunization of pregnant mothers who have received tetanus containing vaccines in infancy and childhood as per the EPI schedule

Pregnant mothers with documented evidence of having received tetanus containing vaccine according to the EPI schedule during infancy and childhood i.e: six doses of tetanus containing vaccines -3doses of DPT/ penta in infancy + DPT at 18 months + DT at 5 years + aTd at 12 years, **do not need to** be immunized with tetanus toxoid during the pregnancy, **if:**

- ◆ the gap between the 6th dose of tetanus containing vaccine and the current pregnancy is less than 10 years,
- ◆ the gap between the subsequent dose of tetanus containing vaccine received after the 6th dose and the current pregnancy is less than 10 years.

A pregnant mother who has documented evidence of having received tetanus containing vaccines in infancy and childhood as per the EPI schedule **needs to get one TT booster** dose during her pregnancy if the gap between the 6th dose or any subsequent tetanus containing vaccine and the index pregnancy is more than 10 years.

2. Post exposure vaccination against tetanus

Decision on post exposure vaccination should be taken after considering the nature of the injury and the previous history of immunization with tetanus containing vaccine.

2.1 Immunization of persons who have been immunized with tetanus containing vaccine during infancy and childhood

If a person has documented evidence of receipt of six doses of tetanus containing vaccine (with 4 doses of DTP/ pentavalent, DT, aTd) he/she does not need to be immunized with tetanus toxoid up to 10 years after the 6th dose of tetanus containing vaccine. If a patient presents 10 years after the 6th dose of tetanus containing vaccine immunity could be boosted up with a one dose of tetanus containing vaccine.

However, if a patient presents within 10 years with a **severely contaminated** wound a booster dose of tetanus toxoid could be given even though the gap between the 6th dose of tetanus and the injury is less than 10 years.

If there is documentary evidence to show that any infant, child or an adult has been immunized as per EPI schedule, it is not necessary to immunize them in between the routine doses again whenever they present with trauma as they are protected against tetanus infection in between the doses. However, if an infant, child or an adult presents with a **severely contaminated wound**, a dose of tetanus could be given to boost up the immunity even in between the recommended routine doses.

2.2 Immunization of persons who have not been immunized with tetanus containing vaccine according to the EPI schedule

Any person who has not been immunized with tetanus containing vaccine during infancy and adolescence according to the national EPI schedule, he / she should be given a dose of tetanus toxoid (1st dose) if there is a risk of developing tetanus. Second dose of tetanus toxoid should be given 4 weeks after the 1st dose and the third dose 6 months after the second dose. A booster dose (4th dose) of tetanus could be given 5 years after the 3rd dose. Fifth dose given 10 years after the 4th dose will produce a long lasting, probably a life long immunity.

Dosage & Administration

0.5 ml. Tetanus toxoid vaccine adsorbed should be injected intramuscularly into the deltoid muscle in older children and in adults. If there are indications for the use of tetanus toxoid in infants, the preferred site for intramuscular injection is the anterolateral aspect of the mid thigh since it provides the largest muscle mass. The vaccine should be shaken well before use.

0.5 ml of Pentavalent vaccine (DTwP-Hep B-Hib) is, administered intramuscularly in the anterolateral thigh in infants and in the deltoid muscle in those 12 months of age and older.

Storage

Tetanus containing vaccines should be stored and transported between + 2°C and +8°C and should not be exposed to freezing as it can reduce their potency. Opened tetanus containing vaccine vials should be stored between + 2°C and +8°C and could be re used in subsequent immunization sessions within 4 weeks of opening if the criteria for open vial policy is fulfilled .

Cautions and contraindications

Tetanus toxoid used alone or in various fixed combinations is considered very safe. Immunodeficiency including HIV infection is not a contraindication to their use.

Reinforcing doses of tetanus toxoid at less than 5 year intervals may provoke hypersensitivity reactions and therefore should be avoided.

Precautions

When vaccines containing tetanus toxoid stand for a long time, the vaccine separates from the liquid and looks like fine sand at the bottom of the vial. Shake the vial to mix the vaccine and liquid again before administration. TT/DT/aTd/DTP vaccines should never be frozen. The “shake test” will determine if the vaccine has been damaged by freezing.

Adverse Events

Tetanus toxoid causes minor local reactions such as pain, redness and swelling round the injection site and may persists for several days. Mild systemic reactions including fever, aches and malaise occur in 0.5–1% of vaccinees following booster injections. In general, both local and systemic reactions increase with increasing numbers of doses. Severe generalized adverse events such as anaphylactic reactions and brachial neuritis are extremely rare.

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Introduction

Diphtheria has been known since ancient times, although in the pre-microbiological age it was not clearly distinguished from streptococcal infections. The first accurate description of the disease was done by Bretonneau in 1826. Klebs described the morphological appearance of the organism in a diphtheritic membrane in 1883, and a year later Loeffler isolated the organism.

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 (croup) or damage to myocardium and other tissues. Throughout history, diphtheria has been one of the most feared childhood diseases, characterized by devastating outbreaks. In countries endemic for diphtheria, the disease occurs mostly as sporadic cases or in small outbreaks. Although most infections with *C. diphtheriae* are asymptomatic or run a relatively mild clinical course, high case-fatality rates (>10%) have been reported even in recent outbreaks.

Before the introduction of antitoxin in the 1890s, case-fatality rates from some diphtheria outbreaks reached or exceeded 50%. Although antitoxin, tracheostomy and modern intensive care facilities have dramatically reduced case-fatality rates in diphtheria when the disease occasionally occurs in industrialized countries, lethality is still high in many developing countries.

Bacteriology

Diphtheria is an acute illness caused by toxigenic strains of *Corynebacterium diphtheriae*, a Gram-positive, non-sporing, non-capsulate slender club-shaped bacillus that exists in 4 biotypes namely *C. gravis*, *C. mitis*, *C. intermedius* and *C. belfanti*.

The exotoxin produced by *C. diphtheriae* acts locally on the mucous membranes of the respiratory tract or, less commonly, on damaged skin, to produce an adherent pseudomembrane. Systemically, the toxin acts on cells of the myocardium, nervous system and adrenals.

Mode of transmission

Humans are the only natural host for *C. diphtheriae*. The disease is communicable for up to 4 weeks, but carriers may shed organisms for longer. Spread is by respiratory droplets or by direct contact with skin lesions or articles soiled by infected individuals. Effective antibiotic therapy promptly terminates shedding. The rare chronic carrier may shed organisms for 6 months. In developing countries, a high rate of skin infection caused by a diphtheriae creates a primary reservoir of diphtheriae organisms. Symptoms of respiratory diphtheria occur usually after an incubation period of 1–5 days.

Clinical Features

Diphtheria is a disease affecting the tonsils, the pharynx, the larynx, and the nose. In developing countries skin diphtheria is common with lesions indistinguishable from or a component of, impetigo. Although most infections are asymptomatic or run a relatively mild clinical course, some patients succumb to airway obstruction caused by laryngeal diphtheria or toxic myocarditis. The onset is relatively slow and characterized by moderate fever and a mild exudative pharyngitis. In severe cases, so called pseudo-membranes gradually form in the throat, recognizable by their typical asymmetric, greyish-white appearance and strong attachment to the underlying tissue. Such pseudo-membranes may extend into the nasal cavity and the larynx causing obstruction of the airways. Laryngeal diphtheria, which sometimes occurs even without pharyngeal involvement, is a medical emergency that often requires tracheostomy. Exotoxin absorbed from the mucosal (or cutaneous) lesions may account for toxic damage to organs such as the myocardium, kidneys and nervous system.

During outbreaks, clinical diagnosis based on typical pseudo-membranous pharyngitis is quite reliable. Although laboratory investigation of suspected cases is strongly recommended, treatment should not be delayed while waiting for the laboratory results. Bacterial culture is the mainstay of aetiological diagnosis.

Urgent treatment of diphtheria is mandatory to reduce complications and mortality. The mainstay of treatment is intramuscular or intravenous administration of diphtheria antitoxin. Antibiotics (penicillin or erythromycin) have no impact on established exotoxic lesions but limit further bacterial growth and the duration of corynebacterial carriage that often persists even after clinical recovery. Antibiotic treatment usually renders patients non-infectious within 24 hours.

Epidemiology

Global Situation

Diphtheria is still a significant child health problem in countries with poor childhood immunization coverage. Where childhood immunization coverage is high and natural boosting low, as in most industrialized countries, a large proportion of the adult population is gradually rendered susceptible to diphtheria as a result of waning nature of the immunity.

In temperate climates, most cases occur during the cold season; whereas in warm climates, transmission takes place throughout the year. In countries where diphtheria is still endemic, preschool and school-age children are most commonly affected. In most industrialized countries, endemic diphtheria has disappeared or become extremely rare. However, the importance of maintaining high vaccination coverage against diphtheria among both children and adults has been demonstrated by outbreaks of the disease in many parts of the world, notably in countries of the former Soviet Union during the 1990s.

Situation in Sri Lanka

Diphtheria is a notifiable disease in Sri Lanka. The last laboratory confirmed case was reported in 1996. Thereafter not a single case of diphtheria has been reported from the entire country. Active immunization against diphtheria by using DTP vaccine was initiated in 1961. Currently immunization against diphtheria is carried out by using pentavalent vaccine (DTwP-Hep B-Hib), DT and aTd vaccines.

Diphtheria vaccine

The primary aim of diphtheria vaccination is to reduce incidence and severity of the disease among young children. It has been postulated that given high and sustained coverage, vaccination could eliminate diphtheria as a public health problem as in the case of Sri Lanka.

Diphtheria toxoid is prepared from cell-free purified diphtheria toxin treated with formaldehyde. It is a relatively poor immunogen, which, to improve its effectiveness, is usually adsorbed onto an adjuvant, either aluminium phosphate or aluminium hydroxide.

Characteristics of the Vaccine

Currently, diphtheria toxoid is almost exclusively available in combination with tetanus toxoid (T) as DT, or with tetanus toxoid and pertussis vaccine as DTP (the origin of the pertussis component often specified as whole-cell (wP) or acellular (aP)). Diphtheria toxoid may also be combined with additional vaccines, such as hepatitis B and *Haemophilus influenzae* type b.

Diphtheria vaccines are based on diphtheria toxoid, a modified bacterial toxin that induces protective antitoxin. Diphtheria toxoid combined with tetanus toxoid and pertussis vaccine (DTwP), has been part of the EPI since its inception in 1974. During the period 1980–2000, the total number of diphtheria cases reported globally was reduced by >90%. Following the primary immunization series, the average duration of protection is about 10 years. Protective immunity may be boosted through exposure to circulating strains of toxigenic *C. diphtheriae*. Where natural boosting does not occur, booster doses of diphtheria toxoid beyond infancy, early school age and school leaving were required to maintain protective immunity.

The recommended schedule for vaccination against diphtheria varies considerably between countries. According to the WHO EPI schedule, the primary series of DTwP- or DTaP-containing vaccines should be administered in 3 doses, starting as early as 6 weeks of age and given with a minimum interval of 4 weeks. Where resources permit, additional doses can be given after the completion of the primary series. Many national immunization programmes offer 1–2 booster doses, for example one at around 2 years of age and a second at around 5 years of age.

The acronym DTP, using capital letters, signifies child formulations of diphtheria and tetanus toxoid and pertussis-containing vaccines. The acronym aTd is used for adolescent/adult formulations which contain substantially lesser amounts of diphtheria toxoid.

Types of diphtheria containing vaccine preparations

- ◆ **Diphtheria-tetanus-whole cell pertussis vaccine (DTwP)** - Refer to chapter on pertussis
- ◆ **Diphtheria-tetanus-acellular pertussis vaccine (DTaP)** - Refer to chapter on pertussis
- ◆ **DTaP-HepB vaccine** - Refer to chapter on pertussis
- ◆ **DTwP-Hib vaccine** - Refer to chapter on pertussis
- ◆ **DTwP-Hep B-Hib vaccine** - Refer to chapter on Pertussis
- ◆ **DTaP-HepB-IPV-Hib** - Refer to chapter on Pertussis
- ◆ **(Adolescent/adult formulation) dTpa** - Refer to chapter on pertussis
- ◆ **Diphtheria-tetanus toxoids vaccine (adsorbed) DT**

Diphtheria and tetanus toxoids vaccine (adsorbed) is prepared by combining purified diphtheria toxoid and purified tetanus toxoid. The antigens are adsorbed onto aluminium phosphate as adjuvant.

Each 0.5 ml dose of DT contains diphtheria toxoid ≤ 25 Lf (≥ 30 IU) and tetanus toxoid ≥ 5 Lf (≥ 40 IU) adsorbed onto aluminium phosphate (AlP_0_4) ≥ 1.5 mg.

- ◆ **Adolescent/adult formulation diphtheria and tetanus toxoids vaccine (adsorbed) aTd**

Diphtheria and tetanus toxoid vaccine adsorbed for adolescents and adults is prepared by combining purified diphtheria toxoid and purified tetanus toxoid. The antigens are adsorbed on to aluminium phosphate as adjuvant.

Each 0.5 ml dose of aTd contains diphtheria toxoid ≤ 5 Lf (≥ 2 IU) and tetanus toxoid ≥ 5 Lf (≥ 40 IU) adsorbed on aluminium phosphate (AlP_0_4) ≥ 1.5 mg.

This vaccine, with a lower titre of diphtheria toxoid, is for immunization of children aged over 7 years and adults. This reduction of diphtheria toxoid titre.

minimizes reactogenicity at the injection site but is still sufficient to provoke an antibody response in older children and adults.

Indications

1. Diphtheria, tetanus and pertussis vaccine preparations (DTwP or 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, with a booster dose at 18 months of age, unless there is an absolute or temporary contraindication. If the primary course is interrupted, it should be resumed but not repeated, allowing appropriate intervals (minimum of 6 weeks) between the remaining doses.
- ◆ Vaccination of unimmunized older children against diphtheria, tetanus and pertussis who are less than 5 years of age.

2. Adsorbed diphtheria and tetanus vaccine (DT)

- ◆ This vaccine is used for primary immunization in place of DTwP or DTaP vaccine when immunization against pertussis is contraindicated.
- ◆ It is recommended for booster vaccination of children against diphtheria and tetanus at the age of 5 years (immediately before school entry). It should be given at least 3 years after the most recent dose of DTwP or DTaP vaccine.

3. Adolescent/adult formulation diphtheria and tetanus vaccine (aTd)

- ◆ This vaccine is for booster immunization of children over 7 years of age and adults. As per the national EPI schedule children aged 12 years (at Grade 7 in school) who have already received a primary course of DPT (and/or DT) will receive a dose of aTd.

Dosage & Administration

Refer to chapter on pertussis

Storage

Refer to chapter on pertussis

Cautions and contraindications

Refer to chapter on pertussis

Adverse Events

DTP

Refer to chapter on pertussis

DT

Transient fever, headache, malaise and local reactions may occur; a small painless nodule may form at the injection site but usually disappears without sequelae; severe anaphylactic reactions are rare; neurological reactions have been reported on rare occasions.

aTd

Adverse events following aTd are generally mild and confined to the site of injection. Some inflammation may occur together with transient fever, malaise and irritability. Occasionally a nodule may develop at the site of injection but this is rare.

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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 major cause of acute and chronic hepatitis in the world. It ranges in severity from a mild illness, lasting a few weeks (acute), to a serious long-term (chronic) illness that can lead to liver disease and/or liver cancer.

In 1883, a form of hepatitis transmitted through blood or blood products was first documented in Germany during a smallpox immunization campaign. McCallum proposed the term hepatitis B for 'serum' hepatitis in 1947. The Australia antigen, now called the hepatitis B surface antigen (HBsAg), was first identified in 1967 and is the basis of the vaccine.

Hepatitis B virus infection is a major global health problem. Worldwide, an estimated two billion people have been infected with the hepatitis B virus (HBV), and more than 350 million are thought to be chronic carriers of hepatitis B.

A vaccine against hepatitis B has been available since 1982. Hepatitis B vaccine is 95% effective in preventing HBV infection and its chronic consequences, and is the first vaccine against a major human cancer. The vaccine has an outstanding record of safety and effectiveness. Since 1982, over one billion doses of hepatitis B vaccine have been used worldwide. In many countries where 8 - 15% of children were used to become chronically infected with HBV, vaccination has reduced the rate of chronic infection to less than 1% among immunized children.

Virology

HBV is a double-stranded enveloped virus of the *Hepadnaviridae* family. HBV replicates in the hepatocytes of humans and other higher primates, but does not grow in artificial cell cultures. HBsAg is a lipoprotein of the viral envelope that circulates in the blood as spherical and tubular particles of 22 nanometres in size.

HBV is a virus with three major antigens, known as hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg) and hepatitis B core antigen (HBcAg). HBsAg can be detected in serum 30-60 days after exposure and persists until the infection resolves. Any person positive for HBsAg is considered infectious.

Mode of transmission

Hepatitis B virus is transmitted among people by contact with the blood or other body fluids (i.e. semen and vaginal fluid) of an infected person. Modes of transmission are the same for the human immunodeficiency virus (HIV), but HBV is 50 to 100 times more infectious.

Unlike HIV, HBV can survive outside the body for at least 7 days. During that time, the virus can still cause infection if it enters the body of a person who is not infected. Common modes of transmission are; sexual contact, injecting drug use, perinatal (from mother to baby at birth), unsafe injection practices and blood transfusions. HBV is a major infectious occupational hazard for health workers. The virus incubation period is 90 days on average, but can vary from about 30 to 180 days.

Clinical Features

The outcomes of HBV infection are age-dependent and include asymptomatic infection, acute HBV infection, chronic HBV infection, cirrhosis and hepatocellular carcinoma (HCC). Acute hepatitis B occurs in approximately 1% of perinatal infections, 10% of early childhood infections (children aged 1–5 years) and 30% of late infections (people aged >5 years). Fulminant hepatitis develops in 0.1–0.6% of acute hepatitis cases; mortality from fulminant hepatitis B is approximately 70%. The development of chronic HBV infection is inversely related to the age of acquisition, occurring in approximately 80–90% of people infected perinatally, about 30% of children infected before the age of 6 years, and in <5% of infections occurring in otherwise healthy adults. People with chronic HBV infection have a 15–25% risk of dying prematurely from HBV-related cirrhosis and HCC.

It is not possible, on clinical grounds, to differentiate hepatitis B from hepatitis caused by other viral agents, hence, laboratory confirmation of the diagnosis is essential. In serological terms, acute HBV infection is characterized by the presence of HBsAg and IgM antibody to the core antigen, HBcAg. During the initial highly replicative phase of the infection, patients are also seropositive for HBeAg. Antibody to HBsAg (anti-HBs) is discernible after a few weeks and is followed by clearance of the HBsAg.

Chronic infection is characterized by the persistence (>6 months) of HBsAg. Persistence of HBsAg is the principal marker of risk for developing chronic liver disease and HCC later in life. The presence of HBeAg indicates that the blood and body fluids of the infected individual are highly contagious.

Epidemiology

Global Situation

Diseases caused by the HBV has a worldwide distribution. It is estimated that >2 billion people worldwide have been infected with HBV. Of these, approximately 350 million individuals are chronically infected and at risk of serious illness and death, mainly from liver cirrhosis and hepatocellular carcinoma (HCC).

Situation in Sri Lanka

Serological surveys among general population and special groups have found that the presence of HBV is not common in Sri Lanka although located in a region where HBV infection is highly prevalent. Sero-prevalence of HBsAg in the country ranges from 0.24 - 2.5% in the community according to findings of Sero-epidemiological studies done before the introduction of Hepatitis B vaccine. Data from several studies carried out by Central Blood Bank shows that HBsAg positivity among blood donors range from 0.1 – 0.7%. Therefore, Sri Lanka is considered a low endemic country for HBV infection.

Hepatitis B vaccine

The main objective of hepatitis B immunization strategies is to prevent chronic HBV infection and its serious consequences, including liver cirrhosis and HCC.

Universal immunization with hepatitis B vaccine has resulted in a dramatic reduction of HBV transmission in many countries with historically high endemicity. This will gradually result in a reduction of HBV-related chronic hepatitis, liver cirrhosis and HCC, which have caused major concerns for public health and the economy in these areas. As of 2008, 177 countries had incorporated hepatitis B vaccine as an integral part of their national infant immunization programmes, and an estimated 69% of the 2008 birth cohort received 3 doses of hepatitis B vaccine. In recent years, the significantly reduced price of hepatitis B vaccine in developing countries has facilitated its introduction into many HBV-endemic areas. Following the primary vaccination schedule, almost all children are protected, probably for life, without the need for booster injections.

Sri Lanka introduced Hepatitis B vaccine into National Immunization schedule in year 2003 (on a phased basis) in the form of liquid monovalent vaccine. With the introduction of Hib vaccine in year 2008, Hep B vaccine is given in the form of liquid pentavalent vaccine (DTP-HepB+Hib).

Characteristics of the Hepatitis B vaccine

Recombinant hepatitis B vaccine was introduced in 1986 and has gradually replaced the earlier used plasma-derived hepatitis B vaccine. The recombinant hepatitis B vaccines use HBsAg synthesized in yeast or mammalian cells into which the HBsAg gene (or HBsAg/pre-HBsAg genes) has been inserted by plasmids. Following thorough purification from host-cell components, alum (and, in certain formulations, thiomersal) is added as adjuvant.

The Hepatitis B vaccines available in Sri Lanka are those developed using recombinant DNA technology.

Types of Hepatitis B containing vaccine preparations

Available hepatitis B vaccine formulations are, either monovalent or in combination with one or more other vaccines (multivalent), such as DTP, Hib vaccine and inactivated polio vaccine. Many countries, including Sri Lanka, give Hepatitis B vaccine combined with DTP and Hib vaccines (DTP-HepB+Hib).

Currently the EPI programme uses pentavalent vaccine (DTwP-Hep-B-Hib) to immunize infants against five diseases including hepatitis B.

- ◆ **DTwP-Hep B-Hib vaccine (Pentavalent vaccine)** - Refer to chapter on Pertussis
- ◆ **Monovalent Hepatitis B vaccine**

Each 0.5 ml dose contains hepatitis B surface antigen 10µg, Aluminium hydroxide gel as Al⁺⁺⁺ 0.25mg and thiomersal as preservative 0.01 v/w%.

When immunizing against HBV at birth, only monovalent hepatitis B vaccine should be used: the other antigens found in combination vaccines are currently not approved for use at birth.

- ◆ **Hepatitis A & B vaccine**

Each 0.5 ml dose of paediatric preparation contains 360 ELISA units of HAV antigens, 10 µg recombinant DNA hepatitis B surface antigen protein, 0.225 mg aluminum phosphate/hydroxide, 0.5%w/v phenoxyethanol, traces of formaldehyde and neomycin. May contain yeast proteins.

Each 1 ml dose of adult preparation contains 720 ELISA units of HAV antigens, 20 µg recombinant DNA hepatitis B surface antigen protein, 0.45mg aluminum phosphate/hydroxide, 0.5%w/v phenoxyethanol, traces of formaldehyde and neomycin. May contain yeast proteins.

- ◆ **DTaP-HepB vaccine** - Refer to chapter on Pertussis
- ◆ **DTaP-HepB-IPV-Hib** - Refer to chapter on Pertussis

Indications

1. Hepatitis B Vaccine:

- ◆ Primary course of immunization against Hep B infection is

recommended for all infants on completion of 2, 4 and 6 months of age.

- ◆ Those at high risk of contracting HBV infection, including persons with high-risk sexual behaviour, partners and household contacts of HBsAg-positive persons, injecting drug users, persons who frequently require blood or blood products, recipients of solid organ transplantations.
- ◆ Those at occupational risk of HBV infection, including health care workers.
- ◆ International travellers visiting HBV-endemic countries.
- ◆ Together with passive immunization if required, for babies born to mothers who have had hepatitis B infection during pregnancy or are hepatitis B surface antigen positive
- ◆ Post-exposure vaccination following needle stick injuries.

Efficacy

The protective efficacy of hepatitis B vaccination is directly related to the induction of anti-HBs antibodies. The complete vaccine series induces protective antibody levels in >95% of infants, children and young adults. After the age of 40 years, protection following the primary vaccination series drops below 90%; by 60 years, protective antibody levels are achieved in only 65–75% of vaccinees.

According to the current scientific evidence the duration of protection is considered to be lifelong.

Immunization Schedule

Multiple options are available for incorporating the hepatitis B vaccine into the national immunization programmes and the choice of schedule depends on the country's epidemiological situation and programmatic feasibility.

Hepatitis B immunization schedule recommended for routine immunization of infants and children in Sri Lanka has been decided on the epidemiology of hepatitis B, feasibility of implementation of the EPI in the country and the objectives of the hepatitis B control Programme. A three-dose schedule has been adopted by the EPI for hepatitis B immunization considering the above factors and to achieve very high levels of immunization coverage.

Therefore, three doses of pentavalent vaccine (DTwP-Hep B-Hib) are given routinely to all infants on completion of 2, 4 and 6 months of age according to the EPI schedule in Sri Lanka.

Anyone who has not received the routine hep B vaccination during infancy can get hepatitis B vaccine at any age, followed by a second dose one month after the first and the third dose 6 months after the first dose.

For the travellers to endemic areas, accelerated schedule of 0, 1, 2 months and a booster at 12 months from the initial dose is recommended.

Countries with high perinatal transmission of hep B have schedules with the first vaccination at birth, followed by a second and third dose at the time of the first and third DTP vaccination, respectively.

Booster doses are not recommended for immunocompetent individuals after a primary course, as there is good evidence that a completed primary course of hepatitis B vaccination provides long-lasting protection.

However, booster doses are recommended for individuals with impaired immunity, in particular those with either HIV infection or renal failure. The time for boosting in such individuals should be decided by regular monitoring of anti-HBs levels.

Dosage & Administration

In the National EPI hep B vaccine is given to all infants in the form of pentavalent vaccine (DTwP-Hep B-Hib). The dose is 0.5 ml, administered intramuscularly in the anterolateral aspect of mid thigh in infants and in the deltoid muscle in those 12 months of age and older. The vaccine should be shaken well before use.

The recommended dose of hep B containing vaccines varies by product and with the age of the recipient. Therefore, manufacturer's recommendation for dosage should be followed. In most cases, infants and adolescents (aged ≤ 15 years) receive 50% of the adult dose. All hep B containing vaccines are administered by intramuscular route.

Storage

Hepatitis B containing vaccine should be stored at $+2^{\circ}\text{C}$ to $+8^{\circ}\text{C}$ temperature. Exposure to freezing temperature must be avoided as it dissociates antigen from the alum adjuvant and lead to lose the vaccine potency.

Cautions and contraindications

The following conditions are considered as contraindications for the use of hepatitis B containing vaccine preparations:

- ◆ presence of one of the general contraindications for any vaccine,
- ◆ history of an allergy to any of the vaccine components,
- ◆ anaphylactic reaction to a previous dose of hepatitis B vaccine.

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

Adverse Events

Adverse events after hepatitis B vaccination are transient and minor, and include soreness at the injection site, fever, nausea, dizziness, malaise, myalgia and arthralgia. Reports of severe anaphylactic reactions are extremely rare.

Post-exposure prophylaxis for hepatitis B infection

Among unimmunized, both passive-active postexposure prophylaxis (PEP) using HBIG & hepatitis B vaccine and active PEP using hepatitis B vaccine alone are highly effective in preventing infection after exposure to HBV. The major determinant of the effectiveness of PEP is early administration of the initial dose of vaccine. The effectiveness of PEP diminishes the longer after exposure it is initiated. HBIG may be administered simultaneously with hepatitis B vaccine but in a different injection site.

Hepatitis B Immune Globulin (HBIG)

The standard dose of HBIG is 0.06 mL/kg for all applications in adults. HBIG may be administered simultaneously with hepatitis B vaccine but in a different injection site. HBIG is administered by intramuscular injection. An appropriate muscle mass (i.e., deltoid or gluteal) should be chosen in which to deliver the large volumes of HBIG required by using a needle length appropriate for the person's age and size. HBIG should be stored at +2°C to +8°C and should not be frozen.

HBIG in conjunction with hep B vaccination (i.e. is, active immunization) is used as Prophylactic treatment to prevent infection after exposure to HBV in the following situations:

◆ Perinatal exposure

For the newborn infants whose mothers are HBsAg-positive, HBIG at birth and hep B vaccination at 0, 1, 2, 12 months schedule is recommended.

◆ Sexual partners of persons with acute hepatitis B virus infection

People who have been sexually exposed to an HBsAg-positive persons, HBIG and hep B vaccination at 0, 1, 2, 12 months schedule is recommended.

◆ **Accidental Percutaneous or mucosal exposure to HBsAg**

People who have had percutaneous (e.g. needle stick exposures) or mucous-membrane exposure to HBsAg-positive blood or body fluids, management are as in the table below

Exposed persons vaccination status	If the source is		
	HBsAg +ve	HBsAg -ve	HBsAg status unknown
Unvaccinated	HBIG x 1 & HBV immunization	HBV immunization	HBV immunization
Vaccinated responder- anti-HBs titre in exposed \geq 10m IU/ml (tested within the past 24 months)	No immunization	No immunization	No immunization
Vaccinated non responder - anti-HBs titre in exposed < 10m IU/ml	HBIG x 2 one month apart	No immunization	If high risk source treat as if source was HBsAg +ve

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Introduction

Haemophilus influenzae type b disease, primarily pneumonia and meningitis in young children, is a significant public health concern in many parts of the world where large-scale Hib immunization has not yet been implemented. Hib disease is defined as invasive when the bacterial agent is detected in body fluids or tissue that normally are sterile (blood, cerebrospinal fluid, peritonea fluid, pleural fluids or lung aspirates).

Bacteriology

Haemophilus influenzae b is a Gram-negative coccobacillus first described by Pfeiffer in 1889. It is a common commensal in the upper respiratory tract of children. In the pre-vaccination era, the majority of non-immune children were colonized by Hib in their nasopharynx at some time, occasionally for months, although the bacterial colonization rate varied considerably with age and socio-economic factors. Upper respiratory tract colonization of this agent drops dramatically in populations where Hib immunization has achieved high coverage. Only a tiny fraction of those who harbour this organism on their respiratory mucosa subsequently develops clinical disease.

Mode of transmission

Humans are the only known natural host for *Haemophilus influenzae* bacteria, which is spread by droplets released when an infected child sneezes or coughs and by direct close contact with an infected person.

Clinical Features

The disease burden is highest among those aged between 4 months and 18 months, but Hib disease is occasionally observed in infants aged less than 3 months and among those aged more than 5 years. In unvaccinated populations, Hib is the dominant cause of non-epidemic bacterial meningitis especially during the first year of life. Even with prompt and adequate antibiotic treatment, 3–20% of patients with Hib meningitis die. Where medical resources are limited, fatality rates for Hib meningitis may be much higher, and severe neurological sequelae are frequently observed in survivors in up to 30–40%.

In developing countries, pneumonia is more common than meningitis in children with Hib disease. Other important manifestations of Hib infection include septicaemia, septic arthritis, osteomyelitis, pericarditis, cellulites and epiglottitis, particularly in industrialized countries.

The classical clinical signs of meningitis (neck stiffness and photophobia) are often not detected in infants, who usually present with drowsiness, poor feeding and high fever.

There are no specific clinical features of any of the focal infections due to Hib which enable them to be differentiated from those due to other organisms.

Epidemiology

Global Situation

According to the WHO, in year 2000, Hib was estimated to have caused two to three million cases of serious disease, notably meningitis and pneumonia, and 386,000 deaths in young children globally. Another significant proportion of children with serious Hib disease end up with long term consequences such as deafness, learning disabilities, paralysis and mental retardation. Although this problem occurs worldwide the burden of Hib disease is most significant in resource-poor countries. Systematic vaccination has now virtually eliminated Hib disease in industrialized nations.

Situation in Sri Lanka

A recent (2004) disease burden study on *haemophilus influenzae b* carried out in Sri Lanka has indicated that it is an emerging public health issue.

Haemophilus influenzae type B (Hib) vaccine

Fortunately, *Haemophilus influenzae b* disease (Hib) is preventable. Vaccines are the only public health tool capable of preventing the majority of cases of serious Hib disease. There is a highly safe and effective vaccine routinely used in the industrialized world for over 15 years in their childhood immunization programmes and has documented virtual elimination of Hib disease. Despite recommendations from WHO that Hib vaccine be included in all countries' routine infant immunization programmes, in 2006, only 26% of children worldwide received Hib vaccine.

Sri Lanka has introduced Hib vaccine into its National Immunization schedule in year 2008 in the form of liquid pentavalent vaccine (DTP-HepB+Hib).

Characteristics of the Hib Vaccine

The second generation Hib vaccines currently licensed for use in infants consist of polyribosylribitol phosphate (PRP- the capsular polysaccharide of Hib) conjugated to a protein carrier. The first generation Hib vaccine was an unconjugated vaccine and not used now. These conjugate Hib vaccines are more immunogenic and effective in young infants.

The protein carriers used are either a mutant diphtheria toxin (Hb-OC Hib vaccine), or an outer membrane protein of *Neisseria meningitidis* (PRP-OMP Hib vaccine) or tetanus toxoid (PRP-T Hib vaccine). It should be noted that the protein conjugates used in Hib vaccines are not themselves immunogenic and do not give protection against diphtheria, tetanus or *N. meningitides*.

Types of Hib containing vaccine preparations

Available formulations include liquid Hib vaccine as well as lyophilized (freeze-dried) Hib vaccine, either monovalent or in combination with one or more other vaccines (multivalent), such as DTP, hepatitis B vaccine and inactivated polio vaccine. Many countries including Sri Lanka give Hib vaccine combined with DTP and HepB vaccines (DTP-HepB+Hib).

- ◆ **Hib with diphtheria, tetanus, whole cell pertussis and hepatitis B (DTwP-Hep B-Hib) vaccine**
Liquid preparation of this presentation is currently used in the National Immunization programme.
Refer to the chapter on pertussis for details
- ◆ **Monovalent Hib vaccine**
Each 0.5 ml dose contains 10 micrograms of purified capsular polysaccharide of Hib covalently bound to approximately 30 micrograms of tetanus toxoid.
- ◆ **Hib with diphtheria, tetanus and whole cell pertussis (DTwP-Hib) vaccine**
Refer to the chapter on pertussis for details
- ◆ **Hib with diphtheria, tetanus, acellular pertussis, hepatitis B and inactivated polio (DTaP-HepB-IPV-Hib) vaccine**
Refer to the chapter on pertussis for details

Indications

To prevent *haemophilus influenzae* type b infection in infants and children upto 5 years.

Efficacy

The conjugate Hib vaccines currently licensed for immunization of infants induce protective circulating antibodies and immunological memory in all age groups. Hib vaccination also reduces nasopharyngeal colonization with the organism, leading to substantially greater reduction in disease incidence than can be directly attributed to the effects of the vaccine. This indirect effect has been amply demonstrated in several post-introduction effectiveness studies in which near-elimination of the disease occurred in both industrialized and developing countries, even when vaccine coverage was suboptimal. The duration of protection following completion of primary Hib immunization is poorly defined, and it is

likely to vary according to factors such as age at vaccination, ethnicity, immune competency and natural boosting. However, in most cases primary immunization is protective during the years of highest susceptibility to invasive Hib disease.

Immunization Schedule

National immunization schedules may slightly differ depending upon local epidemiological and programmatic considerations. In general, a 3-dose primary series of Hib vaccine is given at the same time as the primary series of diphtheria–tetanus–pertussis (DTP). The first dose may be given to infants as young as 8 weeks of age, and the second and third doses may be given at 6–8 week intervals usually along with DTP. The vaccine is not generally offered to children aged more than 24 months owing to the limited burden of Hib disease among children older than that age.

For children aged more than 12-24 months who have not received their primary immunization series, a single dose of the vaccine is sufficient.

Sri Lankan National Immunization policy is to give Hib vaccination in the form of pentavalent (DTP-HepB+Hib) vaccine to all infants on completion of 2 months, 4 months and 6 months.

Dosage & Administration

All conjugate Hib containing vaccines are given intramuscularly: in infants, they are administered into the anterolateral aspect of the mid thigh or in older children into the deltoid muscle. The standard dose is 0.5 ml.

Liquid Hib vaccines are used directly from the vial, whereas freeze-dried vaccines must be reconstituted before administration, either with diluent or with another vaccine that has been specifically identified and indicated for this purpose by the manufacturer, such as DTP.

Storage

All Hib-containing vaccines should be stored at between +2 °C and +8 °C. Liquid Hib vaccine should never be frozen, stored or transported in contact with ice or ice packs.

Lyophilized vaccine may be frozen until reconstitution, but since the most commonly used diluents used for reconstitution cannot be frozen, it is recommended that lyophilized Hib vaccine should also be stored at temperatures between +2 °C and +8 °C .

Cautions and contraindications

The following conditions are considered as either contraindications or cautions for the use of Hib vaccine.

- ◆ Presence of one of the general contraindications for any vaccine.
- ◆ People who are known hypersensitivity to any component of the vaccine.

Adverse Events

Usually Hib vaccine has not been associated with any serious adverse effects. However, redness, swelling and pain at the site of injection may occur in those who have been vaccinated. Such reactions usually start within 1 day after immunization and resolve within 1–3 days.

Usage of vaccine in specific circumstances

Although immunization against Hib disease is not routinely recommended for individuals aged more than 24 months, older children and adults who are at an increased risk for invasive Hib infection should be vaccinated where resources are available. Such high-risk individuals include:

- ◆ those with HIV infection or immunoglobulin deficiency,
- ◆ recipients of stem cell transplants,
- ◆ patients undergoing chemotherapy for malignant neoplasms,
- ◆ those with asplenia (due to sickle-cell disease or splenectomy).

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JAPANESE ENCEPHALITIS (JE) VACCINE

Introduction

Japanese encephalitis (JE) is an infection of the central nervous system caused by a virus transmitted to man through mosquitoes. This virus was first isolated in Japan in 1935 from the brain of a patient dying from encephalitis. JE is a major debilitating communicable disease with a case fatality rate of 5-30%. Nearly half of the survivors of the disease suffer long term neuro- psychiatric sequelae.

Virology

JE virus is a zoonotic flavivirus belonging to the family of *Flaviviridae*. It is a single, RNA stranded virus antigenically related to several other *flaviviruses* including dengue. The major genotypes of the virus have different geographical distribution but all belong to the same serotype and are similar in terms of virulence and host preference.

Mode of transmission

JE virus circulates in zoonotic cycles involving *culecine* mosquitoes (*Culex tritaeniorhynchus*, *C.gelidus* are the principal vectors) and several vertebrate species. Pigs and wading birds serve as reservoirs and amplifying hosts. Man is an accidental host of the disease under ecological conditions which facilitate the transmission of the virus. Following an infectious mosquito bite, initial viral replication occurs in local and regional lymph nodes. Viral invasion of the central nervous system occurs probably via blood. JE does not spread from man to man due to low and transient viraemia; hence humans are also dead end hosts without contributing to the transmission cycle.

Clinical Features

JE has an incubation period ranging from 4-14 days. JE may present as a mild disease leading to recovery or ending up with severe encephalitis. The course of the disease is conveniently divided into three stages;

Prodromal stage: This stage starts before the involvement of the CNS. The onset of the disease is acute and heralded by fever often with rigours. Severe frontal or generalized headache, nausea and vomiting are common. This period is variable as short as 24 hours to as long as 14 days.

Acute encephalitic stage: This stage is characterized by altered sensorium, convulsions, stiff neck, muscular rigidity, mask like face, abnormal movement, dehydration and weight loss. Altered sensorium includes symptoms such as clouding of consciousness, excitement and confusion. Continuous fever, nuchal rigidity, focal CNS signs, convulsions and altered sensorium are predominant. In many cases, the conditions may be worsened by coma.

Late stage: This stage is marked by recovery or persistence of signs of CNS. Increased deep tendons reflexes, thick and slow speech, aphasia and paresis are other signs and symptoms which may be present. Convalescence is usually slow.

Epidemiology

Global Situation

JE is the most common form of encephalitis in Asia and Western Pacific regions. The disease is endemic across temperate, sub tropical and tropical zones of Asia. Epidemics have occurred in Japan, Korea, and Taiwan later extending to Thailand, Burma, India, Nepal and Sri Lanka. Annual incidence of the disease differs from country to country. It ranges from less than 10 to more than 100 per 100000 population. Given the lack of routine standardized JE surveillance in many countries, the true incidence is underestimated. Only less than 1% of JE cases manifest as encephalitis. Incidence and mortality of this crippling disease is high among paediatric groups. The case fatality among clinically presented is estimated to be between 5 -30%.

Situation in Sri Lanka

JE virus was isolated for the first time in Sri Lanka at the Medical Research Institute in 1968. However, the first recorded major outbreak occurred in Sri Lanka in 1985-86 in the North Central Province. Three hundred and eighty five cases were reported in this outbreak with 64 deaths with a case fatality rate (CFR) of 17%. The disease occurred in epidemic proportions in 1986-87 and 1987-88 too. The latter outbreak was the largest reported so far with 812 cases and 192 deaths (CFR - 24%). This outbreak spread to three new districts adjoining the North Central Province

Subsequent to these outbreaks, immunization against JE with the inactivated JE vaccine was introduced on a phased basis in 1988 in Sri Lanka. The target group identified for vaccination was children in the age group of 1-10 years. Before 2011, JE immunization campaigns were conducted in selected 18 high endemic districts. Deviating from the campaign mode, JE vaccine has been introduced into the EPI programme as a routine vaccine covering the entire country since 2011. The success of immunization against JE is reflected in the fact that since 1988, incidence of JE has decreased drastically with the increased coverage of vaccination. Since 2003, only sporadic JE cases have been reported from different parts of the country.

Japanese Encephalitis Vaccines

Vaccination is the single most important control measure available for controlling JE. Currently, the two types of JE vaccines in large scale use are:

1. The cell culture based live JE vaccine (LJEV) based on the SA 14-14-2 strain of the JE virus.
2. The mouse brain derived, purified, inactivated vaccine based on either the Nakayama or Beijing strains of the JE virus.

Both Nakayama (from 1988-1992) and Beijing (from 1992 – 2008) strains of inactivated JE vaccine had been used in the National Programme of Immunization in Sri Lanka to vaccinate children against JE in selected high risk districts.

Though introduction of the inactivated JE vaccine successfully combated the JE outbreaks during the last two decades, an increasing trend of AEFI due to the inactivated JE vaccine was observed. Rates of AEFI for JE were reported to be the highest after that for the DTP. Reactogenicity of the inactivated JE vaccine has played a major role in this trend affecting the acceptance of the vaccine.

Meanwhile, the WHO's Strategic Advisory Group of Experts (SAGE) had recommended the live, attenuated JE vaccine SA 14-14-2 as an adequately immunogenic and safer vaccine than the killed JE vaccine and an appropriate alternative for the killed JE vaccine. These recommendations were based on studies conducted in some countries and China's experience of using live JE vaccine for a very long period in their immunization programme.

After considering the WHO's SAGE recommendations and findings of the clinical trial carried out in Sri Lanka in 2007, the Advisory Committee on Communicable Diseases recommended replacement of the inactivated JE vaccine with the live attenuated JE vaccine with effect from July, 2009. Currently the National Immunization Programme in Sri Lanka uses the live attenuated JE vaccine SA 14-14-2 to vaccinate children against JE.

Cell culture derived live JE vaccine (LJEV) SA 14-14-2:

Characteristics of the Vaccine

Manufacturing of this vaccine is based on growth of the genetically stable, neuro attenuated SA 14-14-2 strain of the JE virus on a mono layer of primary hamster kidney cells. After cultivation and harvest, an appropriate stabilizer is added to the virus suspension and then lyophilized. It elicits broad immunity against heterologous JE viruses with sufficient viral replication.

Indications

Prevention of infections caused by JE virus and resulting deaths and disabilities

Efficacy

Several studies have demonstrated an excellent immune response after a single

dose of LJEV, with neutralizing antibody responses produced in 85 - 100% of non-immune children. According to the available data, a significant long term protection spanning a period of 11 years has been reported following a single dose of LJEV.

Immunization Schedule

LJEV can be administered to children above 8 months of age and adults. In the National Immunization Programme, all children are immunized with the LJEV on completion of 9 months. If due to any reason, the vaccine is missed or delayed on the due date, it should be given at the next earliest available opportunity for immunization.

Though in certain other countries, a further booster dose is given one year after the primary immunization, many research studies suggest that the immunogenicity observed following a single dose is equivalent to that when two doses (primary and the booster dose) are given separately. Based on these data, a single dose has been recommended to be used in Sri Lanka.

Dosage & Administration

The recommended dosage is 0.5ml of reconstituted vaccine administered subcutaneously to the outer upper arm of the child.

LJEV is a lyophilized powder which looks like a light yellow crisp cake. After reconstitution, it turns into a clear orange- red or light pink liquid. LJEV can be administered with other EPI vaccines.

Storage

LJEV should be stored in a temperature between +2°C to +8°C and protected from sun light. The vaccine should not be frozen. It should preferably be kept in the middle shelf of the main compartment of the refrigerator with the diluents. If the vaccine is not used immediately after reconstitution, it should be stored at +2° C to +8°C. no longer than 6 hours and away from light. After 6 hours it should be discarded.

Cautions and contraindications

LJEV is contraindicated in specific instances given below:

- ◆ children with proven or suspected hypersensitivity to LJEV or its components such as Kanamycin or Gentamicin,
- ◆ congenital or acquired severe immunodeficiency status such as impaired

immunological mechanisms, malignant conditions and Acquired Immune Deficiency Syndrome (AIDS) etc,

- ◆ pregnancy.

Though it is not contraindicated, LJEV should be temporarily postponed in following instances:

- ◆ fever more than 38.5°C,
- ◆ any acute infectious disease,
- ◆ acute stage of any chronic disease,
- ◆ temporarily acquired severe immunodeficiency states due to recent immunosuppressive therapy such as systemic corticosteroids, chemotherapy, irradiation etc,
- ◆ history of convulsions during the last 12 months.

The following conditions are NOT contraindications:

- ◆ minor illnesses such as respiratory tract infection or diarrhoea with temperature below 38.5°C (101°F),
- ◆ family history of convulsions,
- ◆ treatment with topical corticosteroids or systemic use of corticosteroids at low dosages (less than 0.5mg/kg of prednisolone or equivalent) in case of skin diseases like dermatitis, eczema or other localized skin disorders,
- ◆ stable neurological conditions e.g. cerebral palsy, down syndrome.

Precautions:

There should be a gap of at least four weeks between the LJEV and another live vaccine administered before or after the LJEV.

Adverse Events

The general conclusion is that the LJEV SA14-14-2 is safe and even rare adverse events are unlikely. In studies conducted in many countries involving as large as 13000 to 60000 vaccine recipients, hypersensitive reactions nor encephalitis/ meningitis have been reported following the LJEV. Fever exceeding 38°C has been observed in about 10% of vaccine recipients whereas swelling and redness at the injection site is reported in less than 1%. Occasionally sporadic skin rashes which do not require treatment may appear.

Use in pregnancy:

LJEV is contraindicated for pregnant women. However, if the vaccine is required in pregnancy, it is advisable to administer the inactivated JE vaccine. The Physician should assess the risk benefit of recommending the vaccine to the pregnant woman.

Mouse brain derived inactivated JE vaccine

The mouse brain derived, purified inactivated JE vaccine is based on either the Nakayama or Beijing -1 strain. Nakayama strain protects against JE strains from different Asian regions. However, since the Beijing-1 strain introduces stronger, broader neutralizing antibodies and because of high antigen yield of the Beijing strain, Nakayama strain has been replaced with the Beijing strain. Sri Lanka used the Beijing strain in its National Immunization Programme from 1992-2008.

Characteristics of the Vaccine

Mouse brain derived JE vaccine of the Beijing strain is prepared by inoculating the “Beijing – 1” strain of JE virus into the mouse brain. Then, the virus is separated and inactivated with formalin.

One ml of vaccine contains:

Inactivated JE virus, Gelatin - 0.02%, Tween 80 - 0.0003%, Thimersal- 0.009%, M 199 (without phenol red) qs 1ml.

Indications

Prevention of infections caused by JE virus and resultant deaths and disabilities

Efficacy

In several Asian trials, primary immunization based on 2 doses given at an interval of 1–2 weeks has induced protective concentrations of neutralizing antibodies in 94–100% of children aged >1 year.

Immunization Schedule

Due to likely interference with acquired maternal immunity during the first months of life, vaccination with inactivated JE is not recommended before 6 months of age. In the National Immunization Programme, the vaccine was not given to children below one year of age when it was used earlier.

Primary immunization consists of two injections given at 1-4 weeks interval on completion of one year.

Booster immunization doses are recommended after one year following the primary two doses (3rd dose) and about 4-5 years following the primary 2 doses (4th dose).

Dosage and administration

For children under 3 years of age (1-3 years), the recommended dose is 0.25 ml. The recommended dose for those above 3 years of age is 0.5 ml.

Vaccine is administered sub cutaneously. Liquid vaccine vial should be shaken well before being administered.

Simultaneous administration of the inactivated JE vaccine with EPI vaccines such as measles, DPT and polio does not interfere with sero-conversion. However, impact of co administration with non EPI vaccines has not been systematically studied.

Contraindications

Other than general contraindications for any vaccination, inactivated JE Vaccine is contraindicated in specific instances given below:

- ◆ history of an allergy to any component of the inactivated JE vaccine,
- ◆ history of convulsions or spasmodic symptoms within one year before vaccination.

Adverse events

Inactivated JE vaccine is generally considered safe. According to global data, local reactions such as swelling, tenderness and redness are reported in about 20% of vaccine recipients. A similar proportion of vaccinees have experienced, systemic reactions including headache, myalgia, gastro-intestinal symptoms and fever. Acute Disseminated Encephalomyelitis (ADEM) temporally coinciding with inactivated JE vaccine has been reported at frequencies ranging from 1 per 50000 to 1 per 100000 doses administered. However, according to the Global Advisory Committee on Vaccine Safety, ADEM is not a cause for concern when offering the vaccine as there is no increased risk of ADEM temporally associated with the inactivated JE vaccine. Occasionally, hypersensitive reactions such as severe urticaria, facial angio-oedema and respiratory distress have been reported, in particular, in vaccinees from non endemic areas. Practitioners need to remember that these reactions may occur as late as 12-72 hours following vaccination.

Storage

Inactivated JE vaccine is stable at +2°C to +8°C . It should not be frozen nor should it

be exposed to direct sunlight. It should preferably be kept in the middle shelf of the main compartment of the refrigerator. This vaccine is a colourless or slightly white turbid liquid.

Usage of vaccine in specific circumstances

For travellers aged more than one year visiting JE endemic area for at least two weeks, current established practice is to administer 3 primary doses of inactivated JE vaccine at days 0,7 and 28 ; alternatively 2 primary doses preferably 4 weeks apart. If continued protection is required, boosters should be given after one year and then every three years. A single dose of LJEV can also be used to vaccinate travellers.

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[\[www.who.int.wer\]](http://www.who.int/wer)

MEASLES VACCINE

Introduction

Measles is a highly contagious acute febrile illness caused by the measles virus. References to this disease can be found as far back as the 7th Century A.D. It is a human disease and is not known to occur in animals. More than 20 million people are affected each year by measles globally. Prior to introduction of immunization against the disease in 1963, measles was very common in childhood and more than 90% of people had been infected by the age of 20 years. However Measles still remains a leading cause of death among young children in some countries of Asia and Africa, despite the availability of the safe and effective vaccine for the past 40 years.

Virology

Measles virus is a single-stranded RNA virus, from the family *Paramyxovirus*, of the genus *Morbillivirus*. It is antigenically stable and only one serotype exists. It normally grows in the cells that line the back of the throat and in the cells that line the lungs.

Mode of transmission

The highly contagious measles virus probably is the most infectious agent causing human disease spreads through airborne droplets by coughing and sneezing and close personal contact or direct contact with infected nasal or throat secretions. It is infectious from the beginning of the prodromal period to four days after the appearance of the rash. The incubation period is usually 10 to 12 days.

The virus remains active and contagious in the air or on infected surfaces for up to two hours. Measles virus is rapidly inactivated by heat, light, acidic pH, ether, and trypsin (an enzyme).

An infection provides a lifelong immunity. Infants born to mothers who have had the disease are immune to the disease during the first 6-9 months of life until the passively transmitted maternal antibodies are decayed.

Clinical Features

Usually Measles is an acute, mild to moderately severe illness. Severe measles is particularly likely in poorly nourished young children, especially those who do not receive sufficient vitamin A or whose immune systems have been weakened by HIV/AIDS or other diseases.

Viraemia peaks towards the end of the incubation period, when patients develop prodromal symptoms of high fever, cough, coryza, conjunctivitis and small spots with bluish-white centers on an erythematous base on the buccal mucosa

(Koplik's spots) which is pathognomonic of measles.

The typical maculopapular rash appears after another 3–4 days. It spreads from the face and neck to the trunk and extremities, fading after about 3 days. Patients normally improve by the third day of rash, and are fully recovered 7–10 days from the onset of disease.

Complications

Mortality from measles is usually due to its complications. Most persons recover from measles without sequelae. Around 10% of measles infections may end up with complications. Complications are more common in children under the age of five or adults over the age of 20 years. Measles virus causes a depression in cellular immunity making secondary infections more likely. Furthermore, severe measles is more likely in poorly nourished children and in immunocompromised patients.

The most serious complications of measles include blindness, encephalitis, severe diarrhoea (possibly leading to dehydration), otitis media and severe respiratory tract infections such as pneumonia, which is the most common cause of death associated with measles. Subacute Sclerosing Panencephalitis (SSPE), a rare degenerative central nervous system disease resulting from persistent measles virus infection is usually fatal.

The case fatality rate of measles in developing countries is generally in the range of 1 to 5%, but may be as high as 25% in populations with high levels of malnutrition and poor access to health care.

Epidemiology

Global Situation

Measles is still a common vaccine preventable cause of death among children throughout the world despite the availability of a safe and effective vaccine for the past 40 years. The Global Burden of Disease Study in 1990 ranked it eighth both as a cause of death and as a cause of Disability Adjusted Life Years (DALYs) lost in the global population (all ages combined).

According to the World Health Organization, there were 297,000 reported cases of measles and 197,000 deaths in the world in 2007. Measles is common in the developing countries particularly in parts of Africa, the Eastern Mediterranean and Asia. More than 95% of measles deaths occur in low income countries with weak health infrastructure.

Situation in Sri Lanka

According to the hospital in-ward statistics available at the Medical Statistical

Unit, the annual incidence of measles in Sri Lanka during the period from 1951 to 1960 varied from about 20 to 47 cases per 100,000 populations. In the periods 1961 to 1970 and 1971 to 1980, the incidence varied from 18 to 38 and 12 to 49 per 100,000 populations respectively. In the year 1982, a total of 13,273 measles cases (87 cases per 100,000 populations) were reported through the special surveillance activities carried out before introduction of the measles vaccine.

Measles vaccine was introduced to the EPI in 1984 and it resulted in a gradual decline in the disease incidence and its morbidity and mortality. In 1998, 263 cases were reported from government hospitals (0.5 per 100,000 populations) and by 2010 only 89 clinically suspected measles cases were notified from the whole country.

A large measles outbreak occurred in Sri Lanka from October 1999 through June 2000 following a period of low incidence. During this period, more than 15,000 suspected measles cases were reported to the Epidemiological Unit. Among the clinically confirmed cases, the highest morbidity rate (114/100,000 population) was observed among children less than 9 months of age. Nearly 54% of the cases were among persons more than 15 years old. Forty percent of cases had a history of measles vaccination.

Measles vaccine

No specific treatment exists for measles and, because of the extreme infectiousness of the disease; measures to control outbreaks in highly susceptible communities almost invariably will be unsuccessful. Vaccination of the vulnerable populations is the only rational approach available for measles control. A safe, highly effective and relatively inexpensive vaccine has been available for more than 40 years, and both morbidity and mortality rates from measles have been drastically reduced after its introduction.

The cost–benefit of measles vaccination is well documented. In fact, measles immunization saves more lives per unit cost than any other health intervention. Thus, the public health impact of large-scale measles immunization programmes has been clearly demonstrated.

Before 2011, children in Sri Lanka were immunized against measles with 2 vaccines; the Measles vaccine at 9 months of age and the Measles-Rubella (MR) vaccine on completion of 3 years. Measles vaccine was introduced to Sri Lanka in 1984 and the MR vaccine in 2001 through the EPI. Over the years both vaccines had achieved satisfactory immunization coverage throughout the country. They had been successful in reducing mortality and morbidity of the disease in the country to a great extent. In 2011 both measles and MR vaccines were replaced with the MMR. According to the current National immunization programme, children in Sri Lanka are immunized against measles with Measles- Mumps-Rubella (MMR) Vaccine since 2011.

Characteristics of the measles Vaccines

The live, attenuated measles vaccines that are now internationally available are safe, effective and relatively inexpensive and may be used interchangeably in immunization programmes. Where measles vaccine has been combined with rubella vaccine (MR) or mumps and rubella vaccine (MMR), the protective immune response to the individual components remains unchanged. The use of such combined vaccines is logistically and programmatically sound and is recommended in areas where the disease burden of mumps and rubella is high, when the vaccine is affordable and, in the case of rubella, where vaccine coverage rates can be sustained at more than 80%.

Most of the live, attenuated measles vaccines used now originate from the Edmonston strain of measles virus which has been propagated on human diploid cells. Measles vaccine may also contain sorbitol and hydrolysed gelatin as stabilizers, as well as a small amount of neomycin.

Measles vaccine induces both humoral and cellular immune responses comparable to those following natural infection, although the serological titres are usually lower.

Types of measles containing vaccine preparations

A number of live, attenuated measles vaccines are available, either as single-antigen vaccines or in combination with either rubella or mumps and rubella vaccines. When the combined MR or MMR vaccines are used, the protective immune response to each of the components remains unchanged. The use of such combined vaccines is logistically and programmatically sound.

◆ Measles –Mumps- Rubella (MMR) Vaccine

Each 0.5mL dose of the reconstituted MMR vaccine contains not less than 103.0 CCID₅₀ (cell culture infectious dose 50%) of the Schwarz measles, not less than 103.7 CCID₅₀ of the RIT 4385 mumps and not less than 103.0 CCID₅₀ of the Wistar RA 27/3 rubella virus strains. The three virus strains are mixed prior to lyophilisation. The lyophilised vaccine also contains lactose, neomycin sulphate, amino acids and sorbitol and mannitol as stabilizers.

◆ Monovalent Measles Vaccine

A single dose of the Measles vaccine previously used in the EPI, when reconstituted to 0.5 ml contains no less than 1000 CCID₅₀ of live virus particles.

◆ Measles – Rubella(MR) Vaccine

A single dose when reconstituted to 0.5 ml contains not less than 1000 CCID₅₀ of live measles virus particles and 1000 CCID₅₀ of live rubella virus.

Indications

Measles containing Vaccines are indicated for:

- ◆ primary and booster immunization of infants and children against measles,
- ◆ preventing infection in susceptible contacts during measles outbreaks.

Since antibodies develop faster following vaccination than following the natural infection, measles vaccine can be used effectively to protect susceptible contacts during outbreaks. However it should be administered within 3 days following exposure to be effective.

Efficacy

A single dose of live, attenuated measles containing vaccine is generally felt to provide lifelong protection. However, it is recommended that all children have two opportunities for measles immunization to reduce the number both of unvaccinated children and of those who are vaccinated but fail to respond optimally to the vaccine (primary vaccination failures).

In most developing countries, children are vaccinated against measles at 9 months of age, seroconversion rates of 80–85% are expected because of the presence of passively transferred maternal antibodies in some proportion of children at 9 months. Those who do not seroconvert after the initial dose almost always seroconvert after the second dose.

Immunization Schedule

Measles immunization schedule recommended for routine immunization of infants and children in Sri Lanka has been decided on the epidemiology of Measles, feasibility of implementation of the EPI in the country and the objectives of the Measles Elimination Programme. A two-dose schedule has been adopted by the EPI for Measles immunization considering the above factors and to achieve very high levels of immunization coverage.

First dose of the MMR vaccine is given to all infants on completion of one year of age. This has been decided, considering the protection offered by the residual maternal antibodies for measles and the risk of infection during the first year of life.

The second dose of the MMR vaccine is administered on completion of 3 years. This second dose would boost up the suboptimal immunity achieved from the first dose due to the possible interference from the residual maternal antibodies.

Dosage & Administration

All measles containing vaccines (Measles, MR and MMR vaccines) are lyophilized vaccines and are provided with a vaccine specific diluent. It should be reconstituted only with the diluent supplied using a sterile syringe and needle. Using incorrect diluents may result in damage to the vaccine and/or serious reactions in those receiving the vaccine.

Preparation, dosage and administration of measles containing vaccines are similar to those of the MMR vaccine. A single dose of 0.5 ml of MMR vaccine should be administered by deep subcutaneous injection into the upper arm.

Measles containing vaccine can be safely and effectively administered simultaneously with other vaccines.

Storage

Measles containing vaccine (Measles, MR and MMR vaccines) should be stored in the dark at +2°C to +8°C temperature. For long term storage, a temperature at –20°C is recommended. It is important to protect both the lyophilized and reconstituted vaccine from light. The diluent should not be frozen but should be kept cool in the main compartment of the refrigerator.

The reconstituted measles containing vaccines can be stored at +2°C to +8°C for up to 6 hours if not used immediately. Any opened vaccine vials remaining at the end of an immunization session after (6 hours) should be discarded.

Cautions and contraindications

The following conditions are considered as contraindications for the use of measles containing vaccine preparations (Measles, MR and MMR vaccines).

- ◆ Presence of one of the general contraindications for any vaccine.
- ◆ History of an allergy to neomycin, gelatin or other vaccine components .
- ◆ Those who are severely immunocompromised as a result of congenital disease, HIV infection, advanced leukaemia or lymphoma, serious malignant disease, or treatment with high-dose steroids, alkylating agents or antimetabolites, or in persons who are receiving immunosuppressive therapeutic radiation.
- ◆ Pregnancy.

Considering the severity of the disease in patients with advanced HIV infection, measles vaccination should be routinely given to potentially susceptible, asymptomatic HIV-infected children and adults. Vaccination may even be considered for those with symptomatic HIV infection who are not severely immunosuppressed, according to conventional definitions.

Precautions

The expected immune response to measles vaccination may be impaired after receipt of antibody-containing blood products. The duration of interference with response to measles vaccination depends on the amount of immunoglobulin contained in each product, and ranges from 3 to 11 months.

After vaccination with measles containing vaccine, immunoglobulin-containing products should not be administered for 2 weeks unless the benefits exceed those of vaccination. If immunoglobulin-containing products are administered within this interval, the vaccinee should be revaccinated later.

Measles containing vaccine may exacerbate tuberculosis and therefore patients with tuberculosis should be under anti TB therapy when taking the measles containing vaccine. Persons who are tuberculin test (Mantoux test) positive may become tuberculin negative for up to one month after measles immunization or infection since measles virus inhibits the response to tuberculin.

Adverse Events

Adverse reactions following measles vaccination, alone or in fixed combinations, are generally mild and transient. Symptoms characteristic of measles, rubella or mumps component may be observed following MMR vaccine.

Measles component may cause a slight increase in temperature (37.6°C) in 5-15% of those vaccinated. A rash which usually lasts less than 48 hours is observed in 1-2% of those vaccinated. Both fever and rash tend to occur 7-10 days after administration and may last up to 1-2 days. There may be enlargement of cervical and occipital lymph nodes. Rarely, transient thrombocytopenia occurs within 2 months after immunization. Adverse effects except anaphylactic reactions occur less frequently after the second dose of the vaccine. Risk of anaphylactic reactions following measles vaccination is closer to 1 in 1 000 000. There is no association between history of egg allergy and allergic reactions to the measles vaccine

The rubella component may commonly result in joint symptoms manifested as arthralgias (25%) or arthritis (10%) among adolescent and adult female vaccine recipients. However these transient reactions are rare in children and males receiving the MMR vaccine.

Mumps virus component sometimes causes mild parotitis and, on rare occasions, benign aseptic meningitis or orchitis.

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Introduction

Mumps is a viral infection of humans, primarily affecting the salivary glands. Although it is mostly a mild childhood disease, with peak incidence occurring among those aged 5 - 9 years, the mumps virus may also affect adults.

In the fifth century BC Hippocrates first described the features of mumps. The infectious nature of the disease was recognized in the 19th century. Large outbreaks of mumps occurred among the armed forces during the 1st World War. In 1934 Johnson and Goodpasture demonstrated that a virus in human saliva was responsible for this disease.

Virology

Mumps virus belongs to the genus *Rubulavirus* of the family *Paramyxoviridae*, whereas only one distinct serotype of mumps virus exists.

Mode of transmission

Humans are the only known natural host for mumps virus, which is spread by airborne droplets released when an infected person sneezes or coughs and by direct contact with an infected person. The average incubation period for mumps infection is approximately 16 - 18 days with a range of 2 - 4 weeks.

Natural infection with this virus is thought to confer lifelong protection. Most adults are likely to have been infected naturally in the past and may be considered to be immune, even if they did not have the apparent illness. Approximately 85% of adults have evidence of past mumps infection.

Clinical Features

Mumps typically begins with non-specific symptoms, such as myalgia, headache, malaise and low-grade fever; within a day these are followed by the characteristic unilateral or bilateral swelling of the parotid glands. Other salivary glands are visibly affected in approximately 10% of cases. After about 1 week, fever and glandular swelling disappear, and unless complications occur, the illness resolves completely. In approximately 30% of cases, only non-specific symptoms occur or the infection is asymptomatic. Most infections in children aged less than 2 years are subclinical. It should be noted that subclinical infections can also be communicable. People with mumps are contagious from about 2 days before the onset of swelling of the salivary glands up to 9 days after the onset of swelling. No specific therapy for mumps exists.

Complications:

Mumps is generally a mild self-limiting disease, although complications may occur. They may occur even without the involvement of salivary glands. In up to

20% of affected post-pubertal males, an inflammatory condition of testicles (orchitis) may occur. This condition is characterized by painful swelling and sometimes may cause sterility. In up to 5% of affected post-pubertal females, oophoritis and/ or mastitis may occur.

There are other rare complications that can occur in people infected at any age. Symptomatic meningitis is reported in as many as 15%. Mumps encephalitis is reported in 0.02 - 0.3% of cases. Although the case fatality rate of mumps encephalitis is low (1.4%), permanent sequelae, including paralysis, seizures, cranial nerve palsies and hydrocephalus may occur. Acquired sensory nerve deafness (usually unilateral) caused by mumps is one of the leading cause of deafness in childhood, affecting approximately 5/100,000 patients. Pancreatitis is reported as a complication in approximately 4% of cases, but the relationship between mumps pancreatitis and diabetes mellitus remains speculative. The overall mumps case fatality rate is reported as 1 per 10,000 cases. Mumps in the first trimester of pregnancy may cause spontaneous abortion (25% incidence), but there is no evidence that it causes foetal abnormalities.

Epidemiology

Global Situation

Mumps remains endemic in many countries throughout the world. In most parts of the world, the annual incidence of mumps in the absence of immunization is in the range of 100 - 1000 cases per 100,000 populations with epidemic peaks every 2 - 5 years. In hot climates the disease may occur at any time of the year, whereas in temperate climates the incidence peaks in winter and spring.

In Western countries, before the widespread use of mumps vaccine, mumps was the leading identified cause of viral meningitis and encephalitis in children. Since the introduction of mumps vaccine, disease is now responsible for only 0.5% of cases of viral encephalitis and the overall incidence of reported mumps and its complications has reduced dramatically. Still, these countries experience small epidemics of mumps among older teenagers and young adults.

Situation in Sri Lanka

Mumps is a notifiable disease in Sri Lanka and all cases of mumps should be notified to the Medical Officer of Health.

According to the statistics available at the medical statistics unit 3127 and 3441 cases of live discharges of mumps cases have been reported from the government hospitals during the years of 2008 and 2009 respectively. This may not be the true situation as generally mumps is considered as a mild disease and only cases with complications seek inward medical attention. Majority either seek care at out patients departments or do not seek formal medical care.

Mumps vaccine

Safe and efficacious vaccines against mumps – based on live, attenuated viral strains have been available since the 1960s. By December 2005, 110 of the 193 (57%) WHO Member States had included mumps vaccine in their National Immunization Programmes, the vast majority using the combined MMR vaccine. In countries where large-scale immunization against mumps has been implemented, the incidence has dropped dramatically.

In view of the moderate morbidity and low mortality of mumps, information on the burden of the disease, including the socioeconomic impact, is important when deciding whether to introduce mumps vaccines into the EPI. Cost effectiveness studies indicate that the incorporation of effective mumps vaccines into the EPI is highly beneficial from the standpoints of costs and benefits and from a societal perspective.

Characteristics of the Mumps Vaccine

Mumps vaccine is a live attenuated freeze dried vaccine [lyophilized] and must be reconstituted before use. Depending on the manufacturer, gelatin and/or sorbitol are used as stabilizers and neomycin is added as a preservative to the mumps vaccines. Mumps vaccine is prepared in chick embryo fibroblast tissue culture.

Mumps vaccines are produced as monovalent, bivalent measles-mumps (MM) vaccine and trivalent measles-mumps-rubella vaccine (MMR). In most countries including Sri Lanka, immunization against mumps is delivered through MMR.

Measles –Mumps- Rubella (MMR) Vaccine

Each 0.5mL dose of the reconstituted MMR vaccine contains not less than 103.0 CCID₅₀ (cell culture infectious dose 50%) of the Schwarz measles, not less than 103.7 CCID₅₀ of the RIT 4385 mumps and not less than 103.0 CCID₅₀ of the Wistar RA 27/3 rubella virus strains. The three virus strains are mixed prior to lyophilisation. The lyophilised vaccine also contains lactose, neomycin sulphate, amino acids and sorbitol and mannitol as stabilizers.

Indications

Mumps containing vaccines are indicated for:

- ◆ primary and booster immunization of infants and children against mumps,
- ◆ preventing infection in susceptible contacts during mumps outbreaks.

Efficacy

The protective efficacy of the mumps containing vaccine against mumps is about 95% i.e. a single dose of mumps containing vaccine produces an antibody response in 95% of susceptible individuals. However, field studies have demonstrated lower estimates of vaccine effectiveness usually around 80% with single-dose regimens. Serologic and epidemiologic data show the persistence of antibody after vaccination suggesting continued protection against infection for at least 20 years, though the antibody levels following vaccination are lower than those that follow natural disease. A two-dose strategy and good immunization coverage have led to the elimination of mumps in some countries e.g. Finland.

Although mumps immunization after exposure to mumps may not prevent the disease, it is not harmful. Should the exposure not result in an infection the vaccine should confer protection against future exposures.

Immunization Schedule

Accumulated global experience shows that two doses of the vaccine are required for long-term protection against mumps. The first dose of the mumps containing vaccine should be given at the age of 12 - 18 months. This is because of persistent maternal antibodies to mumps virus from previous infection or vaccination interferes with the response to mumps vaccines in young infants. The age of administration of the second dose may range from the second year of life to age at school entry. The minimum interval between the first and second doses is 4 weeks.

Mumps immunization schedule recommended for routine immunization of infants and children in Sri Lanka has been decided based on the epidemiology of Mumps, feasibility of implementation of the EPI in the country and the objectives of the EPI Programme. A two-dose schedule has been adopted by the EPI for Mumps immunization considering the above factors and to achieve very high levels of immunization coverage.

First dose of the MMR vaccine is given to all infants on completion of one year of age. This has been decided considering the protection offered by the residual maternal antibodies and the risk of infection during the first year of life.

The second dose of the MMR vaccine is administered on completion of 3 years. This second dose would boost up the suboptimal immunity achieved from the first dose due to the possible interference from the residual maternal antibodies. Absence of previous documented doses, catch-up for MMR consists of 2 doses given at least 4 weeks apart. If only 1 dose was given earlier, 2nd dose should be given as early as possible.

Dosage & Administration

MMR is a lyophilized vaccine and is provided with a vaccine specific diluent. It should be reconstituted only with the diluent supplied using a sterile syringe and needle.

After reconstitution, MMR vaccine should be used within six hours of reconstitution. A dose consists of 0.5 ml is recommended for children and adults and should be administered by subcutaneous injection into the upper arm.

MMR can be administered simultaneously with other vaccines, at separate anatomical sites and in separate syringes. When administered with other live vaccines, MMR should be given at the same time or separated by a minimum 4-week interval.

Storage

MMR vaccine should be stored in the dark at +2°C to +8°C temperature. For long term storage, a temperature at -20°C is recommended. It is important to protect both the lyophilized and reconstituted vaccine from direct sun light. The diluent should not be frozen but should be kept cool in the main compartment of the refrigerator.

The reconstituted MMR vaccines can be stored at +2°C to +8°C for up to 6 hours if not used immediately. Any opened vaccine vials remaining at the end of an immunization session (or after 6 hours) should be discarded.

Cautions and contraindications

The following conditions are considered as contraindications for the use of mumps containing vaccine preparations .

- ◆ Presence of one of the general contraindications for any vaccine
- ◆ History of an allergy to neomycin, gelatin or other vaccine components
- ◆ Anyone who has experienced anaphylaxis to a previous dose of mumps containing vaccine preparations
- ◆ persons who are severely immunocompromised as a result of congenital disease, HIV infection, advanced leukaemia or lymphoma, serious malignant disease, or treatment with high-dose steroids, alkylating agents or antimetabolites, or in persons who are receiving immunosuppressive therapeutic radiation.

Precautions

The expected immune response to mumps vaccination may be impaired after receipt of antibody-containing blood products. The duration of interference with response to mumps vaccination depends on the amount of immunoglobulin contained in each product, and ranges from 3 to 11 months.

Adverse Events

In general, adverse reactions to mumps vaccination are rare and mild. Apart from slight soreness and swelling at the injection site, the most common adverse reactions are parotitis and low-grade fever. Occasionally, orchitis and sensorineural deafness have been observed after mumps vaccination. Very rarely moderate fever and aseptic meningitis has been reported following mumps vaccination.

For adverse events following MMR –Refer to measles chapter.

Usage of vaccine in specific circumstances

MMR vaccine can be given in the following circumstances:

- ◆ may be given from 9 months of age if in contact with mumps case, but dose must be repeated at 12 months of age,
- ◆ can be administered to HIV-infected children at 12 months of age unless they have severely impaired immunity,
- ◆ can be used to immunize susceptible adults against mumps.

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Introduction

Rubella, normally a mild febrile viral disease, commonly known as German measles, occurs worldwide. It is a common childhood disease that can affect adults and often occurs in epidemics. It is most common in children of early school age. It is considered important since the infection of a mother in early pregnancy can cause foetal death or congenital rubella syndrome (CRS), with multiple birth defects such as cataract, hearing loss, cardiac malformations and mental retardation.

Rubella has probably affected humans for centuries but its often mild symptoms and similarity of its rash to many other infections has prevented its recognition as a separate entity until late 18th century. It was first described by Gorge Maton in 1814 and was named as 'Rubella' by Henry Veale more than 50 years later. Its association with CRS was first published in 1941.

Virology

Rubella virus is a single-stranded RNA virus, from the family *togavirus*, of the genus *Rubivirus*. It is antigenically stable and only one serotype exists. Humans are the only known host. It normally replicates in the nasopharyngeal mucosa and local lymph nodes.

Mode of transmission

Rubella virus spreads via respiratory transmission from human to human through airborne droplets or by direct contact with nasopharyngeal secretions of infected people.

The incubation period ranges from 12 to 23 days, with an average of 18 days. The period of communicability ranges from about 1 week before and at least 4 days after the onset of the rash. In closed environments such as military establishments, all exposed susceptibles may be infected.

In pregnant women the virus crosses the transplacental barrier and infects the placenta and the developing foetus. Infants with CRS shed large quantities of virus in their pharyngeal secretions and in urine for months after birth, and serve as a source of infection to their contacts.

An infection provides a lasting immunity. Infants born to mothers who have had the disease are immune to the disease during the first 6-9 months of life.

Clinical Features

Nearly 50% of rubella infections are subclinical. Children usually present with few or no constitutional symptoms, but adults may experience a 1-5 day prodromal

period with symptoms consisting of low-grade fever, headache, malaise, mild coryza, conjunctivitis and enlargement of lymph nodes (post auricular, occipital and posterior cervical) which precedes the onset of rash by 5-10 days. In adult females, mild polyarthritis may occur. Rubella virus infection typically has no lasting effect.

The primary symptom of Rubella virus infection is usually the appearance of fine, erythematous maculoapular rash on the face. This rash may resemble that of measles. The rash typically spreads to the trunk and limbs and fades within 48 hours.

Complications

Rare complications of rubella virus infection include haemorrhagic manifestations, Guillain-Barré syndrome and encephalitis.

Rubella infection in early pregnancy often results in miscarriage or stillbirth. Infants born with CRS may have intellectual disabilities, cataracts, deafness, cardiac abnormalities, intrauterine growth retardation and inflammatory lesions of the brain, liver, lungs and bone marrow. Those who survive the neonatal period may face serious developmental disabilities and have an increased risk for developmental delay, including autism, type I diabetes mellitus and thyroiditis.

Congenital Rubella Syndrome (CRS) occurs in up to 90% of infants born to women who acquire confirmed rubella infection during the first trimester of pregnancy. The risk of a single congenital defect falls to approximately 10 - 20% if infected by the 16th week of gestation and defects are rare when the maternal infections occur after the 20th week of gestation.

Epidemiology

Global Situation

In the pre-vaccine era the highest incidence of clinical cases occurred in the spring season in temperate countries among 5-9 year olds. Over 80% of adults were immune to the disease. Extensive outbreaks occurred every 6 to 9 years resulting in many children with CRS. In 1996 approximately 22 000 children with CRS were born in Africa, and approximately 46 000 and 12 634 children were born with CRS in the South-East Asia and the Western Pacific Regions, respectively.

Immunization against rubella, introduced to prevent CRS has resulted in a significant reduction of its incidence in countries with high immunization coverage.

Situation in Sri Lanka

Rubella and CRS have been notifiable diseases in Sri Lanka and immunization against the disease had been available through the EPI since 1996. Most recent epidemic of rubella occurred in Sri Lanka during 1994 and 1995.

A post epidemic survey done in 1994 revealed that there were 275 cases of congenital rubella syndrome (CRS) in 1994 and a further 169 cases in the first four months of 1995. In response to this outbreak vaccination against rubella (using rubella vaccine) for child bearing age females (13-44 years) was initiated in 1996 with a view of controlling CRS.

Later, in order to control the rubella transmission, all the children in Sri Lanka are immunized against rubella with 2 vaccines through the EPI; the monovalent Rubella vaccine and the bivalent Measles-Rubella (MR) vaccine. Monovalent rubella vaccine was introduced to Sri Lanka in 1996 and the MR vaccine in 2001 through the EPI and over the years both vaccines had achieved satisfactory immunization coverage throughout the country.

Before 2011, the first dose of rubella immunization was given as the MR vaccine on completion of 3 years to all children (both males and females) in the country. EPI offers the second opportunity of rubella immunization to all children in the country at grade eight in school (13 years of age) through the monovalent Rubella vaccine. They had been successful in reducing morbidity of the disease in the country to a great extent. In 2011 both rubella and MR vaccines were replaced with the MMR vaccine.

Rubella vaccine

No specific treatment exists for rubella and CRS. Vaccination of the vulnerable populations is the only rational approach available to rubella and CRS control. A safe, highly effective and relatively inexpensive vaccine has been available since 1969.

The primary purpose of rubella vaccination is to prevent the occurrence of congenital rubella infection including CRS. Two immunization approaches are recommended:

- ◆ prevention of CRS only, through immunization of adolescent girls and/or women of child bearing age; or
- ◆ elimination of rubella as well as CRS through universal vaccination of infants and young children (both girls and boys), surveillance, and assuring immunity in women of child bearing age.

Rubella vaccines are available in a monovalent form, a bivalent combination with measles vaccine or mumps vaccine, or as trivalent measles-mumps-rubella vaccine (MMR). Following well-designed and implemented programmes, rubella and CRS have almost disappeared from many countries.

Characteristics of rubella containing vaccines

A number of live, attenuated rubella vaccines are available, either as single-antigen vaccines or in combination with either measles or mumps and measles vaccines. When the combined MR or MMR vaccines are used, the protective immune response to each of the components remains unchanged. The use of such combined vaccines is logistically and programmatically sound.

As with other live virus vaccines, immunity provided by the rubella vaccine is long term.

According to the National Immunization Programme, children in Sri Lanka are immunized against rubella with MMR Vaccine since 2011.

Types of rubella containing vaccine preparations

◆ Measles –Mumps- Rubella (MMR) vaccine

Each 0.5ml single dose contains not less than 1000CCID₅₀ of Edmonston-Zagreb Measles virus propagated on human diploid cell culture, 000CCID₅₀ of Wistar RA27/3 rubella virus propagated on human diploid cell culture and 5000 CCID₅₀ of L-Zagreb Mumps virus propagated on chick embryo fibroblast cells.

◆ Rubella vaccine

Rubella vaccine used in the EPI is a freeze dried vaccine prepared from the live attenuated strains of Wistar RA 27/3 rubella virus. This vaccine virus has been propagated on human diploid cells (HDC). It is lyophilized and is provided with its own diluent.

Each 0.5ml single dose contains not less than 1000CCID₅₀ of Wistar RA27/3 rubella virus propagated on human diploid cells.

◆ Measles – Rubella(MR) vaccine

Each 0.5ml single dose contains not less than 1000CCID₅₀ of Edmonston-Zagreb Measles virus and 1000CCID₅₀ of Wistar RA27/3 rubella virus propagated on human diploid cells. This vaccine was previously used in the EPI.

For details refer to chapter on Measles

Indications

Rubella containing Vaccines are indicated for;

- ◆ primary and booster immunization of infants and children against rubella,

- ◆ for active immunization of adolescents and young adults against rubella,
- ◆ to prevent infection in susceptible contacts during rubella outbreaks.

Rubella vaccine can be safely and effectively administered simultaneously with DTP, DT, TT, aTd, BCG, OPV, IPV, Hepatitis B, HiB and yellow fever vaccines.

Efficacy

Rubella-containing vaccines stimulate the formation of antibodies to rubella virus in over 95% of susceptible individuals after a single dose, and this is likely to be higher with a two dose schedule. However titres are generally lower than those observed in response to natural rubella infection.

Immunization Schedule

The present National immunization schedule recommended for routine immunization of children and adolescents has been decided on the epidemiology of the disease, feasibility of implementation of the EPI in the country and the objectives of the National Elimination Programme of Rubella and CRS.

First dose of the MMR vaccine is given to all infants on completion of one year of age. This has been decided, considering the protection offered by the residual maternal antibodies for rubella, the risk of infection during the first year of life and programmatic feasibility.

The second dose of the MMR vaccine is administered on completion of 3 years. This second dose would boost up the suboptimal immunity achieved from the first dose due to the possible interference from the residual maternal antibodies.

All females of 13-44 years who have not been previously immunized with rubella containing vaccines, who are not pregnant or who have not undergone a permanent method of contraception are also given the rubella containing vaccine in order to prevent CRS.

Dosage & Administration

All rubella containing vaccines (Rubella, MR and MMR) are lyophilized vaccines and are provided with a vaccine specific diluent (sterile water for injection). It should be reconstituted only with the diluent supplied using a sterile syringe and needle. Using incorrect diluents may result in damage to the vaccine and/or serious reactions in those receiving the vaccine.

Preparation, dosage and administration of rubella containing vaccines are similar to that of the MMR vaccine. A single dose of 0.5 mL of MMR vaccine should be administered by deep subcutaneous injection into the upper arm.

Storage

Rubella containing vaccines (Rubella, MR and MMR) should be stored at +2°C to +8°C temperature. For long term storage, a temperature at -20°C is recommended. It is important to protect both the lyophilized and reconstituted vaccine from direct sun light. The diluent should not be frozen but should be kept at +2°C to +8°C temperature in the main compartment of the refrigerator.

The reconstituted rubella containing vaccines can be stored at +2°C to +8°C for up to 6 hours if not used immediately. Any opened vaccine vials remaining at the end of an immunization session should be discarded.

Cautions and contraindications

The following conditions are considered as contraindications for the use of rubella containing vaccine preparations (Rubella, MR and MMR vaccines).

- ◆ Presence of one of the general contraindications for any vaccine
- ◆ History of an allergy to neomycin, gelatin or other vaccine components
- ◆ Persons who are severely immunocompromised as a result of congenital disease, HIV infection, advanced leukaemia or lymphoma, serious malignant disease, or treatment with high-dose steroids, alkylating agents or antimetabolites, or persons who are receiving immunosuppressive therapeutic radiation.

According to available data rubella containing vaccines can be safely administered to those with asymptomatic HIV infections.

Previous administration of human anti rho (D) immune globulin (RhoGam) is not a contraindication to postpartum vaccination. Breastfeeding is also not a contraindication.

Precautions

Rubella containing vaccine should be avoided for at least 3 months following administration of gammaglobulins or blood transfusions or blood products containing immunoglobulins (e.g. blood, plasma) since there is a risk of inactivation of the vaccine. Also, immunoglobulins should be avoided for at least 2 weeks following administration of rubella vaccine.

Persons with active tuberculosis should not be vaccinated until treatment has been established.

Rubella vaccination should be avoided in pregnancy because of the theoretical, but never demonstrated, teratogenic risk. Consequently, there is no need to screen

women for pregnancy before rubella vaccination. If pregnancy is being planned, then an interval of 1 month should be observed after rubella immunization. Rubella vaccination during pregnancy is not an indication for abortion. Reassurance can be given that no foetal damage has been observed in the babies of over 1,000 susceptible women who received vaccine during their pregnancy and carried to term.

Adverse Events

Adverse reactions following rubella containing vaccination, alone or in fixed combinations, are generally mild and transient, particularly in children.

Common adverse events include pain, redness and induration at the site of injection. Low grade fever and rash, lymphadenopathy, myalgia and paraesthesiae are commonly reported following rubella containing vaccines. Joint symptoms tend to be rare in children (0-3%) and in men, but are common among vaccinated adolescents and adult females; they include arthralgias (25%) and arthritis (10%) that usually last from a few days to 2 weeks.

Anaphylactic reactions and reactions involving central nervous system have also been rarely reported.

For adverse events following MMR –Refer to measles chapter.

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Introduction

Rabies is an acute encephalomyelitis caused by a rhabdo virus. It is primarily an infection of mammals, spread mainly through bites of infected animals. Rabies in dogs is the source of nearly 97% of human infections and poses a potential threat to > 3.3 billion people, primarily in Asia and Africa.

In Sri Lanka, rabies has been detected also in cats, mongoose, cattle, goats, bandicoots, jackals, pole cats, rock squirrels, monkeys, horses and elephants. Domestic rats have not been implicated in the transmission of rabies in Sri Lanka. Human to human transmission also has not been documented.

Virology

Rabies virus is a RNA virus which belongs to the genus *Lyassa* virus of the *Rhabdoviridae* family. Currently this genus comprises of 7 geno types.

Mode of transmission

The virus can penetrate through broken skin or intact mucous membranes. Human infection usually occurs following a transdermal bite or scratch by an infected animal. Transmission may also occur when infectious material, usually saliva, comes in contact with the victim's mucosa, or with fresh abraded skin lesions or by drinking raw milk from a rabid cow or goat.

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.

Clinical Features

In human cases, the incubation period is typically several weeks to several months (average 1-3 months), but may vary from less than a week to more than a year. Once the clinical symptoms have occurred, rabies is almost invariably fatal. The initial symptoms of rabies are often mild fever and pain or paraesthesia at the wound site. As the virus spreads in the central nervous system, progressive encephalitis develops characterized by hydrophobia or aerophobia, hyperactivity and fluctuating consciousness, dysphagia, generalized convulsions and within a few days cardio-respiratory arrest. These symptoms are generally seen in the furious form of the disease in about 70% of patients.

Paralytic rabies, which may represent as much as 20% of the total number of human cases, runs a less dramatic, although ultimately fatal, course.

Epidemiology

Global Situation

The estimated 55,000 deaths in the world per year may be an underestimate. In India alone, 20,000 deaths are estimated to occur annually. Although all age groups are susceptible, rabies is most common in children aged below 15 years.

Situation in Sri Lanka

Human rabies is a notifiable disease in Sri Lanka. In Sri Lanka. Human deaths due to rabies reported in years 2008, 2009, 2010 and 2011 were 52, 58, 49 and 41 respectively

Vaccines against human rabies

Prevention of rabies in humans depends on a combination of interventions, including provision of post-exposure prophylaxis to potentially exposed patients, pre-exposure immunization of people who are at frequent risk of exposure, control of infection in animal reservoirs and control of stray dog populations.

Following inactivated anti rabies cell culture vaccines are available.

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

**Vaccines available in Sri Lanka at present*

Pre exposure immunization

This form of therapy is indicated for persons who are at a higher risk of exposure to rabies virus i.e. laboratory staff handling live rabies virus, veterinarians, rabies control staff

(vaccinators), wild life officers, employees of animal quarantine premises and zoological establishments.

The recommended schedule is IM- ARV :- 1 dose each on D0, D7 and D28. A booster dose is given 1 year after the first dose. Additional booster doses are given once every five years even if they do not have a definitive exposure. Any person in this category should seek expert advice if exposed to a suspected rabid animal.

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

They should only be given additional doses of IM-ARV 1 dose each on D0 and D3 as boosters even in a case of major exposure to a suspected rabid animal.

Post exposure immunization (PET)

Choice of therapy depends on the screening of the person exposed, the animal involved in the incident and the type of exposure.

Anti rabies PET when indicated:-

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

Patients in the minor exposure category should be given only a course of ARV.

Type of exposure

◆ Major exposures

- a. Single or multiple bites with bleeding on head, neck, face, chest, upper arms, palms, tips of fingers and toes and genitalia.
- b. Multiple deep scratches with bleeding on the head, neck and face.
- c. Multiple or single 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 or scratch with bleeding on the lower limbs (excluding tips of toes), upper limbs (excluding upper arms, palms and tips of fingers), abdomen and back.
- b. Nibbling of uncovered skin.
- c. Contamination of open wounds with saliva.
- d. Single or multiple bites or scratches without bleeding on any part of the body
- e. Drinking of raw milk of rabid cow or goat.

The following are **not considered** as exposures:-

Contamination of intact skin with saliva of suspected rabid animal

Petting, bathing or coming in contact with utensils of a suspected rabid animal

Screening the animal

In case of major exposure to dogs and cats:-

- ◆ If the animal is apparently healthy, observable and has had 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.

- ◆ When the animal is suspicious to have rabies or is sick, but observable, initiate PET while observing the animal. Discontinue treatment if the animal is apparently healthy after 14 days.
- ◆ If the animal is having rabies (confirmed by laboratory diagnosis) or unobservable (animal dead, missing or stray animal) initiate PET and continue the full course.

In case of minor exposure to dogs and cats:

- ◆ If the animal is apparently healthy, observable and has had a minimum of 1 rabies vaccination:
 - 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 14 days.

- ◆ 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 (animal dead, killed, missing or stray animal) initiate PET and continue the full course.

The patient must be clearly advised that the animal should be put in a cage or leashed during the observation period. If the animal dies, becomes sick or develop any abnormal behaviour, 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 for laboratory confirmation of rabies.

Rabies immunoglobulin(RIG)

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

RIG should be given immediately after the incident. It is essential to test for sensitivity before administering ERIG. HRIG does not require sensitivity testing prior to its administration. If the patient reports late, RIG could be given up to 3 months after exposure, if the patient has not taken the anti rabies vaccine.

Dosage and administration of RIG

HRIG - 20 IU/Kg body wt

ERIG - 40 IU/Kg body wt

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 subcutaneously (SC) or intramuscularly (IM) on the thighs. 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 small children with multiple bites, if the volume is not sufficient for infiltration of all wounds, dilute RIG with sterile N saline up to double or 3 times.

Anti rabies vaccine (ARV)- Intramuscular schedule

Patients with **major exposures** should be given RIG and ARV IM or deep SC according to the following schedule.

One dose to be given in the deltoid on days 0, 3, 7, 14 and 30

Recommended IM dose is either 0.5mL (PVRV) or 1mL (PCEC)

Patients with **minor exposures** should be given 4 doses of ARV IM or deep SC on the following days.

Day 0: 2 doses to be given IM or SC, one on each deltoid

Day 7: 1 dose IM or SC

Day 21: 1 dose IM or SC

Intradermal (ID) inoculation of ARV

Intradermal (ID) vaccination schedule has been recommended by the WHO to be used in developing countries where cost is a major limiting factor.

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

2 site ID schedule

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

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

The modified 4 site ID schedule

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

The 4 site schedule is helpful in patients with a minor exposure who come late for treatment. It gives an early antibody response than the 2 site schedule.

The 4 site ARV is not recommended as an alternative for RIG in major exposures on a routine basis.

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 8 hours stored at 2°-8°C). Separate disposable syringes and needles should be used for each patient to prevent contamination.

Efficacy

In both pre and post-exposure prophylaxis settings, they induce an antibody response in >99% of vaccinees. Prompt post-exposure use of modern vaccines combined with proper wound care and RIG is nearly 100% effective in preventing rabies, even following high-risk exposure. However, delays in starting or failure in completing correct prophylaxis, especially with severe lesions on the head, neck, hands or multiple wounds, may result in death.

Management of patients following a full course of rabies PET Previously

For both major and minor exposures: If the animal is apparently 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:**

- ◆ Up to 6 months from the last dose of ARV – PET is not indicated.
- ◆ From 6 months - 5 years from the last dose of ARV – 2 site ID ARV 2 doses each or IM ARV one dose each should be given on days 0 and 3. As an alternative to this regimen, the patient may be offered a single visit 4 site ID regimen on day 0, consisting of 4 injections of 0.1 mL, equally distributed over left and right deltoids or prescapular areas.
- ◆ Up to 5 years from the last dose of ARV, RIG is not indicated.

- ◆ After 5 years, a full course of ARV with or without RIG (depending on the category of exposure and animal screening) is recommended.

Storage

Both ARV vaccine and immunoglobulin should be stored at +2 °C to +8 °C. Following reconstitution with the accompanying sterile diluents, the vaccines should be used immediately, or within a maximum of 6 hours when kept at +2 °C to +8 °C.

Cautions and contraindications

In view of the gravity of the disease, all contraindications are secondary in cases of exposure to a suspected rabid animal. This also pertains to post-exposure rabies prophylaxis in infancy and pregnancy.

For pre-exposure immunization, previous severe reaction to any of the vaccine components is a contraindication for further use of the same vaccine.

In immunocompromised individuals, including patients with HIV/AIDS, comprehensive wound management and local infiltration with RIG, in combination with a complete CCV series, are of utmost importance for the successful prevention of rabies.

Adverse Events

Modern CCVs are considered to be safe and well tolerated. Adverse events

following rabies vaccination include:

- ◆ Local reactions - pain, tenderness and erythema at the site of injection,
- ◆ Mild systemic reactions - malaise, headache, nausea, mild fever and urticaria,
- ◆ Severe systemic hypersensitivity reactions following booster injections reported in 6% of vaccinees, but are less common following primary immunization.

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TYPHOID VACCINE

Introduction

Typhoid fever is a clinical syndrome caused by a systemic infection with *Salmonella enterica* subspecies called *enterica* serovar Typhi (*S. Typhi*). Paratyphoid fever, caused by infection with *S. enterica* serovar Paratyphi A or B, is similar to, and often indistinguishable from, typhoid fever. The two infections are collectively known as 'enteric fever'. These pathogens only infect humans. There is no vaccine against paratyphoid fever.

Typhoid fever is spread by the faeco-oral route and closely associated with poor hygiene, lack of pure drinking water and inadequate sanitation. The disease is almost exclusively transmitted by food and water contaminated by faeces and urine of patients and carriers.

The fatality rate is approximately 16% for untreated cases and 1% for those given appropriate antibiotic therapy. Between 2% and 5% of typhoid cases become chronic carriers, sometimes shedding bacteria in stool for years. The risk of severe illness is increased in people with depressed immunity (e.g., due to HIV) or decreased gastric acid levels.

Increasing multidrug resistance of *S. Typhi* reduces the effective treatment options, increases treatment costs and results in higher rates of serious complications and deaths.

Bacteriology

Salmonella is a genus of the family *Enterobacteriaceae*. *Salmonellae* are rod-shaped, Gram-negative, facultative anaerobic bacteria, most of which motile by peritrichous flagella (H antigen). In addition to the H antigen, 2 polysaccharide surface antigens aid in the further characterization of *S. enterica*, namely the somatic O antigen and the capsular Vi (virulence) antigen.

Mode of transmission

Typhoid and paratyphoid bacteria are passed in the faeces and urine of infected people. People become infected after eating food or drinking beverages that have been handled by a person who is infected or by drinking water that has been contaminated by sewage containing the bacteria. Once the bacteria enter the person's body they multiply and spread from the intestines, into the bloodstream.

Clinical Features

After 5 to 21 days of incubation (range 3 to 60 days), patients experience a low-grade fever, dull frontal headache, malaise, myalgia, anorexia, abdominal tenderness, relative bradycardia, splenomegaly, and dry cough. Constipation usually occurs in older children and adults, whereas younger children may suffer

from diarrhoea. The fever tends to increase as the disease progresses

Typhoid fever normally results in lifelong immunity. Reinfections are rare, at least in cases where the primary infection is not aborted by early antibiotic treatment.

Complications:

Complications following typhoid occur in 10 to 15% of patients and tend to occur in patients who have been ill for >2 weeks. The more important complications include gastrointestinal bleeding, intestinal perforation and typhoid encephalopathy.

Relapse occurs in 5 to 10% of patients, usually 2 to 3 weeks after the initial fever resolves. Chronic asymptomatic biliary carriage of *S. Typhi* occurs in up to 5% of patients with typhoid fever, even after treatment.

Epidemiology

Global Situation

Improved living conditions and the introduction of antibiotics in the late 1940s resulted in a drastic reduction of typhoid fever morbidity and mortality in industrialized countries. However in developing areas of Asia, Africa and Latin America, typhoid fever continues to be a public health problem.

In 2004, WHO estimated the global typhoid fever disease burden at 21 million cases annually, resulting in an estimated 216, 000–600, 000 deaths per year, predominantly in children of school age or younger.

The true burden of typhoid fever in developing countries is difficult to estimate. Asia, with 274 cases per 100,000 persons has the highest incidence of typhoid fever cases worldwide, especially in Southeast Asian countries and in the Indian subcontinent, followed by sub-Saharan Africa and Latin America with 50 cases per 100,000 persons. In an urban slum in Dhaka, incidence of bacteremic typhoid fever was found to be 390/100,000 population, with a 9-fold higher risk for pre-school children than for older persons.

Situation in Sri Lanka

Enteric fever is a notifiable disease in Sri Lanka, is endemic in the country within certain geographical areas. A total of 1823 clinically suspected enteric fever cases were notified to the Epidemiology Unit in the year 2010. In the recent past a significant proportion of the reported small scale enteric fever outbreaks were mainly due to para typhoid rather than typhoid fever.

Typhoid vaccine

In view of the continued high burden of typhoid fever and increasing antibiotic resistance, and given the safety, efficacy, feasibility and affordability of 2 licensed vaccines (Vi and Ty21a), countries should consider the programmatic use of typhoid vaccines for controlling the endemic disease. In most countries, control of the disease will require vaccination only of high-risk groups and populations.

Currently, 2 typhoid vaccines of demonstrated safety and efficacy are available in the international market, namely the parenteral Vi polysaccharide vaccine and the live, oral Ty21a vaccine. These vaccines should now replace the old and relatively reactogenic heat-phenol or acetone inactivated whole-cell vaccine.

Characteristics of the typhoid vaccines

◆ The Vi polysaccharide vaccine

This subunit vaccine was first licensed in the United States in 1994. It is a clear colorless solution composed of purified Vi capsular polysaccharide from the Ty2 *S. Typhi* strain

Each 0.5 ml pre-filled syringe contains 25 micrograms Vi polysaccharide of *Salmonella typhi* and inactive ingredients: sodium chloride, disodium phosphate dehydrate, sodium dihydrogen phosphate dehydrate, phenol and water for injection. This vaccine is available in packs of one and ten glass prefilled syringes.

◆ Ty21a oral vaccine

This vaccine, which was first licensed in Europe in 1983 and in the USA in 1989, is an orally administered, live attenuated Ty2 strain of *S. Typhi* in which multiple genes, including the genes responsible for the production of Vi, have been mutated chemically.

Each enteric-coated capsule contains not less than 2×10^9 viable organisms of attenuated *S. Typhi* strain Ty21a Berna.

Indications

Immunization of adults and children over 2 years of age against typhoid fever. Typhoid vaccination is recommended for:

- ◆ high risk groups and populations who are living in typhoid endemic areas e.g. Immunization of school age and/or preschool age children is recommended in areas where typhoid fever in these age groups is shown to be a significant public health problem, particularly where antibiotic-resistant *S. Typhi* is prevalent,

- ◆ travellers to destinations where the risk of typhoid fever is high, especially to those who hope to stay in endemic areas for longer periods and/or in locations where antibiotic resistant strains of *S. Typhi* are prevalent,
- ◆ controlling typhoid fever outbreaks,
- ◆ laboratory workers who frequently handle cultures of *S. typhi*.

Efficacy

◆ The Vi polysaccharide vaccine

The parenteral vaccine stimulates a specific antibody response (i.e. > 4-fold rise in antibody titre) in about 93% of healthy adults. Controlled trials have demonstrated that the serologic response to vaccine is correlated with protective efficacy.

Although antibody titres fall with time after vaccination, immunity following parenteral vaccine is thought to last for 2 to 3 years.

◆ Ty21a oral vaccine

Live, attenuated Typh-oral vaccines stimulate a cell-mediated immune response, as well as inducing both secretory and humoral antibody. Healthy subjects do not shed vaccine-strain organisms in their stool. As a result, secondary transmission to contacts does not occur.

In studies delivering at least three doses of the enteric-coated capsular form of the vaccine in typhoid endemic regions, reported a protective efficacy of 51%.

Immunization Schedule

◆ The Vi polysaccharide vaccine

The vaccine is licensed for individuals aged >2 years. Only 1 dose is required, and the vaccine confers protection 7 days after injection. To maintain protection, revaccination is recommended every 3 years.

After scrutinizing of local and international reports, the Epidemiology Unit suggests to administer the Vi polysaccharide vaccine only for high risk groups in the high risk areas through the EPI programme.

High risk categories are as follows:

- * food handlers: People involved in food processing, cooking at the hotels, common community kitchens in pilgrimage and IDP camp settings,

- * people who do not use or do not have proper toilet facilities,
- * close contacts of typhoid patients (e.g. family members),
- * children getting frequent episodes of diarrhoea (e.g. more than 4 attacks in the preceding six month),
- * communities inaccessible to safe water,
- * health care workers who associate with typhoid patients.

◆ Ty21a oral vaccine

The oral vaccine capsules are licensed for use in individuals aged >5 years; the liquid oral vaccine can be administered from the age of 2 years. Recommended to repeat this series every 3 years for people living in endemic areas and every year for individuals travelling from non-endemic to endemic countries.

Dosage & Administration

◆ The Vi polysaccharide vaccine

A single dose of 0.5 ml is recommended for both children and adults and should be administered by intramuscular injection into the upper arm.

The Vi polysaccharide vaccine can be co-administered with other vaccines relevant for international travellers (such as yellow fever and hepatitis A) and with vaccines of the routine childhood immunization programmes.

◆ Ty21a oral vaccine

Both versions of the oral vaccine are administered every other day (days 1, 3 and 5); a total of 3-doses taken 1 hour before food. The dose (a whole capsule) is the same for both adults and children.

The capsule must be swallowed whole with water and must not be chewed since the organisms can be killed by gastric acid. Do not give the vaccine concurrently with antibiotics, or other drugs that are active against *Salmonellae*. Antibacterial drugs should be stopped from 3 days before until 3 days after giving Ty21a. The oral vaccine is unlikely to be efficacious if administered at the time of ongoing diarrhoea.

The Ty21a vaccine may be given simultaneously with other vaccines, including live vaccines against polio, cholera, and yellow fever, or the measles, mumps and rubella (MMR) combination.

Storage

The recommended storage temperature is +2°C to +8°C for both Vi polysaccharide vaccine and Ty21a oral vaccine.

Cautions and contraindications

The following conditions are considered as contraindications for the use of typhoid vaccines:

- ◆ presence of one of the general contraindications for any vaccine,
- ◆ having a history of an allergy to any vaccine components,
- ◆ anyone having experienced anaphylaxis to a previous dose of typhoid vaccine preparations.

Ty21a oral live attenuated typhoid vaccine

Other than the above conditions the oral live attenuated vaccine is not recommended to:

- ◆ individuals with impaired immunity,
- ◆ pregnant women.

Vi polysaccharide vaccine is safe for HIV-infected individuals, the induction of protective antibodies is directly correlated to the levels of CD4 positive T-cells.

Ty21a live oral vaccine can be administered to HIV positive, asymptomatic individuals as long as the T-cell count (CD4) is $>200/\text{mm}^3$.

Pregnancy is not a contraindication to vaccination with a parenteral Vi polysaccharide vaccine.

Adverse Events

Typhoid vaccines, both oral and parenteral, are associated with very few adverse events and, when adverse events do occur, they tend to be mild and transient.

◆ The Vi polysaccharide vaccine

Vi polysaccharide typhoid vaccine is associated with local adverse events such as erythema, swelling and pain at the injection site. Systemic adverse events are rare and include fever, malaise and nausea.

◆ Ty21a oral live attenuated typhoid vaccine

The reported adverse events following oral immunization are also relatively rare and mild. Local reactions, such as vomiting, abdominal discomfort and diarrhoea seldom prevent completion of the course of immunization. Low-grade fever can be expected in approximately 2% of vaccinees.

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Introduction

Influenza continues to be a major threat to public health world wide because of its ability to spread rapidly through populations. Children are efficient transmitters of influenza viruses and those 5–9 years of age typically manifest the highest rates of infection and illness. However, severe morbidity and mortality are more common among elderly people and in specific high-risk groups. Although morbidity, mortality and affected risk groups appear to be similar all over the world, in many developing countries the disease burden and the socioeconomic impact of influenza are largely unknown. Whereas in temperate climates outbreaks are experienced mainly during the winter season, influenza occurs more unpredictably in tropical regions.

Influenza viruses can also cause pandemics, during which the rates of illness and mortality can rise dramatically. Recorded since the middle of the 18th century, new influenza A subtypes have caused major global outbreaks at unpredictable intervals. Of these pandemics, the “Spanish flu” in 1918 was the most severe, causing an estimated 20–40 million cases or more deaths worldwide. Less severe pandemics occurred in 1957 and 1968.

Virology

The influenza viruses are orthomyxo viruses. They are classified antigenically as types A, B or C, but only influenza A and B are clinically important in human disease. Influenza viruses possess 2 surface glycoprotein antigens, the haemagglutinin (H) which is involved in cell attachment during infection, and the neuraminidase (N) which facilitates the release of newly synthesized virus from the cell. The influenza A viruses can be segregated into subtypes based on differences in these surface antigens, whereas influenza B cannot be segregated into subtypes. Influenza viruses undergo frequent changes in their surface antigens. Immunity resulting from infection by one influenza virus does not protect fully against antigenic or genetic variants of the same subtype (influenza A viruses) or type (influenza B viruses). As a consequence, influenza outbreaks may occur every year. New influenza vaccines must be designed annually to match the circulating viruses which are expected to cause the next epidemic.

Mode of transmission

Influenza is very contagious. The virus is primarily spread from person to person by the aerosol route, via inhalation of droplets formed during coughing and sneezing, or by direct contact with articles contaminated with respiratory secretions. Inhaled virus particles initiate infection in the respiratory tract, although infection can also occur through the mucous membranes of the eyes, nose and mouth. The incubation period can range from 1 to 7 days but is commonly one to 7 days, during which time the virus replicates in the ciliated columnar epithelial cells of the upper and lower respiratory tract.

An infected person is contagious from 1 to 2 days before symptoms start until about day five of illness. Peak viral shedding occurs 1 to 3 days after the development of symptoms, diminishing to a low level by five days. Children shed more virus and remain infectious for considerably longer.

Clinical Features

Influenza is caused by a virus that attacks mainly the upper respiratory tract – the nose, throat and bronchi and rarely the lungs. The infection usually lasts for about a week. It is characterized by sudden onset of high fever, myalgia, headache, severe malaise, non-productive cough, sore throat, and rhinitis. Most people recover within 1 to 2 weeks without requiring any medical treatment. In the very young, the elderly and people suffering from medical conditions such as lung diseases, diabetes, cancer, kidney or heart problems, influenza poses a serious risk. In these people, the infection may lead to severe complications of underlying diseases, pneumonia and death.

Epidemiology

Global Situation

Influenza rapidly spreads around the world in seasonal epidemics and imposes a considerable economic burden in the form of hospital and other health care costs and lost productivity. Precise data on influenza morbidity and mortality are available mainly from industrialized countries.

In annual influenza epidemics, 5-15% of the population is affected with upper respiratory tract infections. Hospitalization and deaths mainly occur in high-risk groups (elderly, chronically ill). Although difficult to assess, these annual epidemics are thought to result in between 3-5 million cases of severe illness and between 250 000 and 500 000 deaths every year around the world. Most deaths currently associated with influenza in industrialized countries occur among the elderly over 65 years of age.

Much less is known about the impact of influenza in the developing world. However, influenza outbreaks in the tropics where viral transmission normally continues year-round tend to have high attack and case-fatality rates.

The annual incidence of influenza varies widely, depending on the virulence of circulating strains and the susceptibility of the population, which is affected by antigenic changes in the virus, vaccine match and vaccine coverage.

Sri Lankan situation

In Sri Lanka Influenza Like Illness (ILI) surveillance has been initiated since 2005 in 20 hospitals identified as sentinel surveillance sites for Avian/Pandemic influenza. They are expected to send at least 30 samples per month from patients with ILI attending OPD to the Medical Research Institute (MRI). MRI is the national influenza centre in Sri Lanka for human influenza surveillance.

Influenza vaccine

Vaccination is the principal measure for preventing influenza and reducing the impact of epidemics. Various types of influenza vaccines have been available and used for more than 60 years. They are safe and effective in preventing both mild and severe outcomes of influenza. Influenza vaccination can reduce both health-care costs and productivity losses associated with influenza illness.

Characteristics of the Influenza vaccine

Constant genetic changes in influenza viruses mean that the vaccines' virus composition must be adjusted annually to include the most recent circulating influenza A(H3N2), A(H1N1) and influenza B viruses.

There are two major types of vaccines available against influenza namely live attenuated and inactivated influenza vaccines.

Live attenuated influenza vaccine

A few countries have licensed live attenuated influenza vaccines for certain target groups. Until live attenuated vaccines are more widely available, they are not yet generally recommended for influenza prevention.

Inactivated influenza vaccines

Inactivated vaccines are classified into several types, depending on whether they contain whole virus particles, partially disrupted virus particles (split. vaccines) or purified envelope antigens (subunit. vaccines). Some subunit vaccines have been combined with an adjuvant or delivery system.

Efficacious and safe inactivated vaccines remain the cornerstone of influenza prophylaxis in most countries. Unless stated otherwise, the data presented in this chapter relate to inactivated trivalent vaccines only.

Efficacy

It is recommended that elderly persons, and persons of any age who are considered at “high risk” for influenza-related complications due to underlying health conditions, should be vaccinated. Among the elderly, vaccination is thought to reduce influenza-related morbidity by 60% and influenza-related mortality by 70-80%. Among healthy adults the vaccine is very effective (70-90%) in terms of reducing influenza morbidity, and vaccination has been shown to have substantial health-related and economic benefits in this age group.

The effectiveness of influenza vaccine depends primarily on the age and immunocompetence of the vaccine recipient and the degree of similarity between the viruses in the vaccine and those in circulation.

Indication

Differences in health priorities as well as limitations of health budgets have so far restricted common use of influenza vaccine to high-risk groups in industrialized countries. However, even in these countries, a large proportion of the population at high risk for severe disease does not receive influenza vaccine. Based on data from industrialized countries, and listed in order of priority, the following groups of individuals may be targeted for influenza vaccination in order to reduce the incidence of severe illness and premature death.

- ◆ Residents of institutions for elderly people and the disabled.
- ◆ Elderly, non-institutionalized individuals with chronic heart or lung diseases, metabolic or renal disease, or immunodeficiencies.
- ◆ All individuals >6 months of age with chronic heart or lung diseases, metabolic or renal disease, or immunodeficiencies.
- ◆ Elderly individuals above a nationally defined age limit, irrespective of other risk factors.
- ◆ Other groups defined on the basis of national epidemiological data and capacities, such as contacts of high-risk people, pregnant women, healthcare workers and others with key functions in society, as well as children 6–23 months of age.

Dosage & Administration

Trivalent, inactivated influenza vaccines (TIVs) are administered IM into the deltoid muscle (vaccinees aged >1 year) or the antero-lateral aspect of the mid thigh (vaccinees aged between 6 and 12 months).

These vaccines should not be given to children aged <6 months; those aged 6–36 months should receive half the adult vaccine dose (0.25 ml). Children aged 3–9 years should receive the adult dose (0.5ml). Previously unvaccinated children aged <9 years should receive 2 doses, administered at least 1 month apart. A single dose (0.5ml) of the vaccine is appropriate for schoolchildren aged >9 years and healthy adults.

Inactivated influenza vaccines will not interfere with other concomitantly administered childhood vaccines. Immunity lasts about one year and the vaccine should be administered annually.

Storage

Influenza vaccine should be stored at a temperature between +2° C to +8° C and should not be frozen. At the end of each year, vaccine should be appropriately discarded to avoid inadvertent use of a product with incorrect formulation in the following year.

Cautions and contraindications

The following conditions are considered as absolute contraindications for the use of influenza vaccine.

- ◆ Persons with history of allergy to egg proteins
- ◆ Hypersensitivity to any component of the vaccine
- ◆ Previous allergic reaction to any influenza vaccine

Patients with a history of Guillain-Barré Syndrome (GBS) with an onset related in time to influenza vaccination may be at increased risk of again developing GBS if influenza vaccine is given. The risk should be weighed against the benefits to the individual patient of influenza vaccination.

Adverse Events

Influenza vaccines conforming to international standards of purity and potency have been used for many years and have an excellent safety record. They are largely free from systemic effects but may cause local tenderness or soreness at the injection site for 1-2 days. Transient systemic reactions such as fever, malaise and myalgias occur in a minority of vaccine recipients within 6–12 hours of vaccination. Split virus vaccines and subunit vaccines show reduced systemic reactivity in both children and adults, compared with whole virus preparations.

Usage of vaccine in specific circumstances

Pregnant women

It is recommended that influenza vaccine be offered in advance to women planning a pregnancy. Although the inactivated influenza vaccine is considered by many experts to be safe at any stage of pregnancy, others prefer to administer the influenza vaccine in the second trimester to avoid a coincidental association with spontaneous abortion. Practitioners should assess the risks for individual women.

planning a pregnancy. Although the inactivated influenza vaccine is considered by many experts to be safe at any stage of pregnancy, others prefer to administer the influenza vaccine in the second trimester to avoid a coincidental association with spontaneous abortion. Practitioners should assess the risks for individual women.

Travellers

People travelling who are at the risk groups should consider immunisation, depending on the season and their destination. In tropical countries influenza activity can occur throughout the year but is more likely during the monsoon, while in the northern hemisphere activity is commonest between the months of December and March.

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Introduction

Chickenpox (*Varicella*) is an acute, highly contagious disease caused by *Varicella zoster* virus (VZV). Chickenpox is mostly a mild disorder in childhood but tends to be more severe in adults. It may be fatal, especially in neonates and in immunocompromised persons. Following infection with VZV, the virus remains latent in neural ganglia, and upon subsequent reactivation VZV may cause herpes zoster (shingles), a disease mainly affecting the elderly and immunocompromised persons.

Varicella was at first confused with smallpox, and the first clinical differentiation was done by Heberden in 1767. The varicella zoster virus was first isolated in cell culture in 1952.

Virology

Varicella zoster virus is a double-stranded DNA virus belonging to the *herpesvirus* family. Only one serotype is known, and humans are the only reservoir. VZV shows little genetic variation. Following infection, the virus remains latent in neural ganglia, and upon subsequent reactivation VZV may cause zoster (shingles).

Mode of transmission

Varicella-zoster virus is transmitted by droplets, aerosol or direct contact and enters the host through the nasopharyngeal mucosa, and almost invariably produces clinical disease in susceptible individuals. Patients are usually contagious from 1 to 2 days before the rash onset until the rash dries up about 7 days later. The infectious period may be more prolonged in immune suppressed individuals. Once a case has occurred in a susceptible population, it is very hard to prevent an outbreak.

The incubation period of chickenpox infection is 10-21 days (average 14–16 days); therefore, it takes 14 – 16 days to develop symptoms after being exposed to a person with chickenpox. Secondary attack rate may reach up to 90% among susceptible household contacts.

Clinical Features

Chickenpox is characterized by fever, tiredness and weakness. These symptoms are followed by an itchy, vesicular rash, usually starting on the scalp and face and then spreading out all over the body. Vesicles are more abundant on covered than the exposed parts of the body. It may appear in mucous membranes of the mouth, upper respiratory tract and in conjunctivae. The rash usually begins as small lumps that turn into blisters and dry out to crust and eventually form scabs. It normally takes about 7-10 days for all crusts to disappear.

In about 10-20% of the cases, varicella is followed later in life by herpes zoster, or shingles, a painful vesicular rash with dermatomal distribution. Most cases of zoster occur after the age of 50 or in immunocompromised persons.

Natural infection induces lifelong immunity to clinical varicella in almost all immunocompetent persons. Newborn babies of immune mothers are protected by passively acquired antibodies during their first months of life.

Complications:

Rarely chickenpox may be complicated by secondary bacterial skin infection, pneumonia, acute cerebellar ataxia, aseptic meningitis, transverse myelitis, encephalitis, and thrombocytopenia. In rare cases, it involves the viscera and joints. Complications are predominantly seen among infants, adults and immunocompromised persons.

Herpes Zoster may occasionally result in permanent neurological damage such as cranial nerve palsies and contralateral hemiplegia, and visual impairment following zoster ophthalmia.

Congenital varicella syndrome has been reported after varicella infection in pregnancy and may result in skin scarring, limb defects, ocular anomalies and neurologic malformations in the new born. Infection early in pregnancy may be associated with less risk of congenital varicella syndrome compared to 13-20 weeks gestation.

Newborn infants whose mothers have varicella at term (5 days before delivery to 2 days after delivery), are at risk to develop severe varicella due to immaturity of their cell-mediated immunity and absence of transplacental maternal antibodies.

Epidemiology

Global Situation

Varicella and herpes zoster occur worldwide. In temperate areas; varicella has a distinct seasonal fluctuation, with the highest incidence occurring in winter and early spring. Less seasonality is reported in tropical areas. Herpes zoster has no seasonal variation and occurs throughout the year. Some data suggest that in tropical areas, varicella infection occurs more commonly among adults than children.

Situation in Sri Lanka

Chickenpox is a notifiable disease in Sri Lanka and all cases of chickenpox should be notified to the local Medical Officer of Health. In year 2010 a total number of 3412 suspected chickenpox cases was notified from the whole country.

Chickenpox vaccine

Except for vaccination, no countermeasures are likely to control the dissemination of varicella or the frequency of zoster in a susceptible community. Varicella-zoster immune globulin and antiherpesviral drugs are very costly, and mainly used for post-exposure prophylaxis or the treatment of varicella in persons at high risk of severe disease.

Varicella vaccines based on the attenuated Oka-strain of VZV have been marketed since 1974. Extensive safety, efficacy and cost-effectiveness have warranted the introduction of varicella vaccine into the childhood immunization programmes of several industrialized countries.

Routine childhood immunization against varicella may be considered in countries where this disease is a relatively important public health and socioeconomic problem, where the vaccine is affordable, and where high (85-90%) and sustained vaccine coverage can be achieved.

Characteristics of the chickenpox Vaccine

Chickenpox vaccine is a live attenuated freeze dried vaccine (lyophilized), derived from the Oka strain of VZV and must be reconstituted before use. The virus was attenuated by sequential passage in human embryonic lung cell culture, embryonic guinea pig fibroblasts, and in WI-38 human diploid cells.

Each 0.5ml dose of the reconstituted vaccine contains not less than $10^{3.3}$ plaque-forming units (PFU) of the varicella-zoster virus. The vaccine also contains amino acids, human albumin, lactose, neomycin sulphate, and polyalcohols. It does not contain a preservative.

Live attenuated varicella vaccine is currently available as a monovalent vaccine. It is anticipated that quadrivalent combination vaccines containing measles, mumps, rubella and varicella vaccines (MMRV) will be available in the near future

Indications

Varicella vaccine is indicated for active immunization against varicella of non-immune susceptible individuals from one year of age.

Groups who would particularly benefit from vaccination include:

- ◆ non-immune people in high-risk occupations where exposure to varicella is likely (such as healthcare workers, teachers and workers in childcare centres),
- ◆ non-immune women before pregnancy to avoid congenital or neonatal

varicella (They should be advised to avoid pregnancy for 3 months following each dose of vaccine),

- ◆ Non-immune household contacts, (both adults and children), of immunocompromised patients with no history of the disease,
- ◆ Close contacts of varicella (or zoster) case may be vaccinated within 3 days, and possibly up to 5 days of exposure.

Efficacy

After observation of study populations for periods of up to 20 years in Japan and 10 years in the United States of America, more than 90% of immunocompetent persons who were vaccinated as children were reported protect from varicella.

Immunity following vaccination appears to be long-lasting, and is probably permanent or life long in the majority of vaccinees. Breakthrough infection is significantly milder, with fewer lesions among them.

Some studies show that varicella vaccine is 70 to 100% effective in preventing illness or modifying the severity of illness if used within 3 days, and possibly up to 5 days, after exposure.

Among healthy adolescents and adults 13 years of age and older, an average of 78% develop antibodies after first dose, and 99% develop antibodies after a second dose given 4 to 8 weeks later.

Immunization Schedule

Varicella vaccine is not yet included into the Sri Lankan National Immunisation Schedule. A single dose of 0.5 ml is recommended to administer sub cutaneously after completion of 12 months of age to 12 years for those who are not previously immune to Varicella Zoster.

Persons above 13 years are recommended to be vaccinated with two doses. After the initial dose, the second dose is given 6-10 weeks apart.

It is not yet sufficiently documented that the varicella vaccine, administered either in childhood or in adult populations, will protect against zoster.

Dosage & Administration

Varicella is a lyophilized vaccine and is provided with a vaccine specific diluent (sterile water for injection). It should be reconstituted only with the diluent supplied using a sterile syringe and needle.

A single dose of 0.5 ml is recommended for children and adults and should be administered by subcutaneous injection into the upper arm.

The vaccine can be administered concurrently with other vaccines, but in a separate syringe and at a different site. If not administered concurrently, the vaccine must be separated from other live vaccines (eg, measles, mumps and rubella – MMR) by at least one month.

Storage

Varicella vaccine should be stored in the dark at +2°C to +8°C temperature. For long term storage, a temperature at –20°C is recommended. It is important to protect both the lyophilized and reconstituted vaccine from light. The diluent should not be frozen but should be kept cool in the main compartment of the refrigerator.

The reconstituted varicella vaccines can be stored at +2°C to +8°C (preferably in the dark) for up to 6 hours if not used immediately. Any opened vaccine vials remaining at the end of an immunization session (or after 6 hours) should be discarded.

Cautions and Contraindications

The following conditions are considered as contraindications for the use of varicella vaccine.

- ◆ Presence of one of the general contraindications for any vaccine.
- ◆ History of an allergy to neomycin, gelatin or any other vaccine components.
- ◆ Anyone who has experienced anaphylaxis to a previous dose of varicella vaccine.
- ◆ persons who are severely immunocompromised as a result of congenital disease, HIV infection, advanced leukaemia or lymphoma, serious malignant disease, or treatment with high-dose steroids or in persons who are receiving immunosuppressive therapeutic radiation.
- ◆ Pregnancy.
- ◆ A family history of congenital or hereditary immunodeficiency, unless the immune competence of the potential vaccine recipient is demonstrated.

Aerosolized steroid preparations are not a contraindication to vaccination. Persons whose immunosuppressive therapy with steroids discontinued for 1 month (3 months for chemotherapy) may be vaccinated.

HIV-infected children with CD4 T-lymphocyte percentage of 15% or higher and older children and adults with a CD4 count of 200 per microliter or higher may be considered for vaccination.

Precautions

Administration of blood, plasma or immunoglobulin less than 5 months before or 3 weeks after varicella immunization is likely to reduce the efficacy of the vaccine.

Due to the theoretical risk of Reye's syndrome, the use of salicylates is discouraged for 6 weeks following varicella vaccination.

Adverse Events

In general, adverse reactions to varicella vaccination are rare and mild. The most common adverse reactions following varicella vaccine are local reactions, such as pain, soreness, erythema, and swelling at the injection site.

A varicella-like rash at injection site is reported by 3% of children and by 1% of adolescents and adults following the second dose. These lesions generally occur within 2 weeks, and are most commonly maculopapular rather than vesicular. A generalized varicella-like rash is reported by 4–6% of recipients of varicella vaccine, with an average of five lesions. Most of these generalized rashes occur within 3 weeks and most are maculopapular.

Systemic reactions are not common following the varicella vaccination.

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Introduction

Hepatitis A is an acute infection of the liver caused by hepatitis A virus (HAV). Hepatitis A is usually a self-limiting viral illness that does not result in chronic infection or chronic liver disease. However, acute disease can vary in clinical severity from a mild illness to a severely disabling illness. Acute liver failure from Hepatitis A is rare.

Hepatitis A virus is transmitted from person to person, primarily by the faeco-oral route and is closely associated with poor sanitary conditions. In the long term, socioeconomic development will reduce transmission of hepatitis A, particularly through improved sanitation and health education.

Virology

Hepatitis A infection is caused by Hepatitis A virus (HAV), a non-enveloped RNA virus belonging to the family *Picornaviridae*. Humans are thought to be the only natural host.

Hepatitis A virus survives well in the environment. It is relatively stable at low pH levels and moderate temperatures. It can remain on a person's hands for several hours and in the environment for months, depending on conditions.

The virus can be inactivated by high temperature (85°C or higher), formalin, and chlorine.

Mode of transmission

Hepatitis A is transmitted primarily via faeco-oral route. The most common modes of transmission include close personal contact with an infected person and ingestion of contaminated food and water.

Clinical Features

The incubation period is approximately four weeks (range 15-50 days). Although replication of the virus is limited to the liver, the virus is present not only in the liver, but also in bile, stools and blood during the late incubation period and acute pre-icteric phase of the illness. Infection usually induces life-long Immunity.

All types of acute hepatitis show more or less the same kind of symptoms and signs, therefore, clinical features of acute hepatitis A are indistinguishable from those of other types of acute viral hepatitis.

Clinical spectrum of illness may vary from asymptomatic infection to symptomatic illness without jaundice (yellow discoloration of sclera and skin) or a classical icteric hepatitis. Rarely it is very severe and may be even fatal.

The occurrence of symptoms is commoner among adults than in infants and children.

Typical clinical symptoms include acute fever, malaise, anorexia, nausea, vomiting and abdominal discomfort followed a few days later by dark urine and jaundice.

A person is most infectious in the latter half of incubation period, and then infectivity wanes during the first week following onset of symptoms. Symptoms usually last several weeks, although up to 15% of cases may have relapsing hepatitis for up to 12 months. No carrier state or chronic sequelae has been identified after HAV infection.

Epidemiology

Global Situation

The incidence of hepatitis A is very much related to socioeconomic development. Sero-epidemiological studies have shown varying degrees of prevalence of anti-HAV antibodies in the general population ranging from 15% to nearly 100% in different parts of the world. In developed countries, the incidence of hepatitis A infection is on the decline, most probably due to improved sanitation and living conditions. In countries of low and intermediate disease endemicity, disease among adults is seen more often. Annual occurrence of clinical cases of hepatitis A is estimated to be around 1.5 million.

Sri Lankan situation

Hepatitis A is endemic in Sri Lanka, particularly in areas where sanitation is poor and access to safe water is an issue. Outbreaks from time to time have occurred in the past and they have mostly been confined to limited geographical areas. Several large outbreaks have been observed in recent times, largest being the one in welfare camps in Cheddikulam, Vavuniya during 2009. The total of 1496 clinically suspected hepatitis A cases were notified to Epidemiology Unit in the year 2010.

Hepatitis A vaccines

Four inactivated vaccines are available internationally. All four vaccines are similar in efficacy and safety.

None of the vaccines are licensed to be used for children below the age of one year. In countries where clinical hepatitis A is an important health problem, immunization is likely to be a cost-effective public health tool to control the disease.

Characteristics of the Hepatitis A Vaccines

◆ Hepatitis A vaccine

Four inactivated hepatitis A vaccines are currently available. The vaccines are given parenterally (IM), as a 2-dose series, 6-18 months apart.

Three vaccines are manufactured from cell culture adapted HAV propagated in human fibroblasts. Following purification from cell lysates, the HAV preparation is formalin-inactivated and adsorbed to an aluminium hydroxide adjuvant. One vaccine is formulated without preservative; the other 2 are prepared with 2-phenoxyethanol as a preservative. The fourth vaccine is manufactured from HAV purified from infected human diploid cell cultures and inactivated with formalin.

◆ Hepatitis A & B combined vaccine:

A combined inactivated hepatitis A and recombinant hepatitis B vaccine has been available since 1996 for use in children aged one year or older. The combination vaccine is given as a three-dose series, using a 0, 1, 6 month schedule.

Indications

Hepatitis A vaccine is indicated for adult and children over 1 year:

- ◆ persons who are at increased risk for hepatitis A infection,
- ◆ persons who are at increased risk for complications from Hepatitis A,
- ◆ control outbreaks.

Use of hepatitis A vaccine to control outbreaks in communities has been most successful in small, self-contained communities, when vaccination is started early in the course of the outbreak, and when high coverage is achieved. Concomitant efforts for health education and improved sanitation should be coupled with vaccination strategies.

Those who may receive hepatitis A vaccine include:

- ◆ persons who have chronic liver disease of any aetiology who have not had Hepatitis A,
- ◆ Persons who frequently receive blood products including those having clotting-factor disorders,
- ◆ persons who have occupational risk for infection (persons who work with HAV in a research laboratory setting, persons who come in contact with faeces/ sewage),

- ◆ men who have sex with men,
- ◆ users of illegal injection and non-injection drugs,
- ◆ persons with intellectual disabilities,
- ◆ persons travelling to or working in countries/ areas of high or intermediate endemicity,
- ◆ at risk patients during the early stages of a hepatitis A outbreak.

Efficacy

Hepatitis A vaccines are highly immunogenic. Vaccine efficacy is shown to be nearly 100% among adults within one month after a single dose of vaccine, with similar results available for children and adolescents in both developing and developed countries.

Dosage & Administration

◆ Hepatitis A vaccine

Manufacturers currently recommend two doses of vaccine, given intramuscularly (IM) adult and children over one year, 6-18 months apart to ensure long-term protection. The duration of protection is likely to be at least 20 years.

From manufacturer to manufacturer, the vaccines may differ in the dose of vaccine to be given, vaccination schedule, ages for which the vaccine is licensed, and whether paediatric and adult formulations are available. Therefore, manufacturer's guidelines should be referred.

Although different production methods are used and different strains and quantities of the HAV antigen are used for their respective vaccines, the 'equivalent' vaccines of different manufacturers are interchangeable.

Hepatitis A vaccine may be administered concurrently with other vaccines

◆ Hepatitis A & B combined vaccine:

The combination vaccine is given as a three-dose series, using a 0, 1, 6 month schedule for children aged more than 1 year and adults.

The dose of vaccine, vaccination schedule, ages for which the vaccine is licensed, and whether there is a paediatric and adult formulation varying from manufacturer to manufacturer.

Storage

Hepatitis A vaccine should be transported and stored at +2°C to +8°C temperature. Do not freeze.

Contraindications

The following conditions are considered as contraindications for the use of hepatitis containing vaccine preparations.

- ◆ Presence of any of the general contraindications for any vaccine
- ◆ Anaphylaxis following a previous dose of hepatitis A containing vaccine
- ◆ History of anaphylaxis following any of the vaccine components

Combination vaccines containing the hepatitis B component are contraindicated where there is a history of anaphylaxis to yeast.

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

Adverse Events

Adverse events, when they occur, are transient and minor. They include soreness at injection site, weakness, headache, disturbances of the gut such as nausea, vomiting, loss of appetite, diarrhea etc., malaise and fever. Reports of severe anaphylactic reactions are extremely rare.

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Introduction

Bacteria called *Neisseria meningitidis* (meningococcus) is a leading cause of meningitis and fulminant septicaemia and a significant public health problem in most countries. Although meningococcal disease frequently occurs as scattered, apparently unrelated cases or in small outbreaks, in some regions this endemic situation may alternate with devastating, unpredictable epidemics.

Meningococcal disease was described as far back as 1805 when an outbreak swept Geneva, Switzerland. However, the causative agent of meningococcal meningitis was identified only in 1887. Major outbreaks were subsequently noted during the two world wars and epidemics have been reported on the African continent since 1909.

As a rule, endemic meningococcal disease occurs primarily in children and adolescents, with highest attack rates among infants aged 3 -12 months, whereas in meningococcal epidemics, rates may rise in older children and young adults.

Bacteriology

Meningococcal disease is caused by the bacterium *Neisseria meningitidis* (*N. meningitidis* or meningococcus), a Gram-negative diplococcus. There are 13 known serogroups distinguished by differences in surface polysaccharides of the outer membrane capsule. Globally, serogroups A, B, C, W135 and Y most commonly cause the disease. Out of all Meningococcal serogroups A, B and C are responsible for the vast majority of morbidity and mortality.

In most parts of the world, serogroups Y and W135 are relatively uncommon causes of meningococcal infection. However, recent reports of endemic occurrence of serogroup Y meningococcal disease in the United States, and outbreaks caused by serogroup W135 strains in Saudi Arabia and sub-Saharan Africa, suggest that these serogroups may be gaining importance, at least among young adults.

Mode of transmission

N. meningitidis is transmitted by inhalation or direct contact with respiratory secretions of patients or healthy human asymptomatic carriers. The carrier rate is relatively low during childhood and high in adolescents and young adults. Transmission is relatively slow in open populations and is greater in isolated closed populations. Transmission is aggravated by smoking or presence of respiratory infections. The average incubation period is 4 days, ranging between 2 - 10 days. There is no animal or environmental reservoir for this organism.

Clinical Features

Neisseria meningitidis can cause meningitis, septicaemia or a combination of both meningitis and septicaemia. Rarely did it cause other localized infections, including pneumonia, arthritis and conjunctivitis. Meningococcal septicemia, with or without meningitis, have overall high mortality risk (about 10%) despite appropriate antibiotic therapy.

The most common symptoms of meningococcal meningitis are stiff neck, high fever, sensitivity to light, confusion, headaches and vomiting. About 10 -15% of survivors of meningococcal meningitis will suffer from significant neurological sequelae, including mental disorders, deafness, palsies and seizures. A less common but more severe form of meningococcal disease is meningococcal septicaemia which is characterized by typical haemorrhagic rash and rapid circulatory collapse. Extensive tissue necrosis, sometimes resulting in amputations of digits or limbs.

Both persons with complement factor deficiencies and functional or anatomical asplenia are at increased risk of getting meningococcal disease.

Treatment with appropriate chemoprophylaxis is an important control measure for meningococcal disease; however, it has limited effectiveness and its use should be restricted to special circumstances. These circumstances include close contacts of cases, such as households, schoolmates and institutionalized subjects. The main purpose of chemoprophylaxis is to prevent the occurrence of secondary cases by eliminating carriers with *Neisseria meningitidis*.

Patients with meningococcal infection treated in a hospital or clinic, who had received an antibiotic, which does not eliminate the carrier state (penicillins or chloramphenicol), should receive chemo-prophylaxis with an effective antibiotic (ciprofloxacin, rifampicin, or ceftriaxone) upon hospital discharge.

Epidemiology

Global Situation

Meningococcal meningitis occurs sporadically in small clusters throughout the world with seasonal variations and accounts for a variable proportion of endemic bacterial meningitis. In temperate regions the number of cases increases in winter and spring.

The largest burden of meningococcal disease occurs in an area of sub-Saharan Africa known as the meningitis belt, which stretches from Senegal in the west to Ethiopia in the east.

Serogroup A disease occurs predominantly in developing populations such as those in Africa and Asia, while serogroup B is the major cause of sporadic meningococcal disease in most developed countries.

In industrialized countries, the overall mortality from meningococcal meningitis is usually 5 - 10%; in Africa, closer to 10%. Case-fatality rates in fulminant septicaemia may exceed 15 - 20%.

Situation in Sri Lanka

No major meningococcal meningitis outbreaks have been reported from Sri Lanka, but few isolated cases mainly among children has been reported the in recent past. Around 4000 Sri Lankans visit Mecca as Hajj pilgrims annually, and it is very important to ensure that all these pilgrims are vaccinated against meningococcal meningitis before they leave

Meningococcal vaccines

Currently available meningococcal vaccines include polysaccharide vaccines and polysaccharide-protein conjugate vaccines. Although purified capsular polysaccharide antigens elicit protective antibody responses, conjugate vaccines are more immunogenic and also induce immunological memory. Both polysaccharide and conjugate vaccines are available against meningococci of serogroups A, C, W135 and Y.

Serogroup B vaccines are based on protein extracted from selected outbreak strains. Strain-specific serogroup B vaccines have been used successfully in some countries to limit outbreaks, but they are not widely available.

Characteristics of Meningococcal vaccines

There are 2 different types of meningococcal vaccine available: the meningococcal conjugate vaccines and meningococcal polysaccharide vaccines . The difference between these 2 types of vaccines lie in the different way that each vaccine stimulates an immune response.

Meningococcal polysaccharide vaccines

Internationally marketed meningococcal polysaccharide vaccines are based on purified, heat-stable, lyophilized capsular polysaccharides from meningococci of the respective serogroup. They are available in bivalent (A,C), trivalent (A, C, W135), and quadrivalent (A, C, W135,Y) formulations. The vaccines contain 50 µg of each of the individual polysaccharides. No adjuvants are included.

Meningococcal conjugate vaccines

Licensed meningococcal conjugate vaccines are currently available in monovalent (A or C) or quadrivalent (A, C, W135, Y) and also include a combination vaccine based on *Haemophilus influenzae* type b and *Neisseria meningitidis* serogroup C vaccines (HibMenC). The protein conjugate of these vaccines consists of either diphtheria toxoid or a non-toxic mutant of diphtheria toxin (CRM 197), or tetanus toxoid.

Indications

Vaccination with meningococcal vaccines is recommended in the following situations;

- ◆ Patients with terminal complement component deficiencies
- ◆ Patients with functional or anatomic asplenia.
- ◆ control of meningococcal outbreaks
- ◆ laboratory personnel who are exposed routinely to *N. meningitidis*
- ◆ people who intend travelling to meningococcal endemic regions
- ◆ pilgrims attending the annual Hajj in Saudi Arabia

Efficacy

Meningococcal polysaccharide vaccines

The antibody responses to each of the four polysaccharides in the polysaccharide vaccine are serogroup-specific and independent. Vaccine efficacy within the year of immunization is between 87% and 94%. Lower efficacy (0- 67%) has generally been observed in young children. Vaccine efficacy was strongly related to age at immunization: 83% for ages 15 to 20 years, 75% for ages 10 to 14years, and 41% for ages 2 to 9 years.

Meningococcal conjugate vaccines

Vaccine effectiveness after one year ranged from 87% - 98%. There was no significant difference in effectiveness between age groups. However, after 4 years of follow-up, the vaccine effectiveness among children declined significantly to 66%.

Dosage & Administration

Meningococcal polysaccharide vaccines

Single dose of 0.5 ml is recommended for both children more than 2 years of age and adults. Reconstituted vaccine administered by subcutaneous injection. Meningococcal polysaccharide vaccine can be administered concurrently with other

vaccines. Protective level of antibody is usually achieved within 7 – 10 days of vaccination. Protection lasts for 3 – 5 years.

Meningococcal conjugate vaccines

Meningococcal conjugate vaccines are licensed for children aged more than 2 months, adolescents and adults. The dose is 0.5 ml given by IM injection.

Infants aged 2–11 months are given 2 doses (0.5 ml per dose) with at least 2 months apart, followed by a booster dose about one year later.

The possible need for boosters is not yet established for individuals >1 year of age, who normally receive one dose only.

Storage

Both polysaccharide and conjugate meningococcal vaccines should be stored at +2°C to +8°C. Do not freeze.

Cautions and contraindications

The following conditions are considered as contraindications for the use of both polysaccharide and conjugate meningococcal vaccines.

- ◆ Presence of one of the general contraindications for any vaccine.
- ◆ History of an allergy to any of the vaccine components.
- ◆ Anyone who has experienced anaphylaxis to a previous dose of meningococcal vaccine.

Both conjugate and polysaccharide meningococcal vaccines are efficacious and safe when used in pregnant women.

Adverse Events

Meningococcal polysaccharide vaccines

Adverse reactions to polysaccharide meningococcal vaccines are usually mild; the most frequent reaction is 1–2 days of pain and redness at the site of injection. Transient fever is reported in <5% of recipients. Very rarely systemic allergic reactions (e.g. urticaria, wheezing, rash) and anaphylaxis have been reported.

Meningococcal conjugate vaccines

All meningococcal conjugate vaccines have an excellent safety records. None has been associated with any serious adverse effects, either during clinical trials or in post-marketing surveillance. Redness, swelling and pain at the site of injection may occur. Such reactions usually start within the first day after immunization and last 1 to 3 days. Less commonly, children may develop fever or be irritable for a short period.

Travellers

Travellers from low-endemic regions visiting countries which are highly endemic or epidemic for meningococcal disease should consider meningococcal vaccination. For travellers to the African meningitis belt, the risk of acquiring infection is greatest in the dry season and for those with prolonged contact with the local population.

Proof of quadrivalent (A,C,W135,Y) vaccination against meningococcal disease is required for all persons more than 2 years travelling to Mecca during the annual Hajj and the Umrah pilgrimages. The vaccine should be given at least 10 days before arrival at Mecca. Vaccination is valid for three years.

In Sri Lanka currently travellers can get meningococcal vaccination with quadrivalent (A,C,W135,Y) polysaccharide vaccine either from Port Health Office at Medical Research Institute or from the private sector.

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Introduction

Yellow fever is an acute viral haemorrhagic disease, found in tropical regions of Africa and the Americas. It principally affects humans and monkeys, and is transmitted via the bite of *Aedes* mosquitoes. It can produce devastating outbreaks, which can be prevented and controlled by mass vaccination campaigns.

The number of yellow fever cases has increased over the past two decades due to declining population immunity to infection, deforestation, urbanization, population movements and climate change.

Yellow fever can be recognized from historic texts stretching back 400 years. Infection causes a wide spectrum of disease, from mild symptoms to severe illness and death. The "yellow" in the name is explained by the jaundice that affects some patients, causing yellow eyes and yellow skin.

Virology

Yellow fever virus is classified in genus *Flavivirus* which is in the family *Flaviviridae*. The yellow fever virus is small (35 to 45 nm) and consists of a core containing single-stranded RNA surrounded by a lipid envelope.

Mode of transmission

Exposure of susceptible persons to bites from infected mosquitoes is the only significant mode of yellow fever transmission. An urban and a jungle (forest, sylvatic) form of yellow fever can be distinguished by differences in their respective transmission cycles. Urban yellow fever, which frequently occurs as large outbreaks, is transmitted from infected to susceptible humans by *Aedes aegypti*, a mosquito species that breeds in the proximity of human habitats. The urban form of transmission is found mainly in Africa. The sylvatic form of yellow fever is primarily an enzootic viral disease of non-human primates, but the various mosquito vectors involved may occasionally cause individual cases or small outbreaks of yellow fever among humans in the forested savanna of Africa and in jungle areas of South America.

Clinical Features

Once contracted, the virus incubates in the body for 3 to 6 days, followed by infection that can occur in one or two phases. The first, "acute", phase usually causes fever, muscle pain with prominent backache, headache, shivers, loss of appetite, and nausea or vomiting. Most patients improve and their symptoms disappear after 3 to 4 days.

However, 15% of patients enter a second, more toxic phase within 24 hours of the initial remission. High fever returns and several body systems are affected.

The patient rapidly develops jaundice and complains of abdominal pain with vomiting. Bleeding can occur from the mouth, nose, eyes or stomach. Once this happens, blood appears in the vomit and faeces. Kidney function deteriorates. Half of the patients who enter the toxic phase die within 10 to 14 days, the rest recover without significant organ damage.

There is no specific treatment for yellow fever. Treatment is symptomatic, aimed at reducing the symptoms for the comfort of the patient.

Epidemiology

Global Situation

Forty-five endemic countries in Africa and Latin America, with a combined population of over 900 million, are at risk. In Africa, an estimated 508 million people living in 32 countries are at risk. The remaining population at risk is in 13 countries in Latin America.

There are an estimated 200,000 cases of yellow fever (causing 30,000 deaths) worldwide each year. Small numbers of imported cases occur in countries free of yellow fever. Although the disease has never been reported in Asia, the region is at risk because the conditions required for transmission are present there.

Millions of travellers to risk areas are also at risk of yellow fever infection. For unvaccinated individuals entering into endemic areas in Africa, the risks of yellow fever illness and death have been estimated at 1:267 and 1:1333, respectively, for a two week trip, although the risks vary considerably according to the season. The corresponding figures for South America are likely to be 10 times lower.

Situation in Sri Lanka

Yellow fever is a notifiable disease in Sri Lanka and all cases of yellow fever should be notified immediately to the local Medical Officer of Health and WHO. Although the vector *Aedes aegypti* mosquito is found in Sri Lanka, yellow fever cases have not been reported.

Yellow fever vaccine

Vaccination is the single most important measure for preventing yellow fever. In high risk areas where vaccination coverage is low, prompt recognition and control of outbreaks through immunization is critical to prevent epidemics.

Preventive vaccination can be offered through routine infant immunization and one-time mass campaigns to increase vaccination coverage in countries at risk, as well as for travellers to yellow fever endemic areas.

WHO strongly recommends routine yellow fever vaccination for children in areas at risk for the disease.

For decades, a safe and effective 17D vaccine has been available and is recommended by WHO for large-scale use by residents of and visitors to at risk countries. The yellow fever vaccine is safe and affordable, providing effective immunity against yellow fever within one week for 95% of those vaccinated. A single dose provides protection for 30–35 years or more, and probably for life. Serious side effects are extremely rare.

Characteristics of yellow fever vaccine

The yellow fever 17D vaccine is the only commercially available vaccine against yellow fever. It is a lyophilized live attenuated vaccine. The vaccine is based on a wild type yellow fever virus (the Asibi strain) isolated in Ghana in 1927 and attenuated by serial passages, principally in chicken embryo tissue culture.

Indications

All persons aged 9 months or older and living in yellow fever at-risk areas should receive yellow fever vaccine.

Immigrants who are above 9 months of age to endemic regions from non-endemic areas should also be vaccinated against yellow fever. Travellers should be vaccinated at least 10 days before arrival in the at risk area.

Efficacy

Protective levels of neutralizing antibodies (log neutralization index of at least 0.7) are found in 90% of vaccinees within 10 days and in 99% within 30 days. In most cases, protection appears to last for 30 - 35 years or more.

Immunization Schedule

In countries at risk for yellow fever, vaccine is recommended for use in all children aged at least 9 - 12 months of age. Vaccination for yellow fever is also recommended for travellers aged above 9 months who plan to visit areas at risk for yellow fever e.g: Africa and South America.

Dosage & Administration

Yellow fever vaccine is a lyophilized vaccine and is provided with a vaccine specific diluent (sterile water for injection). It should be reconstituted only with the diluent supplied using a sterile syringe and needle.

A single dose of 0.5 ml is recommended for both children more than 9 months of age and adults. Reconstituted vaccine can be administered by either intramuscular or subcutaneous injection, although the subcutaneous route is preferred.

The vaccine can be administered concurrently with other vaccines, but in a separate syringe and at a different site. If not administered concurrently, the vaccine must be separated from other live vaccines (e.g. measles, mumps and rubella – MMR) by at least one month.

Storage

The vaccine and diluent should be stored at +2°C to +8°C. Do not freeze. Protect from light. The vaccine should be used within 1 hour of reconstitution.

Cautions and contraindications

The following conditions are considered as contraindications for the use of yellow fever vaccine.

- ◆ Presence of one of the general contraindications for any vaccine.
- ◆ Children aged under 6 months and is not recommended for those aged 6 - 8 months, except during epidemics when the risk of yellow fever virus transmission may be very high.
- ◆ History of a severe allergy to egg or any other vaccine components.
- ◆ Anyone who has experienced anaphylaxis to a previous dose of yellow fever vaccine.
- ◆ Persons who are severely immunocompromised as a result of congenital disease, HIV infection, advanced leukaemia or lymphoma, serious malignant disease, or treatment with high-dose steroids or in persons who are receiving immunosuppressive therapeutic radiation.
- ◆ Pregnancy (However, pregnant women may be vaccinated during epidemics when the risk of yellow fever virus transmission may be very high).

Adverse Events

Mild systemic reactions such as headache, myalgia, malaise and weakness occur during the first few days after vaccination in 10 - 30% of vaccinees. Severe adverse reactions like Post-vaccine encephalitis is an extremely rare event seen among

Yellow fever certificate

A valid certificate of yellow fever vaccination is required under the International health regulations for entry into most yellow fever-endemic countries or for travel from yellow fever endemic countries to countries at risk for introduction of yellow fever virus. Country requirements are published annually by WHO in *International travel health* (available at www.who.int/ith). The International Certificate of yellow fever vaccination is valid for ten years beginning from the tenth day after primary immunization; a booster dose of yellow fever vaccine is required in every 10 years.

The authorized yellow fever vaccination centre in Sri Lanka for travellers to high-risk areas is held at the office of the Assistant Port Health Officer situated at the Medical Research Institute (MRI), Colombo 08.

Travellers, arriving to Sri Lanka from African or Latin American yellow fever endemic countries must have a valid certificate of vaccination against yellow fever.

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Introduction

Pneumococcal disease, a major cause of morbidity and mortality worldwide, is a bacterial infection caused by the bacterium "*Streptococcus pneumoniae*". The bacterium, also called pneumococcus, was first isolated by Pasteur in 1881 from the saliva of a patient with rabies. It is the leading cause of Invasive Bacterial Disease (bacteremia, meningitis, pneumonia) and acute otitis media in children. Invasive pneumococcal disease (IPD) is most common in the very young, the elderly and certain specific high risk groups, such as individuals with functional or anatomic splenia and congenital or acquired immune deficiency.

Bacteriology

Streptococcus pneumoniae are lancet-shaped, gram-positive, facultative anaerobic organisms. They are typically observed in pairs (diplococci) but may also occur singularly or in short chains. Some pneumococci are encapsulated and their surfaces are composed of complex polysaccharides. Encapsulated organisms are pathogenic for humans and experimental animals, whereas organisms without capsular polysaccharides are not.

The virulence of the bacterium is determined by the polysaccharide capsule. Based on the differences in the capsule, approximately 90 serotypes have been identified. Thirteen serotypes are mainly responsible for most of (approximately 75%) the IPD in the world. Although common serotypes are consistently identified throughout the world, the spectrum of capsular types varies with age, time and geographical regions.

Mode of transmission

Pneumococci are common inhabitants of the respiratory tract and may be isolated from the nasopharynx of 5 to 70% of healthy adults. Rates of asymptomatic carriage vary with age, environment, and the presence of upper respiratory tract infections.

Transmission of *S. pneumoniae* occurs as the result of direct person-to-person contact via respiratory droplets and by autoinoculation in persons carrying the bacteria in their upper respiratory tract.

Clinical Features

Clinical manifestation of the pneumococcal disease has two forms namely non invasive or invasive pneumococcal disease.

Transient nasopharyngeal colonization is the normal outcome of exposure to *S.pneumoniae*. However, bacterial spread to sinuses, middle ear and the upper

respiratory tract may lead to the non invasive pneumococcal disease which will be manifested as sinusitis, otitis media, recurrent bronchitis and non bacteraemic pneumonia.

Dissemination of *S.pneumoniae* into the blood stream and Central Nervous System will lead to IPD. The most common manifestations of IPD are bacteraemia, bacteraemic pneumonia and meningitis. *S.pneumoniae* may cause endocarditis and less commonly infections of joints, bones, peritoneal cavity and fallopian tubes. The incubation period is variable but may be as short as one to three days.

Pneumococcal meningitis leaves nearly 50% of surviving children with life long neurological disabilities including deafness, blindness, spasticity, partial paralysis and seizures. Recurrent episodes may delay development of speech, language and mental functions.

Epidemiology

Global Situation

Pneumococcal disease occurs throughout the year in temperate climates although it is common in autumn and winter months. It affects persons of all ages. However, children under two years of age, elderly, both adults and older children with predisposing factors such as viral upper respiratory tract infections and certain underlying conditions are at high risk of contracting the disease.

Infection with pneumococcus is a major cause of morbidity and mortality worldwide. In 2005, WHO estimated that 1.6 million deaths were caused by this agent annually; this estimate includes the deaths of 0.7–1 million children aged <5 years. Most of these deaths occur in poor countries, and children aged <2 years are disproportionately represented among these deaths.

Situation in Sri Lanka

Though pneumonia and meningitis have been identified as a public health issue, like in many developing countries, there is a scarcity of information on the aetiology of these in Sri Lanka. Pneumococcal surveillance conducted among under five year old children at the Lady Ridgeway Hospital for children (LRH) under the South Asian Pneumococcal Network Alliance (SAPNA) has revealed that 4.9% of septicaemia, 2.2% of clinical meningitis and 1.2% of clinical pneumonia were of the aetiology of *Streptococcus pneumoniae*. IPD was manifested as bacteraemic pneumonia (33%), meningitis (31%), septicaemia (22%) and as others (14%) .

The most common serotypes of *S.pneumoniae* isolated at the LRH were 19F, 23 F, 6B, 14. Sixty two percent of these isolated serotypes at the LRH are covered by vaccine serotypes in the currently available seven valent conjugated Pneumococcal

Pneumococcal vaccine

Pneumococcal disease is a major public health problem all over the world. With increasing sophistication of life-saving medical technology, and increasing life expectancy, pneumococcal disease is becoming more common, and more costly to society. Except for vaccines, no public health measures are likely to have any significant impact on the incidence of this disease. Increasing pneumococcal resistance to essential antimicrobial drugs, and the ease with which resistant strains are spread all over the world, underline the importance of control of IPD through vaccination.

Currently, the two types of pneumococcal vaccines are available in use :

- ◆ Pneumococcal conjugate vaccines
 - 7-valent polysaccharide–protein conjugate vaccine (PCV- 7)
 - 13-valent polysaccharide–protein conjugate vaccine (PCV– 13)
- ◆ Unconjugated polysaccharide vaccine covering 23 serotypes

Polysaccharide pneumococcal vaccines:

Characteristics of the Vaccine

23-valent Pneumococcal polysaccharide vaccine contains 25 µg of purified capsular polysaccharide from each of the 23 capsular types (1, 2, 3, 4, 5, 6B, 7F,8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F).

Indication:

This polysaccharide vaccine is indicated for vaccination of individuals **above 2 years of age** against pneumococcal disease, including high risk adults against Pneumococcal disease caused by serotypes included in the vaccine. These high risk individuals include:

- ◆ healthy, elderly above 65 years of age (in particular institutionalized),
- ◆ those with splenic dysfunctions, asplenia, nephritic syndrome, chronic diseases of the heart, lungs, kidney and liver, diabetes, cerebro spinal fluid leakage, alcoholism, congenital immune deficiency, haematological or general malignancies, recipients of organ or haematopoietic cell transplants,
- ◆ those receiving immune suppressive therapy including systemic corticosteroids ,

Dose & Administration:

A single dose of 0.5 ml is recommended. Revaccination with Polysaccharide Pneumococcal vaccine is generally not recommended.

However, immune compromised children (younger than 10 years of age when first immunized) who have received the polysaccharide vaccine may be revaccinated after three years.

In older children and adults belonging to particular high risk groups exhibiting poor immune response should be considered for revaccination in five years.

Vaccine is administered either intramuscularly or sub cutaneous. Co administration with other routine childhood vaccines is possible. If not given at the same time, there is no need for a minimum interval after any other vaccine.

Contraindications:

Other than general contraindications for any vaccination, the only absolute contraindication is hypersensitivity to any component of the vaccine or anaphylactic reactions to a previous dose.

Adverse reactions:

The most common adverse events :

- ◆ Injection site reactions including transient redness, indurations and the pain.

Rare adverse events :

- ◆ Low grade fever.

Very rare adverse events :

- ◆ cellulites like reactions.

Adverse events following revaccination:

- ◆ Self limited local reactions may occur. Revaccination is not associated with an increase in systemic reactions.
- ◆ Severe reactions requiring medical attention may be common with revaccination within 3 years.
- ◆ Overall injection site reactions are higher in older individuals (>65 years) during revaccination than following primary vaccination.

Storage:

In temperature of +2°C to +8°C . should not be frozen.

Efficacy

In healthy adults, duration of protection is 5 years. Sero type specific antibody levels decline after 5-10 years. Duration of protection may be considerably shorter in some high risk groups. Antibody levels decline more rapidly in elders above 60 years of age.

Use in pregnancy

As the safety of the vaccine has not been confirmed in pregnant women, deferral of immunization is preferred unless the risk of infection is substantial.

Precautions

- ◆ When administering the vaccine to individuals with severely compromised cardio-vascular and/or pulmonary functions
- ◆ Vaccine may not prevent pneumococcal meningitis in individuals with CSF leakage due to congenital lesions, skull fractures or neurological procedures
- ◆ Prophylaxis against pneumococcal disease with antibiotics should not be discontinued after vaccination

Pneumococcal polysaccharide conjugate vaccines

7 valent conjugate vaccine

This vaccine contains pneumococcus serotypes 4, 6B, 9V, 14, 18C, 19F and 23F which are individually conjugated to Diphtheria CRM 197 (non toxic variant of diphtheria toxin isolated from cultures of *Corynebacterium diphtheriae* strain C 7) and adsorbed to aluminum salts to enhance the antibody response.

13 valent conjugate vaccine

This vaccine contains pneumococcus serotypes (4, 6B, 9V, 14, 18C, 19F, 23F) included in the 7 valent conjugate vaccine and additional 6 antigens (1, 3, 5, 6A, 7F, 19A) all conjugated to CRM197 carrier protein.

Selection of either the 7 valent or 13 valent conjugate vaccine may depend on the variability of sero type epidemiology in geographical regions.

Indication for vaccination

- ◆ For active immunization of infants and young children under two years of age against IPD.
- ◆ When possible, for vaccination of children in the age group 2-5 years against IPD
(In many countries, vaccine is licensed to actively immunize children from 6 weeks up to nine years against IPD).

Schedule

In infants under 6 months of age ;

Primary immunization series consists of three doses of 0.5 ml each. The usual age for the first dose is 2 months of age. But it can be given as young as 6 weeks of age. The recommended interval between doses is 4 -8 weeks (at least 4 weeks). Accordingly, two schedules have proven clinical efficacy :

- ◆ 6 weeks, 10 weeks and 14 weeks series,
- ◆ 2 months, 4months and 6 months series.

The fourth dose to improve immune response is recommended in the second year of life (it can be given at least 2 months after the third dose)

For previously unvaccinated older infants and children, age at first dose is 7-11 months:

A total of three doses should be given. Two doses should be given at least 4 weeks apart. Third dose should be given after the first birthday separated from the second dose by at least two months.

Age at first dose is 12-23 months ;

A total of two doses should be given with at least two months apart.

Age at first dose is 2-5 years ;

Only one dose should be given. (Do not administer two doses to make up for a missed dose.) .

WHO recommends a single catch up dose to previously unvaccinated children in the age groups 12-24 months and children who are considered to be at high risk in the age group of 2-5 years when the vaccine is initially introduced into the National immunization programmes.

Infants and children who have begun immunisation with 7 valent conjugate vaccine may switch to 13 valent conjugate vaccine at any point in the schedule.

Young children who are considered completely immunised with 7-valent conjugate vaccine should receive one dose of 0.5 ml of 13 valent conjugate vaccine to elicit immune responses to the 6 additional serotypes. This dose of 13 valent conjugate vaccine should be administered at least 8 weeks after the final dose of 7-valent conjugate vaccine.

Dose & Administration

A dose of 0.5 ml. of vaccine is administered intramuscularly. It may be co administered with other routine childhood vaccines in a separate syringe (should not be mixed with other vaccines in the same syringe.) to a separate injection site.

Never administer if a homogenous white suspension cannot be obtained or the suspension is discoloured when shaken well.

Contraindications

Other than general contraindications for any vaccination, Vaccine is contraindicated in specific instances given below:

- ◆ Hypersensitivity to latex or to any component of the vaccine including Diphtheria toxoid.
- ◆ Allergic reactions or anaphylactoid reaction with previous administration of the vaccine

Having contracted the Pneumococcal disease already is not a contraindication to vaccination as the disease has been caused by one serotype of possible 90 serotypes that can cause the disease. Vaccination will protect against other serotypes capable of causing the disease.

Storage:

At a temperature between +2°C to +8°C . It can be refrigerated but not frozen.

Adverse Events Following Immunization

Vaccine is generally safe and well tolerated. In clinical studies, safety profile of 13 valent conjugate vaccine is similar to the 7 valent conjugate vaccine.

Most common AEFI

- ◆ Injection site reactions (slight soreness and swelling)
- ◆ Transient fever above 38.5° C

Rare AEFI

- ◆ Febrile seizures
- ◆ Hypotonic-Hypo responsive Episodes (HHE)

Very rare AEFI

- ◆ Urticaria, angioneurotic oedema, erythema multiforme and hypersensitivity including anaphylaxis

No increase in incidence or severity of adverse reactions with subsequent doses reported.

Vaccine efficacy;

The vaccine provides protection against serotypes responsible for the majority of IPD in children. Duration of protection is at least 2-3 years following primary

immunization in infancy. It may be shorter in immune compromised individuals.

- ◆ Protection against IPD caused by vaccine serotypes may exceed 90%
- ◆ Protection against Otitis media caused by vaccine serotypes is reported to be 57%.
- ◆ The vaccine reduces radiologically confirmed pneumonia by about 20-25%.

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HUMAN PAPILLOMA VIRUS VACCINE

Introduction

Human Papilloma Viruses (HPVs) are highly species specific and widespread throughout the general population. It is known to produce epithelial tumours of the skin and mucous membranes.

Human Papilloma Virus (HPV) genital infection is a common sexually transmitted infection but asymptomatic and sub clinical. Most sexually active men and women will acquire an HPV infection at some time in their lives. Most HPV infections are transient but persistent genital infection with certain HPV genotypes can lead to the development of anogenital warts, anogenital precancers and cancers.

Diseases caused by HPVs include cancers of the cervix, vagina, vulva, penis and anus; a subset of head and neck cancers; anogenital warts; and recurrent respiratory papillomatosis.

Cervical cancer is the second most common cancer in women. Virtually all cervical cancer cases are linked to genital infection with HPVs, which is the most common viral infection of the reproductive tract.

Virology

HPVs are non-enveloped, double-stranded deoxyribonucleic acid (DNA) viruses in the family of *Papilloma-viridae*. The HPV genome is enclosed in a capsid shell comprising major (L1) and minor (L2) structural proteins.

Epitheliotropic nature of the virus favours cutaneous and mucosal epithelial transmission involving skin and ano-genital tract. The virus enters the basal layer of the epithelium via minor trauma, abrasion and skin to skin contact during sexual intercourse. Some gene products in the HPV virus act as onco proteins and are responsible for inactivation of human tumour suppressor gene products of P53 and PRb which cause uncontrolled cellular proliferation and cytological changes in cervical epithelial cells leading to pre malignant and malignant lesions.

Nearly 40 distinct HPV genotypes are sexually transmitted. But almost 15 genotypes (e.g.16,18,31,33,35,39,45,51,52,56,58,59,68,73 & 82) are designated as “high risk” considering the causal association with cervical cancer. Out of this, genotypes, type 16 and 18 are identified to contribute nearly 70% of all cervical cancers worldwide. Genital infection with carcinogenic or high risk HPV is also implicated with a spectrum of other anogenital conditions described as malignancies and pre malignant conditions in vulva, vagina, anus, and penis.

The category of HPV designated as “low risk” for cervical cancer (geno types 6,11,42,43,44,54,61,72 and 81) is associated with the development of viral warts.

Of which genotypes 6 and 11 are associated with 90% of genital warts and 100% of recurrent respiratory papillomatosis (RRP) cases.

Clinical Features

Human Papilloma Virus infection usually does not cause any symptoms. Condylomata accuminatum (genital warts) may appear within several weeks or months after contact with genital infection of low risk geno types (6 and 11). Majority of the HPV infections are transient infections and persistent HPV genital infection with certain viral genotypes (16 and 18) can lead to the development of anogenital precancers and cancers.

Old age, genital infection with multiple HPV types and infection with high risk or virulent HPV geno-types, poor nutrition and poor immunity are factors associated with persistence of infection.

Genital infection with high-risk HPV genotypes are associated with a spectrum of anogenital diseases, including cervical, vulval, vaginal, penile and anal cancers, and their precursors. In addition, genital HPV genotypes are associated with extragenital diseases, including some squamous cell carcinomas of the head and neck.

Epidemiology

Global Situation

Worldwide differences are observed in genital prevalence rates of HPV infection among women at risk (sexually active >15 years). Cervico-vaginal HPV prevalence rates in the general population ranging from 6 – 46% have been reported from different countries. A pooled analysis by WHO, has described a prevalence of cervico-vaginal infection as 6.6% for the South Asian region. The different prevalence rates are described to be closely related to the corresponding risk of cervical cancer relevant to the region.

In 2005, there were about 500 000 cases of cervical cancer and 260 000 related deaths worldwide. Cervical cancer incidence rates vary from 1–50 per 100 000 females; rates are highest in Latin America and the Caribbean, sub-Saharan Africa, Melanesia, and South-Central and South-East Asia. Most cases of cervical cancer are diagnosed in women aged >40 years.

Countries with well-organized programmes to detect and treat precancerous abnormalities and early stage cervical cancer can prevent up to 80% of these cancers. However, effective screening programmes and follow-up of women with abnormal screening tests have been difficult to implement in low-resource and middle-resource settings. Mortality rates from cervical cancer are therefore much higher in the developing world.

Situation in Sri Lanka

In Sri Lanka a community based HPV prevalence study done in 2008 at the district of Gampaha among 2000 women of 20-59 years revealed an overall cervical HPV prevalence of 3.3% and a prevalence of geno type 16 and 18 as 1.2%. Hospital based cervical cancer data reveals that cervical cancer ranks as the 2nd most frequent cancer among women.

According to the Globocan cancer fact sheet, for year 2008 the estimated age standardized cervical cancer incidence rate for Sri Lanka was 11.8 per 100,000 women and age standardized estimated cervical cancer mortality was 6.9 per 100,000 women.

HPV vaccine

A new hope for prevention of cervical cancer and genital warts have evoked with the development of new vaccines against HPV geno types 16, 18 of high risk and 6,11 of low risk. Currently available vaccines are mainly prophylactic vaccines for HPV-naïve women and not a therapeutic vaccine for those who are already infected.

Vaccines are commercially available for use since 2006. Most of the developed countries have initiated vaccinating adolescents in prevention of HPV genital infection with the ultimate goal of preventing cervical cancer.

WHO recognizes the importance of cervical cancer and other HPV-related diseases as global public health problems and recommends that routine HPV vaccination may be included in the national immunization programmes, provided that: prevention of cervical cancer or other HPV-related diseases, or both, constitutes a public health priority; vaccine introduction is programmatically feasible; sustainable financing can be secured; and the cost effectiveness of vaccination strategies in the country or region is considered.

Characteristics of the HPV vaccine

Currently, 2 HPV vaccines are available internationally. 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 (VLPs). Neither vaccine contains live biological products or viral DNA, so they are non-infectious. HPV vaccines are designed for prophylactic use only; they do not prevent the progress of the existing HPV infection or treat HPV-related diseases. Therefore it is important to immunize the target populations before they get exposed to the HPV infection.

Both vaccines are generally safe, well tolerated with high efficacy and immunogenicity.

Types of vaccine

Two types of prophylactic vaccines namely quadrivalent and bivalent are available.

Quadrivalent vaccine consists of a mixture of four HPV geno type specific L1 virus like particles (VLP) of geno type 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 (Gardasil) 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 hydroxyl phosphate sulphate as an adjuvant.

Bivalent vaccine includes L1 VLPs of HPV geno types 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 3-*o*-desacylated mono phosphoryl lipids (Alum and MPL).

Efficacy

Overall sero conversion observed is 99-100%. Exact duration of immunity after vaccination is yet to be explored but observed of at least 5 years duration. Trial showed efficacy of 100% against HPV type 16/18 related persistent infection and CIN 2/3.

Both vaccines appear to have partial efficacy against infection caused by HPV type 31 and 45, which are genetically related to type 16 and 18.

Limited clinical trial data indicates lower sero conversion and lower vaccine efficacy among immuno compromised as a result of disease condition or medication compared to immunocompetent.

Indication

Vaccines are indicated for use in females 9- 26 years of age for prevention of:

- ◆ cervical precancers and cancers,
- ◆ vulvar vaginal and anal precancers and cancers,
- ◆ ano-genital warts(Condylomata acuminata).

HPV vaccines are designed for prophylactic use only; they do not clear existing HPV infection or treat HPV related diseases.

Both vaccines are intended to be administered to females before the onset of

sexual activity – that is, before first exposure to HPV infection. Most countries that have licensed these vaccines, recommend their use in girls aged 10–14 years.

Dosage & Administration

Both bivalent and quadrivalent vaccines, 0.5 ml (each dose) of vaccine is administered intramuscularly (IM) as 3 doses.

The quadrivalent vaccine is given at baseline and again after 2 months and 6 months.

The bivalent vaccine is given at baseline and again after 1 month and 6 months.

Restarting the 3-dose series is not necessary if the programme has been interrupted, but remaining vaccine doses should be administered as close to the recommended schedule as possible. Currently, the manufacturers do not recommend a booster dose following completion of the primary series.

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

Storage

Storage is recommended at +2°C to +8°C, and should not be frozen. Recommended protection from light.

Cautions and contraindications

The following conditions are considered as contraindications for the use of HPV vaccines.

- ◆ Presence of one of the general contraindications for any vaccine
- ◆ People with known hypersensitivity to any component of the vaccine.
- ◆ History of severe allergic reaction following a preceding dose of HPV vaccine

Adverse Events

Mild and transient local reactions at the site of injection (erythema, pain or swelling) were reported following HPV vaccination and usually resolve within 3-4 days.

Systemic adverse events (fatigue, headache, and myalgia) are other symptoms observed. Severe reactions are not observed with HPV vaccination.

Usage of vaccine in specific circumstances

Use in pregnancy

Vaccines are not recommended to be given during pregnancy even though teratogenicity is not observed in animal studies. Vaccines can be administered to lactating mothers but antigen or antibody excretion in breast milk has not yet been observed.

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Introduction

Rotaviruses are a leading cause of severe diarrhoeal disease and dehydration in infants and young children throughout the world. Most symptomatic episodes of rotavirus diarrhoea occur in young children between the ages of 3 months and 2 years. Rotaviruses affect the vast majority of children worldwide before the age of 3 years, and in most developing countries before the first birthday.

Rotaviruses are estimated to be responsible for approximately 527,000 deaths each year, with more than 85% of these deaths occurring in low-income countries in Africa and Asia. Over two million are hospitalized each year with pronounced dehydration due to rotavirus diarrhoea.

Virology

Rotavirus gastroenteritis is caused by a virus belonging to the *Reoviridae* family. Though there are seven major groups of rotaviruses (A-G), only groups A-C infect humans. The viral genome is surrounded by a structure of three concentric protein shells (*capsides*) namely inner, middle and outer capsides. These capsides possess capsid subunits radiating from the inner to the outer capsid giving particles a distinct *wheel like* morphological appearance. Because of this appearance, the virus has been named “*Rota virus*” (wheel like virus in Latin).

The outer capsid bears two viral proteins namely “*Protease Susceptible Haemagglutinin*” VP7 (**G type**) and glycoprotein VP4 (**P type**). These proteins induced neutralizing antibodies provide protective immunity. In humans, at least 15 different G-types and 11 different P-types have been identified. The combination of G and P types can vary independently. Currently, 5 G-P combinations (G1P[8], G2P[4], G3P[8], G4P[8]) and G9P[8]) cause approximately 90% of all human rotavirus infections in large areas of the world; type G1P[8] being the most prevalent. Many different rotavirus types circulate simultaneously, particularly in developing countries. Furthermore, the prevailing types may differ considerably from one season to the next, even within the same geographical area.

Mode of transmission

Rotaviruses are highly contagious. The main mode of transmission is the faeco-oral route. Rotaviruses are shed in very high concentrations ($>10^{12}$ particles/gram) and for many days in the stools and vomitus of infected individuals. Transmission can occur directly from person to person or indirectly through contaminated fomites. Viruses may survive for days to weeks on environmental surfaces and water. Due to the highly infectious nature and the stability of the virus in the environment, hospital acquired rotavirus infections (*nosocomial*) is also widely reported. Asymptomatic virus excretion occurs in half of the infected children

before the onset of the disease and persists in nearly one third of children during the week after symptoms end. Very rarely, respiratory and animal to human transmission may also occur. The universal occurrence of rotavirus infections show that clean water supplies and good hygiene are unlikely to have a substantial effect on rota virus transmission.

Clinical Features

The incubation period for rotavirus gastroenteritis is approximately 2 days. There is a wide spectrum of clinical features which range from transient and mild forms of diarrhoea to severe gastroenteritis associated with dehydration, electrolyte disturbances, shock and death. The disease is characterized by vomiting and watery diarrhoea for 3-8 days, but may last for up to 2–3 weeks. Fever and abdominal pain occur frequently. Recovery is in general complete.

In infants aged more than 3 months, the first exposure to rotavirus frequently results in gastroenteritis, whereas re-infections are mostly asymptomatic or cause mild disease only.

Epidemiology

Global Situation

The burden of the disease is particularly heavy among children less than 2 years of age with the peak incidence occurring between the ages of 6 and 24 months. The age distribution shifts toward relatively younger age groups in developing countries in comparison with developed countries. Each year rotavirus causes 111 million episodes of gastroenteritis requiring only home care, 25 million clinic visits, 2 million hospitalizations and 352,000-592,000 deaths in children less than five years. By the age of five years, nearly every child will have an episode of rotavirus gastroenteritis.

Sri Lankan Situation:

According to the rotavirus surveillance conducted by the Epidemiology Unit at tertiary care settings (Lady Ridgway Hospital) in Sri Lanka, the proportion of rotavirus diarrhoea among all-cause diarrhoeal admissions in children under five years of age was 23.9%. The reported mortality associated with rotavirus infections in Sri Lanka is very low. Although rotavirus diarrhoea patients were hospitalized throughout the year, the observed rotavirus peak was from January to March and was consistent with the pattern of increase in all cause diarrhoeal admissions. The most common G types detected in Sri Lanka were G3(32%) and G9(30%) while the predominant P type was P8 (58%).

Rotavirus vaccine

In 1999, rotavirus vaccine, RotaShield™, licensed in the United States, was withdrawn from the market after less than one year because of its association with intussusception.

Two new live, oral, attenuated rotavirus vaccines were licensed in 2006: the monovalent human rotavirus vaccine (Rotarix™) and the pentavalent bovine-human, reassortant vaccine (RotaTeq™).

Characteristics of the rotavirus vaccine

Both Monovalent Human Rotavirus Vaccine (MVHRV) (**Rotarix™**) and Pentavalent Bovine Human Reassortant Vaccines (PVBHRV) (**Rotateq™**) currently in the market are WHO pre qualified vaccines. Manufacturing efforts in these vaccines have focused on the development of live, attenuated rotavirus vaccine strains of human and/or animal origin that will replicate in the gut. The goal of these vaccines is to mimic the immune response to the natural infection in which the first infection protects about 88% of children against the severe disease while the second infection protects virtually all children against severe disease and most are protected against any rotavirus disease. The immune response is highly dependent on the administered dose of the vaccine and on a variety of host factors, including maternal antibodies, interfering bacterial and viral agents, and possibly malnutrition.

Monovalent Human Rotavirus Vaccine

MVHRV (Rotarix™) is a live, attenuated, oral vaccine developed from the strain, G1P [8] obtained from a case of infantile gastroenteritis. The immune protection is based on the ability of the selected rotavirus strain (G1P [8]) to induce immunity to the same specific serotype (*homotypic immunity*) and to a high proportion of additional serotypes (*heterotypic immunity*).

Pentavalent bovine- human reassortant vaccine (PVBHRV)

PVBHRV (Rotateq™) is a live, oral viral vaccine consisting of five human-bovine reassortant rotaviruses bearing the human outer surface rotavirus proteins (VP7) of the most prevalent rotavirus serotypes G1,G2,G3 and G4. Four reassortant rotaviruses express one of the outer capsid proteins (G1, G2, G3 or G4) from the human rotavirus parent strain and the attachment protein (VP4 protein of the serotype P7 [5]) from the bovine rotavirus strain. The fifth reassortant virus expresses the VP4 attachment protein, P1A [8] from the human rotavirus parent strain and the outer capsid protein of serotype G6 from the bovine rotavirus parent strain. Such a composition is likely to provide the broadest degree of

protection (*homotypic immunity*) against rotavirus gastroenteritis caused by most prevalent rotavirus serotypes.

Efficacy

In general, vaccine provides about 90–100% protection against severe rotavirus disease and about 74–85% protection against rotavirus diarrhoea of any severity, depending on the schedule of administration and the population evaluated.

The duration of immunity from rotavirus vaccine is not known. Efficacy through two rotavirus seasons has been studied for both vaccines. In general efficacy is lower in the second season than in the first.

Indication

To protect against moderate to severe rotavirus gastroenteritis and prevent resultant hospitalizations and deaths.

Dosage & Administration

MVHRV

MVHRV (**Rotarix™**) is a lyophilized vaccine which needs to be reconstituted with a liquid diluent. It is administered orally and should not be injected under any circumstance. The infant's liquid consumption including breast milk need not be restricted before or after the administration of the vaccine.

Dosage and schedule - Two doses within the first 6 months of life.

1st dose - at the age of 6 -12 weeks (but not later than 12 weeks)

2nd dose- should be completed by 16 weeks and not later than 24 weeks.

Minimal interval between doses - at least 4 weeks

Booster doses - not recommended.

Co administration with other vaccines:

Co administration with monovalent or combined Haemophilus influenzae type b (Hib), hepatitis B, inactivated polio vaccine (IPV), Oral polio Vaccine (OPV), Diphtheria-tetanus-acellular pertussis/whole cell Pertussis vaccine will not affect the immune response and the safety profiles of these vaccines.

PVBHRV

PVBHRV (Rotateq™) is a ready to use liquid vaccine administered orally.

Dosage:

Oral solution of 2 ml contains a minimum of $2.0-2.8 \times 10^6$ Infectious Units (IU) per reassortant dose depending on the serotype and not greater than 116×10^6 IU per aggregate dose

Schedule:

A 3 dose series (at ages 2, 4, 6 months) to infants between the ages of 6-32 weeks.

1st dose: at 2 months (should be administered between 6-12 weeks of age)

2nd dose: at 4 months (administered at an interval of 4-10 weeks following the 1st dose)

3rd dose: at 6 months (should not be given after 32 weeks of age)

Booster doses: not recommended

Interchangeability of the two vaccines is not known and hence not recommended.

Storage

MVHRV

MVHRV (**Rotarix**™) vaccine and the diluent should be stored at $+2^{\circ}\text{C}$ to $+8^{\circ}\text{C}$ in its original package. However the diluent can be stored at an ambient temperature not exceeding 37°C . Vaccine should not be frozen and should be protected from exposure to sunlight. After reconstitution, preferably, the vaccine should be stored in $+2^{\circ}\text{C}$ to $+8^{\circ}\text{C}$. If not used within 24 hours, it should be discarded.

PVBHRV

PVBHRV (**Rotateq**™) vaccine should be stored at $+2^{\circ}\text{C}$ to $+8^{\circ}\text{C}$. Once removed from the refrigerator, vaccine should be administered as soon as possible. It has to be protected from sunlight.

Cautions and contraindications

MVHRV and PVBHRV should not be administered to subjects with:

- ◆ any of the general contraindications for any vaccine,
- ◆ a history of hypersensitivity to any component of the vaccine including latex rubber (contained in oral application)
- ◆ occurrence of symptoms of hypersensitivity to a previous dose of rotavirus vaccine.,

- ◆ any history of chronic gastrointestinal disease including any uncorrected congenital malformations of the gastro intestinal tract,
- ◆ history of intussusception.

No safety or efficacy data are available for the administration of MVHRV and PVBHRV to infants who are potentially immuno-compromised (e.g. HIV/AIDS, on immunosuppressive therapy including high steroid doses, malignancies etc)

For these children, a physician has to assess the potential benefits of rotavirus vaccination on individual basis. Caution is advised when considering whether to administer the vaccine to individuals with immuno-deficient contacts.

Adverse Events

A variety of mild adverse reactions were reported during the 7 or 8 days after rotavirus vaccination in the clinical trials, including vomiting, diarrhoea, irritability, and fever.

According to the WHO's Global Advisory Committee on Vaccine Safety (GACVS), post-marketing surveillance data have indicated the possibility of an increased risk of intussusception shortly after the first dose of rota virus vaccine in some populations . However, in these studies, it has been demonstrated that the benefits of vaccination in preventing gastroenteritis greatly outweigh the potential risk of vaccine associated intussusceptions. GACVS currently collects additional data in this regard and will continue to review them as they become available.

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Introduction

Cholera is an acute intestinal infection caused by the bacterium called *Vibrio cholerae*. Throughout the history, devastating outbreaks of cholera have resulted in millions of cases and hundreds of thousands of deaths. Young children living in endemic areas are most affected by the disease, but any age group may suffer.

Altogether 7 cholera pandemics have been reported. The latest one, which is still ongoing, started in Indonesia in 1961, reached the African continent in the 1970s and South America in 1991. As the pandemic is still ongoing, the number of countries affected continues to increase. The disease is now considered to be endemic in many countries.

Bacteriology

Vibrio cholerae is a motile, curved Gram-negative bacillus and differences in the O antigens have led to the description of more than 200 serogroups, only two of which have been found to cause cholera. Cholera epidemics are caused by enterotoxin producing *V. cholerae* of serogroups O1 and O139 ('Bengal' strain).

V. cholerae O1 causes the majority of outbreaks worldwide. Serogroup O139, first identified in Bangladesh in 1992, possesses the same virulence factors as O1, and creates a similar clinical picture. Currently, the presence of O139 has been detected only in South-East and East Asia.

V. cholerae is a non-invasive organism that colonizes the lining epithelium of the gut after penetrating the mucous layer. It affects the small intestine through its secreted cholera toxin. As a result, water is drawn from the intravascular and extracellular spaces of the body, and rapidly lost into the gut lumen.

Mode of transmission

Humans are the only known natural host for *V. cholerae*, and the disease is spread by faecal contamination of water and food. Thus cholera endemicity and epidemics are closely linked to poor sanitation.

Clinical Features

Most persons infected with *V. cholerae* do not become ill, although the bacterium is present in their faeces for 7-14 days. When illness does occur, about 80-90% of episodes are of mild or moderate severity and are difficult to distinguish clinically from other types of acute diarrhoea. Less than 20% of infected persons develop typical cholera with profuse, watery diarrhoea. It is associated with rapid dehydration and occasionally hypovolemic shock, which may be life-threatening.

Case fatality ranges from 50% or more without treatment to less than 1% among adequately treated patients. The incubation period varies from few hours to five days, usually 2 to 3 days.

Resistance to first-line antibiotics (tetracycline and doxycycline), as well as resistance to multiple drugs, occurs frequently and has been associated with more severe illness and higher rates of secondary infection.

Epidemiology

Global Situation

Globally, the number of deaths from cholera rose from 4948 in 2009 to 7543 in 2010, an increase of 52% with an overall CFR of 2.38%. Of the 32 countries that reported deaths from cholera, 20 were on the African continent: these countries accounted for 3397 deaths and 45% of the global total. In the Americas, Haiti reported 3990 deaths, accounting for 53% of the global total.

In year 2010, a total of 13 819 cases were reported from 14 countries in Asia, which accounted for 4% of the global total.

Situation in Sri Lanka

Cholera is a notifiable disease in Sri Lanka. Last confirmed cholera case in Sri Lanka was reported to the epidemiology unit in 2003. Last outbreak of cholera reported in Sri Lanka, was confirmed as due to sero group O139.

Cholera vaccine

Several oral cholera vaccines have been developed and proved to be safe, immunogenic and effective. Only 2 of these are currently being marketed, only one of which has been prequalified by WHO. Both available vaccines are whole-cell killed vaccines, one with a recombinant B subunit, the other without it.

WHO has never recommended the use of the parenteral cholera vaccine because of its limited protective efficacy (45% for 3 months) and its unsuitability for public health purposes. The previously licensed oral, live, attenuated single-dose vaccine too (CVD 103-HgR) is no longer being produced.

Characteristics of the cholera vaccines

There are two types of inactivated oral cholera vaccines currently available.

◆ Monovalent oral cholera vaccine (WC/rBS)

This monovalent oral cholera vaccine consisting of killed whole-cell *V. cholerae* O1 in combination with a recombinant B-subunit of cholera toxin (WC/rBS) has been marketed since the early 1990s.

Each 3.0 ml liquid vaccine dose vial contains heat and formalin inactivated Inaba, Ogawa, classic and El Tor strains of *V. cholerae* O1, 2.5×10^{10} vibrios of each, combined with 1.0 mg rCTB.

◆ Bivalent oral cholera vaccines

Bivalent oral cholera vaccines Shanchol and mORCVAX are based on serogroups O1 and O139. Unlike monovalent vaccine, these vaccines do not contain the bacterial toxin B subunit and will therefore not protect against ETEC.O139.

Indications

- ◆ Vaccination against cholera is indicated for protection of the population at risk as, preschool-aged children, school-aged children, pregnant women and immunocompromized individuals during outbreaks.
- ◆ For immunization of travellers to highly endemic areas. Recommended to take 2 weeks before departure.

WHO recommends that immunization with currently available cholera vaccines be used in conjunction with the usually recommended control measures in areas where cholera is endemic as well as in areas at risk of outbreaks. Vaccination should not be the mainstay of control measures.

Efficacy

◆ Monovalent oral cholera vaccine (WC/rBS)

Inactivated oral cholera vaccine is well tolerated and confers high level (85 -90%) protection for 6 months after the second immunization in all vaccinees aged > 2 years. The level of protection is still about 50% 3 years after immunization in vaccinees who were aged > 5 years at the time of vaccination.

◆ Bivalent oral cholera vaccines

Bivalent oral cholera vaccines are considered safe and immunogenic against both O1 and O139 infection. This bivalent oral cholera vaccines provide relatively less short-term protection than monovalent vaccine against classical cholera,

than monovalent vaccines against classical cholera, but at 2 years and 3 years of follow up the protection was equal to, or better than with monovalent vaccines.

Immunization Schedule

◆ Monovalent oral cholera vaccine (WC/rBS)

Primary immunization consists of 2 oral doses given >7 days apart (but <6 weeks apart) for adults and children aged ≥ 6 years.

Children aged 2–5 years should receive 3 doses >7 days apart (but <6 weeks apart).

If the interval between the primary immunization doses is delayed for >6 weeks, primary immunization should be restarted.

Protection may be expected about 1 week after the last scheduled dose.

Provided there is continued risk of *V. cholerae* infection, one booster dose is recommended by the manufacturer after 2 years for adults and children aged ≥ 6 years. If the interval between the primary series and booster immunization is >2 years, primary immunization must be repeated.

For children aged 2–5 years one booster dose is recommended every 6 months, and if the interval between primary immunization and the booster is >6 months, primary immunization must be repeated.

◆ Bivalent oral cholera vaccines

According to the manufacturer, bivalent cholera vaccines should be administered orally in 2 liquid doses 14 days apart for individuals aged ≥ 1 year. A booster dose is recommended after 2 years.

Dosage & Administration

◆ Monovalent oral cholera vaccine (WC/rBS)

The vaccine is intended for oral use. Vaccine is provided in 3 ml single-dose vials together with the bicarbonate buffer (effervescent granules in sachets). Vaccine and buffer are mixed in 150 ml of water for persons aged >5 years and in 75 ml of water for children aged 2–5 years. Food and drink should be avoided 1 hour before and 1 hour after vaccination.

The inactivated oral cholera vaccine can be given at the same time as other travel vaccines.

◆ Bivalent oral cholera vaccines

The vaccine is intended for oral use. 1.5 ml single dose vials available.

Storage

The recommended storage temperature for both vaccines is +2^o C to +8 ^o C . Do not freeze. Protect from light.

Cautions and contraindications

Except for possible hypersensitivity to any of the components, no contraindications are known for oral cholera vaccines. It is well tolerated by HIV-positive and immunocompromised individuals.

This vaccine has been proved to be safe even in pregnancy and during breastfeeding.

Postpone administration during either an acute febrile illness or acute gastrointestinal illness with persistent diarrhoea or vomiting, until recovered.

Adverse Events

Occasional mild gastrointestinal disturbances were reported following oral cholera vaccination.

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INTRODUCTION

Anaphylaxis is an acute, life-threatening systemic reaction with varied mechanisms, clinical presentations, and severity that results from the sudden systemic release of mediators from mast cells and basophiles. Anaphylaxis following vaccination is rare but recognition of signs and symptoms of anaphylaxis (Box 1) is crucial for prompt treatment and to prevent confusion with more frequent acute events that may occur after vaccination such as vasovagal collapse, and sudden onset rash without anaphylaxis.

A precise definition of anaphylaxis is not important for the emergency treatment of an anaphylactic reaction. However, experts in the field of allergy and immunology have developed a definition of anaphylaxis as one of three clinical scenarios as described in Box 1:

Box 1: Definition of anaphylaxis

- 1) **Acute onset of a reaction (minutes to hours) with involvement of the skin, mucosal tissue or both and at least one of the following:**
 - a) **Respiratory compromise: airway and breathing (refer Box 2)**
 - b) **Reduced blood pressure (BP) or symptoms of end-organ dysfunction (refer Box 2)**
- 2) **Two or more of the following that occur rapidly after exposure to a likely allergen for that patient**
 - a) **Involvement of the skin/mucosal tissue (refer Box 2)**
 - b) **Respiratory compromise,**
 - c) **Reduced blood pressure or associated symptoms**
 - d) **Persistent gastrointestinal symptoms (refer Box2)**
- 3) **Reduced age specific blood pressure after exposure to a known allergen for that patient (minutes to several hours) or greater than 30% fall from baseline or less than 90mmHg for adults.**

Note: age specific BP is defined in Box 5

The limited available data from Sri Lanka indicates that in 86% of documented vaccine /drug induced anaphylaxis cases fitted into category three where hypotension was the only manifestation.

Box 2: Diagnostic features of anaphylaxis

<p>Respiratory</p>	<p>Airway</p> <ul style="list-style-type: none"> ◆ Throat and tongue swelling (pharyngeal/laryngeal oedema) - the patient has difficulty in breathing and swallowing and feels that the throat is closing up. ◆ Hoarse voice. ◆ Stridor <p>Breathing</p> <ul style="list-style-type: none"> ◆ Bilateral wheeze (bronchospasm) ◆ Respiratory distress—2 or more of the following: <ul style="list-style-type: none"> • Tachypnoea • Increased use of accessory respiratory muscles • Recession • Cyanosis ◆ Grunting ◆ Respiratory arrest
<p>Cardiovascular</p>	<ul style="list-style-type: none"> ◆ Feeling faint or collapse with measured hypotension ◆ Clinical diagnosis of uncompensated shock, indicated by combination of at least 3 of the following: <ul style="list-style-type: none"> • Tachycardia • Capillary refill time >3 s • Reduced central pulse volume • Decreased level of consciousness or loss of consciousness ◆ Cardiac arrest <p>Note</p> <ul style="list-style-type: none"> ◆ Anaphylaxis can cause myocardial ischaemia and electrocardiograph (ECG) changes even in individuals with normal coronary arteries. ◆ Bradycardia (a slow pulse) is usually a late feature, ◆ often preceding cardiac arrest.
<p>Disability (because of decreased brain perfusion)</p>	<ul style="list-style-type: none"> ◆ Confusion ◆ Agitation ◆ Headache, ◆ Feeling of impending doom, ◆ Loss of consciousness

Dermatologic or mucosal	<ul style="list-style-type: none"> ◆ Tingling of lips ◆ Generalized urticaria or generalized erythema ◆ Angioedema, localized or generalized (angioedema is similar to urticaria but involves swelling of deeper tissues, most commonly in the eyelids and lips, and sometimes in the mouth and throat). ◆ Generalized itching of skin especially hands, forehead and eyes in children <p>Note Although skin changes can be worrying or distressing for patients and those treating them, skin changes alone without life-threatening airway, breathing or circulation problems do not signify an anaphylactic reaction.</p>
Gastrointestinal	<ul style="list-style-type: none"> ◆ Diarrhoea ◆ Colicky abdominal pain ◆ Incontinence
Ocular	<ul style="list-style-type: none"> ◆ Pruritus ◆ Conjunctival injection ◆ Lacrimation

The limited available data from Sri Lanka indicates that in 86% of documented vaccine /drug induced anaphylaxis cases fitted into category three where hypotension was the only manifestation. Increased vascular permeability, a characteristic feature of anaphylaxis, allows transfer of as much as 35% of the intravascular fluid into the extravascular space within 10 minutes. As a result, hemodynamic collapse may occur rapidly with little or no cutaneous or respiratory manifestations. Respiratory compromise and cardiovascular collapse are of greatest concern, since they are the most frequent causes of fatalities.

Anaphylaxis often produces signs and symptoms within minutes of exposure to the vaccine but some reactions may develop later (e.g., greater than 30 minutes even up to 12 hours after exposure). Late phase or “biphasic” reactions, which occur 1 to 72 hours (most within 10 hours) after the initial attack, have also been reported. Protracted, severe anaphylaxis may last up to 32 hours despite aggressive treatment.

During vaccination older children and adults may faint (Box 3) or have a panic attack due to fear or pain mimicking anaphylaxis. Fainting attacks in the younger child may be due to anaphylaxis.

Box 3 Differences between a fainting, panic attack and anaphylaxis

Clinical features	Fainting	Anaphylaxis
Timing	Before, during or few minutes after injection	A short time, up to few hours
Skin	Generalized pallor, cold clammy skin	Itching, generalised erythema, urticaria, swelling of lips, face, tingling around lips
Respiratory system	Normal breathing Shallow breathing	Tachypnoea, difficulty in breathing, wheezing, stridor, hoarseness, cyanosis, recession of intercostal spaces
Cardiovascular	Bradycardia, weak pulse, carotid pulse felt, hypotension may occur - reversed by supine position	Tachycardia, weak pulse, carotid pulse may be weak, hypotension - not reversed by supine position
GIT	Vomiting	Vomiting, diarrhoea, abdominal cramps
CNS	Faintishness, light headedness relieved by supine posture	Anxiety and distress, loss of consciousness not relieved by supine posture
Panic attack - No hypotension, pallor, wheeze, or urticarial rash or swelling. May have flushing or blotchy skin		

ANAPHYLAXIS

Initial Management of Anaphylaxis at Field Immunization Clinic Settings

Guidelines for initial management of Anaphylaxis at field immunization clinic settings have been provided in Director General of Health Services General Circular No: 01-20/2001 dated 23rd August 2011.

According to instructions in the above circular, a person who develops anaphylaxis at field setting should be treated immediately to prevent life-threatening reactions and death. Hence it is very important to recognize the condition immediately in field clinic settings by the vaccinator. If anaphylaxis is suspected, administer the age appropriate first dose of adrenalin 1:1000 immediately and transfer the patient as soon as possible to the closest hospital for further management. To implement the contents of the guidelines in the above circular, immunization programme managers at all levels are requested to adhere to the following.

- a) All field health staff including Medical Officers, Nursing Officers, Public Health Inspectors and Public Health Midwives should be competent to recognize anaphylaxis early and administer the **first dose of adrenaline**, by thorough training of all field health staff as per national guidelines.
- b) Make available required quantities of Adrenaline 1: 1000 vials and 1 CC disposable syringes with 23 Gauge one inch needles at all field immunization clinics.
- c) Health staff in charge of field clinics should be authorized to hire a vehicle in such an emergency to transport the patient to the nearest hospital. The vehicle hire could be reimbursed to the field health staff subsequently.

Treatment of anaphylaxis at Field Immunization Clinic Settings

The vaccine recipient with suspected anaphylaxis should never be left alone. Obtain help from those who are around and arrange transport of the patient to the nearest hospital immediately with the clear airway. If the vaccine recipient is conscious he/she should be kept supine with the feet raised higher than the head. If the patient is unconscious he/she should be kept in the left lateral position.

Adrenaline is the most important and effective drug in the treatment of anaphylaxis. Complications and death could be prevented by giving this drug as soon as possible.

Adrenaline 1:1000 solution should be given intra muscular (IM). **It should NEVER be given subcutaneous (SC) or intravenous (IV).**

It should be given IM into the middle 1/3 of the anterolateral aspect of the thigh.

Box 4 : Dosage of adrenaline 1:1000

Age	Dose of Adrenaline (1:1000)
12 months to 06 years	0.15 mg (0.1ml)
06 years to 12 years	0.2 mg (0.2ml)
12 years and over	0.3 mg (0.3ml)

Anaphylaxis among infants (less than 1 year of age) is very rare and **infants should not be given adrenaline in field clinic settings.**

Dose of adrenaline should not be changed even if the child is obese. A one inch 23 Gauge needle could be used to inject adrenaline to make sure it is delivered into the muscle. Before injecting the piston of the syringe should be drawn back to make sure that there is NO blood flows into the syringe and hence the needle is not in a vein.

Immediately after administration of adrenaline patient should be transferred to the closest hospital.

Management of Anaphylaxis at MOH offices and other medical settings

Adrenaline (epinephrine) and oxygen are the most important life saving therapeutic agents administered in anaphylaxis. If there is any doubt regarding diagnosis, it is still advisable to administer adrenaline intramuscular (IM). The more rapidly anaphylaxis develops; the more likely the reaction is to be severe and potentially life-threatening. Any delay before the administration of adrenaline or a history of asthma are significant risk factors for anaphylactic death. Death due to anaphylaxis usually occurs as a result of respiratory obstruction or cardiovascular collapse, or both.

A life threatening reaction requires immediate treatment; do not refer the patient during the acute phase without resuscitation. Stocking and maintaining supplies for the treatment of anaphylaxis with regular written documentation of supplies and expiration dates and ready availability of the items in BOX 7 are bare essentials. Regular anaphylaxis practice drills are strongly recommended.

1. Initial management

- ◆ **Reassure patient /parents/guardian.** The patient is usually anxious and can experience a “sense of impending doom”. Do not leave the patient alone.

- ◆ Use the **ABCD (Airway, Breathing, Circulation, Disability)** approach (Box 2) to recognize clinical problems. It will also help in the differential diagnoses. Rapid assessment of systolic blood pressure is critical to guide treatment. As auscultation may be difficult or misleading, measure systolic blood pressure by simple **palpation**.

Box 5: Assessment of blood pressure and pulse rate in anaphylaxis

Age	Systolic blood pressure (mm Hg) For diagnosis of hypotension	Pulse rate / minute (count the patient's pulse rate for 1 minute)
Term neonates (0 - 28 d)	<60	>140
Infants (1 - 3 months)	<70	>140
Infants (3 - 12 months)	<70	>130
1 - 2 years	< [70 mmHg + (2 x age)]	>130
>2 to 10 years		>80
> 10 yrs	Sudden drop below 90	>75
Adults		> 100

Adults: Treatment should aim for a systolic blood pressure above 100 mm Hg. In older adults, who are normally hypertensive, a blood pressure of 100 mm Hg may constitute severe hypotension and a higher target may be required to maintain neurological function. **Child:** A child cuff should be used for measurement of BP.

2. Patient positioning

- ◆ Place the patient in a recumbent position and elevate the lower extremities, as tolerated symptomatically.

- ◆ If the patient feels faint, do not sit or stand them up (can cause cardiac arrest).
- ◆ Patients with airway and breathing problems may prefer to sit up as this will make breathing easier.
- ◆ Patients who are breathing and unconscious should be placed on their left lateral position.
- ◆ Pregnant patients should lie on their left side to prevent caval compression
- ◆ Patients who are hypotensive should be kept in the recumbent position until stabilized, and asymptomatic.

3. Pharmacologic treatment

If anaphylaxis is suspected management in order of importance is: adrenaline, oxygen, intravenous fluids, nebulized therapy, vasopressors, antihistamines, corticosteroids, and other agents. The basic principles of treatment are the same for children and adults. Any differences will be highlighted.

◆ Adrenaline (epinephrine)

Give **adrenaline 1: 1000 dilution via the intramuscular (IM) route** at the first suspicion of anaphylaxis (Box 6). Do not delay treatment as it is the most effective, safe and life saving treatment and works best when given early after the onset of the reaction. Adrenaline has a rapid onset of action after IM administration and a greater margin of safety. The time to highest blood concentration (C_{max}), when studied in asymptomatic subjects, is shorter when injection is given intramuscularly in the vastus lateralis muscle (lateral thigh) than when it is administered either subcutaneously or intramuscularly in the deltoid muscle of the arm.

Reassess the pulse rate and BP regularly: every 5 min, (essential to monitor the response to adrenaline) aiming for the patient's normal BP. If this is unknown, in adults aim for a systolic BP greater than 100 mmHg, for children aim at BP higher than the values given in Box 5. Repeat IM adrenaline every 5 minutes as determined by BP and bronchospasm. If the clinician deems it appropriate, more frequent injections of adrenaline can be given.

Do not routinely administer adrenaline via the intravenous (IV) route because of the risk of potentially lethal arrhythmias. The IV route should only be considered in profoundly hypotensive patients who have not responded to several IM doses of adrenaline or patients in cardio/respiratory arrest. **If it has to be given IV, administer as an infusion (Box 9). Intravenous bolus injections of adrenaline are not recommended because of the risk of potentially lethal arrhythmias.** Continuous hemodynamic monitoring is

recommended if adrenaline is given via the IV route even as an infusion. However, use of IV adrenaline should not be precluded in a scenario where such monitoring is not available, if the specialist deems its administration is essential **after several IM adrenaline injections**. In these special circumstances, monitoring by available means (e.g. every-minute blood pressure and pulse measurements and ECG monitoring, if available) should be considered.

Child: Hypotension and the pulse rate can be difficult to assess in small children and this fact should be taken into consideration before giving escalating intravenous doses of adrenaline in error. Absorption of adrenaline from the IM site is good in children. **IV route should be considered** mainly for persistent shock or cardio/respiratory arrest (Box 9).

- ◆ **Establish airway**
- ◆ **Give high flow oxygen**, (6 - 8 L/minute) and airway/ventilation support if needed. **Measure oxygen saturation with pulse oximeter.**
- ◆ **Give sodium chloride** 0.9% solution infusion via a wide bore access (i.e. 14G or 16G in adults). One to 2 L of normal saline may need to be administered to adults at a rate of 5-10 mL/kg in the first 5 minutes. If hypotension continues repeat normal saline boluses: sodium chloride 0.9% solution 10 to 20 mL/kg IV bolus, up to total of 50 ml/kg over the first 30 minutes. Children should receive up to 30mL/kg in the first hour. Adults receiving colloid solution should receive 500 mL rapidly, followed by slow infusion.
- ◆ **Monitor the patient for adverse effects of adrenaline**
Adrenaline is a drug with a narrow toxic/therapeutic ratio. Transient pharmacologic effects such as pallor, tremor, anxiety, palpitations, headache, and dizziness are common after the correct therapeutic dose. If the patient develops a **persisting or worsening cough associated with pulmonary oedema the administration of adrenaline should be stopped and the patient assessed as it is an important sign of adrenaline overdose and toxicity.**

4. After initial resuscitation with adrenaline and oxygen (Box 8)

- ◆ **Antihistamines:** These agents have a much slower onset of action than adrenaline and **should never be used alone** in the treatment of anaphylaxis. A combination of chlorphenamine and ranitidine is superior to chlorphenamine alone. The doses are given in Box 10. **Do not use two H1 receptor blockers such as chlorphenamine and promethazine as they will only potentiate the hypotension.** Intravenous promethazine should not be used as it is highly caustic to the intima of blood vessels, and serious tissue

reactions including thrombosis, nerve damage, tissue necrosis and gangrene have been reported. Deep IM is the preferred route of administration if chlorphenamine is not available.

- ◆ **Steroids:** They are of secondary value in the initial management of anaphylactic shock because the onset of action is delayed for several hours. Steroids are given to prevent further deterioration in severely affected patients and continued for 24 to 48 hours according to clinical response. **Administer only ONE of the corticosteroids** slowly intravenously or intramuscularly, taking care to avoid inducing further hypotension.
 - **Hydrocortisone:** Box 10
 - **Oral prednisolone 1mg/kg up to 50mg maybe sufficient for milder attacks.**
 - **Dexamethasone IV 0.1-0.4 mg/kg every 6 hours.**

5. Other therapeutic options:

- ◆ **Persistent bronchospasm:**

Continuous salbutamol to be nebulized (3 - 5 mg by nebuliser, driven by oxygen at least 8 L/minute), or continuous actuations of metered dose 2 -6 puffs salbutamol into ventilation circuit if intubated.

- ◆ **Severe bradycardia**

If present consider atropine 0.02 mg/kg IV

- ◆ **If refractory to volume replacement and adrenaline infusion**

Dopamine (400mg in 500ml of 5% dextrose) administered at 2-20 mg/kg/min and titrated to maintain systolic blood pressure greater than 90 mm Hg, should be administered if adrenaline and volume expansion fail to alleviate hypotension. Dopamine will usually increase blood pressure while maintaining or enhancing blood flow to the renal and splanchnic circulation. It has been shown that a dose of dopamine > 10 mg/kg/min is usually required to produce peripheral vasoconstriction which would be required to maintain systolic blood pressure. In cases of intractable hypotension vasopressin 10 to 40 units IV maybe considered

Child: Dopamine 2-20 mg/kg/min. Calculate as $6 \times$ body weight (in kg) = # mg diluted to total 100 mL saline; then 1 mL/h delivers 1 mg/kg/min

- ◆ **For continuing respiratory deterioration**

Further treatment with bronchodilators including intravenous salbutamol, inhaled ipratropium, intravenous aminophylline or intravenous magnesium sulphate can be tried.

◆ **For upper airway obstruction,**

There is anecdotal evidence that nebulised adrenaline may provide some relief. **Adrenaline 5 mg in 5 ml (= 5 ml of 1:1000 solution) via nebuliser**

◆ **Preparation for surgical airway.**

If anaesthesia is required for intubation use fentanyl 1 –10 mcg per kg IV . Do not use thiopentone or propofol. Suxamethonium 1 – 2mg/kg may be used to facilitate intubation, provided the doctor is sure of being able to intubate.

◆ Tranexamic acid has been used to treat anaphylactic episodes associated with disseminated intravascular coagulation.

6. Treatment of cardiopulmonary arrest occurring during anaphylaxis

◆ Start cardiopulmonary resuscitation and advanced cardiac life support measures.

◆ Rapid escalation to high-dose IV adrenaline may be tried for adults. A common sequence is 1 to 3mg (1: 10, 000 dilution) IV slowly administered over 3 to 5 minutes, 3 to 5mg (1: 10, 000 dilution) IV over 3minutes, and then 4 – 10mcg / minutes infusion.

Child: 0.01mg/kg (0.1mg/kg of a 1in 10,000 solution up to 10mcg/minute rate of infusion) repeated every 3 to 5 minutes for ongoing arrest.

Higher subsequent dosages (0.1 – 0.2mg/kg; 0.1ml/kg of a 1:1000 solution) maybe considered for unresponsive asystole or pulseless electrical activity (PEA).

◆ Rapid volume expansion.

◆ Atropine if asystole or PEA is present.

◆ Prolonged resuscitation is encouraged if needed since a successful outcome is more likely in anaphylaxis.

7. Patients taking beta adrenergic antagonists

They are more likely to experience severe anaphylactic reactions; these features may include severe hypertension and cerebral haemorrhage, to unresolving hypotension, bradycardia and bronchospasm. If adrenaline is ineffective in these patients, both glucagon administration and isotonic volume expansion might be necessary;

Glucagon: 1- 5 mg (child 20 – 30 mcg/min, maximum dose 1 mg) IV over 5 minutes followed by infusion 5-15 mcg/min titrated to clinical response.

Protection of the airway is important, as glucagons may cause emesis and aspiration in drowsy patients. The left lateral position may be sufficient in most patients.

8. 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 clinical area with facilities for treating life-threatening ABC problems. They should then be reviewed by a senior clinician 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 warned of the possibility of an early recurrence of symptoms and in some circumstances should be kept under observation for up to 24 hours. This caution is particularly applicable to:

- ◆ severe reactions with slow onset,
- ◆ reactions in individuals with a history of severe asthma or with a severe asthmatic component in the current episode,
- ◆ reactions with the possibility of continuing absorption of allergen such as vaccines.
- ◆ patients with a previous history of biphasic reactions,
- ◆ patients presenting in the evening or at night, or those who may not be able to respond to any deterioration,
- ◆ patients in areas where access to emergency care could be delayed .

Biphasic reactions occur in 1 – 23% of patients, up to 72 hours; however, in most instances, it is within 10 hours. There are no clinical criteria to predict the risk of a biphasic reaction, and the observation period should be individualized.

9. Laboratory studies

Serum tryptase can sometimes be helpful in establishing the diagnosis of anaphylaxis. Serum tryptase levels peak one to one and half hours after the onset of anaphylaxis and can persist for as long as five hours after the onset of symptoms. The best time to measure serum tryptase is between one to two hours but not longer than six hours after the onset of symptoms.

10. Reporting

It is mandatory that all vaccine associated cases of anaphylaxis be reported to the Epidemiology Unit. As global experience indicates that the AEFI reports often do not contain sufficient details to allow for the classification of adverse events. Make sure that the features described in Box 1 are included in the report.

Box 6 : Key points

Anaphylaxis is likely when all of the following 3 criteria are met following vaccination:

- ◆ Sudden onset and rapid progression of symptoms.
- ◆ Life-threatening Airway and/or Breathing and/or Circulation problems.
- ◆ Skin and/or mucosal changes (flushing, urticaria, angioedema).

But

- ◆ The limited documented data from Sri Lanka indicates that in the majority hypotension was the only manifestation and urticaria was uncommon
- ◆ Skin or mucosal changes alone are not signs of an anaphylactic reaction
- ◆ There can also be gastrointestinal symptoms (e.g. vomiting, abdominal pain, incontinence)

Remember

- ◆ Adrenaline is the most important drug for the treatment of an anaphylactic reaction
 - intramuscular (IM) route is the best for most persons
 - The best site for IM injection is the anterolateral aspect of the middle third of the thigh

IV adrenaline: there is a much greater risk of causing harmful side effects by inappropriate dosage or misdiagnosis of anaphylaxis. Leave it for those experienced in the use and titration of vasopressors in their normal clinical practice (e.g., anaesthetists, consultant physicians, intensive care doctors),

Box 7 : Pharmaceuticals and other items needed for the emergency tray

- ◆ Clearly labelled adrenaline vials
- ◆ Hydrocortisone vials
- ◆ Chlorphenamine vials
- ◆ 0.9% Sodium chloride intravenous solution
- ◆ Water for injection
- ◆ Syringes
- ◆ Airways (small, medium, and large)
- ◆ ET tubes
- ◆ Oxygen
- ◆ Sphygmomanometer (adult and child cuffs)
- ◆ Stethoscope
- ◆ Alcohol swabs
- ◆ Tourniquet
- ◆ Tongue depressors
- ◆ Flashlight with extra batteries

Box 8 : Adrenaline in the INITIAL management of acute anaphylaxis

Drug, site and route of administration	Frequency of administration	Dose (adult)	Dose (child) *
Adrenaline (epinephrine) 1:1000, IM to the midpoint of the anterolateral aspect of the middle third of the thigh immediately, then every	5–15 min as needed until there is resolution of the anaphylaxis or signs of hyperadrenalism: palpitation, tremor, uncomfortable apprehension and anxiety occur.	0.3 – 0.5 mL (300 - 500 mcg) 0.3 ml for smaller adults (30 - <50kg) 0.5 mL (>50kg)	0.01 mL/kg (up to 0.3 mL) <u>According to age</u> ♦ < 1 yr 0.05 mL ♦ 1– 3 yrs (10-15 kg) 0.10 - 0.15 mL ♦ 3- 5 yrs (15-20 kg) 0.15 - 0.20 ml ♦ 5 - 7 yrs (20-25 kg) 0.20 - 0.25 mL ♦ 7 – 12 yrs (25-30kg) 0.25 - 0.30 mL
	Persisting or worsening cough associated with pulmonary oedema is an important sign of adrenaline overdose and toxicity.		

Note:

- ♦ The needle used for injection needs to be sufficiently long to ensure that adrenaline is injected into the muscle.
- ♦ A 25mm needle is best and is suitable for all ages.
- ♦ In pre-term or very small infants a 16mm needle is suitable for IM injection.
- ♦ In some adults, a longer length needle (38 mm) may be needed.
- ♦ Give IM injections with the needle at a 90° angle to the skin.
- ♦ The skin should be stretched, not bunched.

BOX 9: Intravenous infusion of adrenaline for life-threatening anaphylaxis-induced hypotension who have failed to respond to intravenous volume replacement and several IM doses of adrenaline.

Adrenaline strength: **1: 100, 000 (0.1mg [1ml of a 1in 1,000]** in 100 mL sodium chloride 0.9% (10 mcg /mL)

Continuous monitoring (ECG, SpO₂, BP every 3 to 5 minutes) is important

- ◆ **1:100,000 solution of adrenaline (0.1 mg [1 mL of 1:1000] in 100 mL saline) intravenously by infusion pump at an initial rate of 30-100 mL/hr (5-15 mg/min), titrated up or down depending on clinical response or adrenaline side effects (toxicity).**
- ◆ **If an infusion pump is not available and life threatening situation is considered likely without intervention: Give through a dedicated intravenous line:**
- ◆ **adrenaline 1mL of 1 : 1,000 in 100 mL sodium chloride 0.9% IV, at approximately 100 mL/hour, which is 1 drop every 2 seconds for most standard drip sets**

OR

If you only have a 500 mL bag of infusion fluid_use:

- ◆ **adrenaline 1 mL of 1 : 1,000 in 500 mL sodium chloride 0.9% IV, at approximately 500 mL/ hour, which is 2 drops per second for most standard drip sets**

OR

If you only have a 1000 mL bag of infusion fluid_use:

- ◆ **adrenaline 1 mL of 1 : 1,000 in 1000 mL sodium chloride 0.9% IV, at approximately 1000 mL/hour, which is 5 drops per second for most standard drip sets.**

Children with cardiac arrest or profound hypotension: adrenaline 0.1 mcg/kg/min (0.1 mL/kg of a 1:10,000 solution up to 10mcg/min; maximum dose, 0.3 mg) OR calculate as $(0.6 \times \text{body weight (in kg)}) = \# \text{ of mg diluted to total 100 mL saline; rate of 1 mL/h delivers 0.1 mcg/kg/min}$

- ◆ 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. Reduce the infusion rate (if toxicity is severe, stop the infusion briefly before recommencing at a lower rate). 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.

Box 10: Pharmacologic treatment once patient's condition is stabilized with adrenaline and fluids

Drug and route of administration	Frequency of administration	Dose (adult)	Dose (child)
Chlorphenamine IM or slow IV over 1 min once patient's condition is stabilized with adrenaline and fluids.	Continue orally every 4 hours for 48 hours.	10mg	◆ 1 month - 1 year 250 mcg/kg (maximum 2.5 mg) 1- 6 years: 2.5 mg

<p>Child: IM/Slow IV over 1 minute (If small dose is required, dilute with 0.9% sodium chloride)</p> <p>For doses of promethazine refer text. Do not administer both to the same patient</p>			
<p>Hydrocortisone Once patient's condition is stabilized with adrenaline and fluids, administer IM or IV slowly</p>	Repeat every 8 h as needed	Adults and >12 years: 200 mg follow up with prednisolone 50 mg orally	<p>◆ Child: 2 mg/kg every 6 hours</p> <p>◆ <6 months: 25 mg</p> <p>◆ >6 months – 6 years: 50 mg</p>
<p>For doses of other corticosteroids refer text</p>		50 mg orally daily for 4 days	<p>◆ >6 – 12 years: 100 mg</p> <p>follow up with prednisolone 1 mg/kg up to a maximum of 50 mg orally daily for 4 days</p>
<p>Ranitidine Once patient's condition is stabilized with adrenaline and fluids if given IV: dilute in 5% dextrose to a total volume of 20 ml and give over 5 minutes. Repeat every 4 – 6 hours</p>	Repeat every 8 hrs as needed	Adult 1mg/kg IV	1mg/kg IV (maximum 50mg) or 2mg/kg orally

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ADVERSE EVENTS FOLLOWING IMMUNIZATION

Introduction

As vaccine-preventable infectious diseases continue to decline, people have become increasingly concerned about the risks associated with vaccines. Furthermore, technological advances and continuously increased knowledge about vaccines have led to investigations focused on the safety of existing vaccines which have sometimes created a climate of concern.

No biological or pharmaceutical product has yet been developed which is 100% safe and 100% effective. Vaccine manufacturers develop products with the highest safety and efficacy possible, given current technology.

Vaccines used in the national immunization programmes are safe and effective. But no vaccine is perfectly safe and adverse reactions can occur following immunization. In addition to the vaccines themselves, the process of immunization is a potential source of adverse events.

An adverse event following immunization (AEFI) refers to *any* adverse event that occurs following vaccination. Reported adverse events can either be true adverse events, i.e. really as a result of the vaccine or the immunization process, or incidental events that are not due to the vaccine or immunization process but are temporally, associated with immunization.

Adverse Event Following Immunization (AEFI) is defined as,

Any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine.

Careful investigation of all serious AEFI is critical. The ultimate goal of an investigation is to determine the likelihood of a causal link between a reported AEFI and the vaccine(s) administered or the vaccination process, or alternately to find another cause. The findings of the investigation should lead to appropriate action,

where needed, to prevent further AEFI. Effective and efficient management of AEFI is an essential component of all immunization programmes in order to ensure continued public confidence in vaccination, and ultimately to ensure high immunization coverage and thereby reduction in disease and death due to vaccine-preventable diseases.

Classification of adverse events following immunization

Table 1 Cause –specific categorization of adverse events following immunization (CIOMS/WHO, 2012)

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

Note: “**Immunization**” as used in these definitions means the usage of a vaccine for the purpose of immunizing individuals. “Usage” includes all processes that occur after a vaccine product has left the manufacturing/ packaging site, i.e. handling, prescribing and administration of the vaccine.

In 2012, Council for International Organizations of Medical Sciences (CIOMS) / WHO revised previous classification concerning particularly cause-specific categorization of AEFIs and a new categorization has been introduced. Basically AEFIs are classified into five categories.

1. Vaccine reaction

A vaccine reaction is an individual's response to the inherent properties of the vaccine, even when the vaccine has been prepared, handled and administered correctly.

The new cause-specific categorization is important for decision making on a vaccine product, as it clearly differentiates the two types of possible vaccine reactions;

(i) **Vaccine product related reaction;** a vaccine reaction is an individual's response to the inherent properties of the vaccine, even when the vaccine has been prepared, handled and administered correctly and

(ii) **Vaccine quality defect-related reaction;** which is important to note that vaccine quality defect during the manufacturing process has an impact on individual's response and thereby increased risk of adverse vaccine reactions. (*Details are available on the "Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance, 2012"*)

Vaccine reactions may be classified into common, minor reactions and rare, more serious reactions. 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.

A reaction is usually one of the three types:

Local: The most common type of reaction usually shows as pain, swelling, or redness at the site of injection. These reactions occur within a few hours of injection, disappear in a short period of time, and pose little danger. Parents should still report any local reaction that persists to a health worker. This type of reaction is most commonly caused by inactivated vaccines.

Systemic: Generalized reactions may include fever, malaise, muscle pain, headache, or loss of appetite. They are similar to a very mild form of the disease but pose no serious health risk. These reactions occur more commonly after injections with live attenuated vaccines than with inactivated vaccines.

Allergic: These are the most serious and most rare reactions. They are caused by the body's reaction to a particular component in a vaccine. Severe allergic reactions can be life threatening, which is why good screening prior to vaccination is important. Health workers who give vaccinations should know the signs of allergic reactions and be prepared to take immediate action.

Further, vaccine reactions may be classified into common, minor reactions and rare, more serious reactions. 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. A serious adverse event or reaction is any untoward medical occurrence following any dose of vaccine that:

- ◆ results in death,
- ◆ requires hospitalization or prolonged hospital stay,
- ◆ results in persistent or significant disability/incapacity ,
- ◆ is life-threatening.

Most of the rare and more serious vaccine reactions [e.g seizures, thrombocytopaenia, hypotonic hyporesponsive episodes (HHE), persistent inconsolable screaming] do not lead to long term problems. Anaphylaxis, while potentially fatal, is treatable without any long term effects.

Local and systemic reactions, or side effects, or minor or serious adverse reactions are described for each vaccine in relevant Chapters.

2. Immunization error- related reactions

“Immunization” as used here means the usage of a vaccine for the purpose of immunizing individuals. “Usage” includes all processes that occur after a vaccine product has left the manufacturing/ packaging site, i.e. handling, prescribing and administration of the vaccine.

Table 2: Immunization Errors (Programme Errors) leading Adverse Events Following Immunization

Immunization error	Adverse Event
<p>Non sterile injections:</p> <ul style="list-style-type: none"> ◆ Contaminated vaccine or diluents. ◆ Reuse of reconstituted vaccine at subsequent session. 	<p>Infection [e.g. local suppuration at injection site, abscess, cellulites, systemic infection, sepsis, toxic shock syndrome, transmission of blood borne virus (HIV, Hepatitis B or Hepatitis C)].</p>
<p>Vaccine prepared incorrectly:</p> <ul style="list-style-type: none"> ◆ Vaccine reconstituted with incorrect diluents ◆ Drugs substituted for vaccine or diluents 	<p>Local reaction or abscess due to inadequate shaking of vaccine vial..</p> <p>Effect of drugs (e.g. Insulin, muscle relaxant) ,used by mistake , instead of vaccine or diluents.</p>
<p>Vaccine injected at wrong site:/ route</p> <ul style="list-style-type: none"> ◆ Use of subcutaneous route instead of intradermal for BCG ◆ Use of subcutaneous route instead of intramuscular for toxoid vaccines (DPT, DT, TT) ◆ Injecting into buttocks 	<p>Local reaction or injection site abscess.</p> <p>Sciatic nerve damage.</p> <p>Ineffective vaccination .</p>
<p>Vaccine transported or stored incorrectly</p>	<p>Increased local reaction from frozen vaccine and ineffective vaccination.</p> <p>Ineffective vaccination</p>
<p>Contraindications ignored</p>	<p>Avoidable serious vaccine reaction</p>

Earlier, this AEFI type was categorised as “Programme errors” (*Syn; Programmatic error or Programme operation errors*) result from errors and mistakes in vaccine preparation, handling, or administration.

Immunization errors are preventable and can controlled. They reduce the overall benefit of the immunization programme. Identification and correction of these errors are of great importance.

An immunization error may lead to a cluster of events associated with immunization. These clusters are usually associated with a particular provider or health facility or even a single vial of vaccine that has been inappropriately prepared or contaminated. Immunization errors can also affect a stock of vaccines (e.g. by freezing vaccines during transport leading to an increase in local reactions in recipients).

3. Coincidental events

The adverse event occurs after a vaccine has been administered but is not caused by the vaccine or its administration (only a temporal association). A coincidental event is one that would have occurred even if the person had not been vaccinated. In other words a chance temporal association (i.e. event happens *after* immunization) is falsely considered to be *caused* by immunization. These purely temporal associations are inevitable given the large number of vaccine doses administered, especially in a mass campaign.

With increasing awareness of AEFI surveillance, even health staff may report more coincidental events. Also, with introduction of new vaccines, there is a trend of reporting many AEFI including coincidental events. It is crucial to differentiate these reported coincidental events from potential ‘signals’.

4. Immunization anxiety-related reactions

Anxiety-related reactions can arise due to fear or pain of the **injection** rather than the vaccine. Individuals and groups can react in anticipation to and as a result of an injection of any kind. This reaction is unrelated to the content of the vaccine.

Some of these reactions are listed below.

- ◆ Fainting – relatively common, usually affects children aged over five years.
- ◆ Hyperventilation – as a result of anxiety about the immunization leads to specific symptoms such as lightheadedness, dizziness, tingling around the mouth and in the hands.
- ◆ Vomiting – a common anxiety symptom in younger children.
- ◆ Breath-holding – in younger children which can end in a brief period of unconsciousness during which breathing resumes.
- ◆ Mass hysteria – in a group situation.

5. Unknown

The adverse event cannot be directly related to the vaccine, its administration, or any other identifiable cause. In other words, cause of the events cannot be determined.

Common, mild vaccine reaction rates

The purpose of a vaccine is to induce immunity by causing the recipient's immune system to react to the vaccine. It is not surprising that vaccination results in certain mild side-effects. Local reaction, fever and systemic symptoms can result as part of the normal immune response. In addition, some of the vaccine's components (e.g. aluminium adjuvant, antibiotics or preservatives) can lead to reactions. A successful vaccine reduces these reactions to a minimum while inducing maximum immunity.

Local reactions including pain, swelling and/or redness at the injection site can be expected in about 10% of vaccinees, except for those injected with DTP (whole cell), or tetanus boosters, where up to half can be affected. BCG causes a specific local reaction that starts as a papule (lump) two or more weeks after immunization. It then becomes ulcerated and heals after several months, leaving a scar.

Systemic reactions

Fever and other systemic symptoms (e.g., irritability, malaise, loss of appetite) can result as part of the immune response. In addition, some of the vaccine's components (e.g. aluminium adjuvant, stabilizers or preservatives) can lead to reactions. Local reactions and fever should be anticipated in nearly 10% of vaccines, except in the case of DPT which produce fever in nearly 50% of those vaccinated. Fever and minor local and systemic reactions usually occur within a day or two of immunization except for those produced by measles, mumps and rubella vaccines which may occur 6 to 12 days after immunization. However, these reactions continue only for one or two days.

For measles/MMR and OPV the systemic reactions arise from vaccine virus infection. Measles vaccine causes fever, rash and/or conjunctivitis, and affects 5-15% of vaccinees. It is very mild compared to 'wild' measles, but for severely immunocompromised individuals, it can be severe, even fatal. Vaccine reactions for mumps (swollen parotid gland) and rubella (joint pains and enlarged lymph nodes) affect less than 1% of children. Rubella vaccine causes symptoms more often in adults, with 15% suffering from joint pains. Systemic reactions from OPV affect less than 1% of vaccinees with diarrhoea, headache and/or muscle pain.

Table 3 : Frequency of common minor vaccine reactions

Vaccine	Local adverse events (pain, swelling, redness) ¹	Fever (> 38°C)	Irritability, malaise and systemicsymptoms
BCG ¹	Common 90%-95%	-	-
Hepatitis B	Adults up to 30% Children up to 5%	1 – 6%	-
Hib	5%-15%	2%-10%	
Pertussis (DTP – whole cell) ²	up to 50%	up to 50%	up to 55%
Measles/MR/ MMR	~10%	5%-15%	5% (Rash)
Tetanus/DT/aTd	~ 10% ³	~ 10%	~ 25%
OPV	None	Less than 1%	Less than 1% ⁴

¹Local reactogenicity varies from one vaccine product to another, depending on the strain and the number of viable vaccine. ² With whole cell pertussis vaccine. Acellular pertussis vaccine rates are lower. ³ Rate of local reactions likely to increase with booster doses, up to 50 -85%. ⁴ Diarrhoea, Headache and/or muscle pains

Rare, more severe reaction rates

Table 4 details the rare vaccine reactions; case definitions are in Annex X. Most of the rare and more serious vaccine reactions (e.g. seizures, thrombocytopenia, hypotonic hyporesponsive episodes, persistent inconsolable screaming) do not lead to long-term problems. Anaphylaxis, while potentially fatal, is treatable without leaving any long-term effects. Although encephalopathy is included as a rare reaction to measles or DTP vaccine, it is not certain whether these vaccines in

fact cause encephalopathy (brain damage). Although other serious events have been reported following immunization, it is likely that those other events are coincidental, rather than true reactions.

Table 4 : Rare, serious vaccine reactions, onset interval and rates

Vaccine	Reaction	Onset Interval	Number of doses per reaction
BCG	Suppurative lymphadenitis	2-6 months	1 in 1-10, 000
	BCG osteitis	1-12 months	1 in 3000 to 1 in 100 million
	Disseminated BCG infection	1-12 months	~ 1 in million
Hib	None known		
Hepatitis B	Anaphylaxis	0 – 1 hour	1 in 6-900 000
Measles/MMR/MR*	Febrile seizures	6-12 days	1 in 3000
	Thrombocytopenia (low platelets)	15-35 days	1 in 30 000
	Anaphylactic (severe allergic reaction)	0-2 hours	~1 in 100, 000
	Anaphylaxis	0-1 hour	~1 in 1, 000, 000
	Encephalopathy	6-12 days	< 1 in 1, 000, 000
Oral poliomyelitis	Vaccine associated paralytic poliomyelitis	4-30 days	1 in 2.4 - 3 million
Tetanus Toxoid	Brachial neuritis	2-28 days	0.5-1 in 100, 000
	Anaphylaxis	0-1 hour	1 in 100, 000 to 1 in 2, 500, 000
Tetanus diphtheria	None extra to tetanus reactions		

Vaccine	Reaction	Onset Interval	Number of doses per reaction
Pertussis (DTP-whole cell)	Persistent (>3 hours) inconsolable screaming	0-24 hours	1 in 15 to 1 in 1000
	Seizures	0-2 days	1 in 1750 to 1 in 12 500
	Hypotonic, hypo responsive episode	0-48 hours	1 in 1000-33 000
	Anaphylaxis	0-1 hour	1 in 50 000
	Encephalopathy	0-2 days	0-1 in 1 million

Notes

- Reactions (except anaphylaxis) do not occur if already immune (~90% of those receiving a second dose)

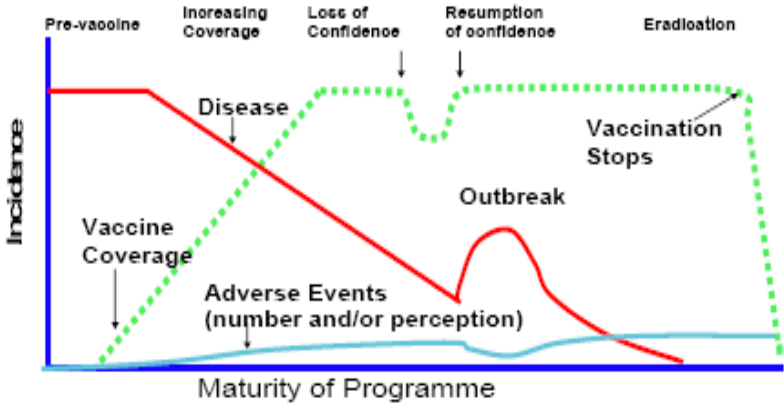
- Seizures mostly febrile and risk depends on age, with much lower risk in infants under the age of 4 months. Children over six years are unlikely to have febrile seizures

VAPP Risk higher for first dose (1 in 750,000 compared to 1 in 5.1 million for subsequent doses), and for adults and immunocompromised.

The importance of detecting AEFI

At a time when the immunization coverage has reached very high levels and the incidence of vaccine preventable diseases are on the decline, it is important to take steps to keep the AEFI to a minimum. When an apparently healthy child receives a vaccine when the disease that it prevents is unheard of and subsequently develops an AEFI, the credibility of the immunization programme may be questioned by the general-public. If the AEFI was due to a programme error it is almost always preventable. Therefore, it is imperative that AEFI are detected, reported, whenever necessary investigated and steps taken to prevent the future occurrence of such AEFI. This is important in order to maintain the confidence of the community in the immunization programme.

Evolution of Immunisation Programmes



Adapted from: Grabstein JD, Hospital Pharmacy 1996

Figure 7: Evolution of immunization programmes

Reporting of AEFI's Following Immunization:

Screening of all children for AEFI for previous immunization was made mandatory since 2001 and a column to that effect was added to the immunization record of the CHDR as given in Figure 8. In this format the last column is specifically meant to record any adverse events that occurred following the previous immunization. For example, when an infant presents for the first dose of pentavalent/OPV vaccines, the health worker screening the child prior to the immunization must specifically inquire about any adverse events following BCG vaccination. If no AEFI are reported an “O” must be marked in the relevant column against the vaccine in question.

Figure 9: Clinic immunization register

Serial No(1)	Registration Number of the CHDR	Date Of Report/Detection (3) (DD/MM/YY)	Adverse Event (4)	Related Vaccine (5)		Batch No/Lot No (6)	Date of Immunization (7) (DD/MM/YY)	Name of Child (8)	Address (9)	Remarks(10)
				Antigen	Dose					

In addition to the above, some AEFI may be detected at medical institutions when affected patients seek treatment for the AEFI. The OPD of these institutions, paediatric wards, and surgical wards are potential places to detect AEFI. Therefore it is important that medical and paramedical personnel are made aware of AEFI. When a patient is detected as having an AEFI at a Medical Institution, the case should be entered in the ward/institution AEFI register and be notified in the prescribed format (AEFI Form 1) to the MOH of the area where the patient resides.

Figure 10: MOH Office AEFI Register

Serial No(1)	Date of Entry (dd/mm/yy)	Adverse Event (3) (PL Specify)	Related Vaccine (4)		Batch No/Lot No (5)	Date of Immunization (6) (DD/MM/YY)	Place of Immunization (7)	Source of Notification (8) (CAR/MI/GP/OS)	Name of Child (9)	Address (10)	Date of Investigation (11) (DD/MM/YY)	Remarks(12)
			Antigen	Dose								

Figure 11: AEFI Form 1

AEFI Form 1

Notification form for Adverse Effects Following Immunization (AEFI)

Name of the Patient:

Name & address of the parent & Guardian :

MOH area :

Adverse Events	BCG	OPV	Penta/DPT (Mark "P" for Penta or "T" for DTP in the row below against the dose)				HepB B	Measles	MMR	MR	DT	aTd	JE		Influenza			
			1	2	3	4							1	2				
1. Local Adverse Events requiring investigation																		
a. Injection site abscess																		
b. BCG lymphadenitis																		
c. Severe local reactions																		
2. Central Nervous System Adverse Events requiring investigation																		
a. Vaccine associated paralysis poliomyelitis																		
b. Guillen-Barre syndrome																		
c. Encephalopathy																		
d. Encephalitis																		
e. Seizures																		
		Febrie																
		Afebrile																
3. Other Adverse Events requiring investigation																		
a. Death																		
b. Anaphylactic shock																		
c. Persistent screaming																		
d. HHE																		
e. Osteitis/Osteomyelitis																		
f. Toxic shock syndrome																		
4. Adverse Events not requiring investigation																		
a. Allergic reaction																		
b. Arthralgia																		
c. High fever (>39 C° / 102°F)																		
5. Others (specify)																		
a.																		
b.																		
c.																		

Instructions:

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

Possible explanation/s for the above AEFI?

Age : Sex : Male Female Outcome: Recovered Still in the hospital Death

Bed head ticket number: Ward : Institution:.....

Date of the notification: / / Designation:

Name & Signature of the notifying officer/General Practitioner:

Medical practitioners who attend any patient suffering from adverse effects following immunization shall notify in this form to the Medical Officer of the area of the patients residence)

At the monthly conference of the MOH office, these notifications must be crosschecked with the AEFI registers of each field clinic (which the PHM in charge of the field clinic should bring with her to every monthly conference) to



Avoid duplicating of cases and entered in the MOH office AEFI Register. The AEFI reported during the month must be consolidated in the prescribed format (“Monthly Surveillance Report on AEFI” by MOH - AEFI Form 2) in triplicate and a copy each must be sent to the Epidemiological Unit and the Regional Epidemiologist of the District. The AEFI that are required to be reported and their case definitions are given on the reverse side of the AEFI notification form and the monthly AEFI return.

Figure 12 : AEFI Form 2

AEFI Form 2

Monthly surveillance report on Adverse Effects Following Immunization (AEFI)

RDHS Division : MOH area : Month : Year: 201...

Adverse Events	BCG	OPV	Penta/DPT (Mark 'P' for Penta or 'T' for DTP in the row below against the dose)				Hep B	Measles	MMR	MR	DT	a/d	JE		Influenza			
			1	2	3	4							1	2				
1. Local Adverse Events requiring investigation																		
a. Injection site abscess																		
b. BCG lymphadenitis																		
c. Severe local reactions																		
2. Central Nervous System Adverse Events requiring investigation																		
a. Vaccine associated paralysis poliomyelitis																		
b. Guillen-Barre syndrome																		
c. Encephalopathy																		
d. Encephalitis																		
e. Seizures																		
3. Other Adverse Events requiring investigation																		
a. Death																		
b. Anaphylactic shock																		
c. Persistent screaming																		
d. HHE																		
e. Osteitis/Osteomyelitis																		
f. Toxic shock syndrome																		
4. Adverse Events not requiring investigation																		
a. Allergic reaction																		
b. Arthralgia																		
c. High fever (>39 C° / 102°F)																		
5. Others (specify)																		
a.																		
b.																		
c.																		

Instructions:

1. 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.
2. Please correctly identify and enumerate the adverse events by correct antigen.
3. If a child/person has developed more than one adverse event, indicate only the most serious/important event here. (in this report under each adverse event reported will represent single individual).
4. AEFI Form 3 (Case Investigation Form) should send to the Epidemiology Unit for each AEFI reported under categories 1-3 in this report. It is recommended to send all investigated forms with this monthly surveillance report.
5. If any important observation is noted, please provide your comment (eg. Adverse events under category 4 here, , if any clustering is observed)

Comments:

.....

.....

Name : Designation:

Signature : Date :

(This form should be completed by MOH/DDHS and sent to the Epidemiologist before the 10th of the following month with a copy to the Regional Epidemiologist of the area)

Table 5: List of AEFI to be reported and Investigated

1. Local adverse events

- a. Injection site abscess
- b. BCG lymphadenitis
- c. Severe local reactions

2. Central Nervous System Adverse events

- a Vaccine derived paralytic poliomyelitis (within 4-30 days of OPV)
- b. Guillen_Barre syndrome (within 30 days after immunizations)
- c. Encephalopathy (within 72 hours after vaccination)
- d. Encephalitis (within 1- 30 days after vaccination)
- e. Meningitis (within 1-30 days after immunization)
- f. Seizures

3. Other adverse events requiring investigation

- a. Anaphylactic shock
- b. Persistent (more than 3 hours) inconsolable screaming
- c. Hypotonic Hyporesponsive Episode
- d. Osteitis/Osteomyelitis (within 8-16 months of vaccination)
- e. Toxic shock syndrome (within few hours of immunization)
- d. Hypotonic hypo responsive episodes

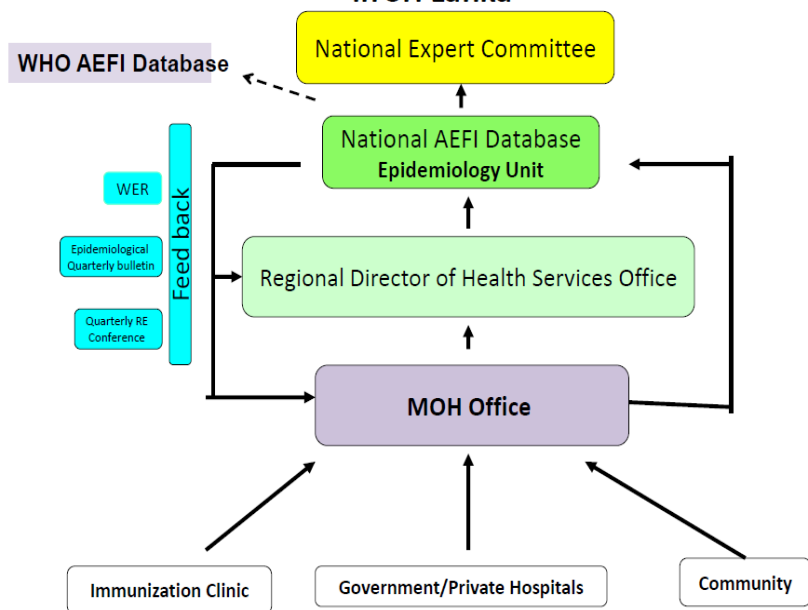
4. Other adverse events not requiring investigation

- a. Allergic reaction
- b. Arthralgia
- c. High fever (>39°C)
- d. Nodule at the injection site

5. Others (Specify)

Figure 13: AEFI surveillance system in Sri Lanka

Adverse Events Following Immunization Surveillance System in Sri Lanka



Investigation of Adverse events Following Immunization

Once AEFI are detected and reported, they should be investigated by the respective MOH of the area concerned. When the cause of an AEFI is identified following an investigation it is necessary to take measures to prevent its recurrence.

Prevention of vaccine reactions

Vaccines are very rarely contraindicated. However, it is important to check for contraindications to avoid serious reactions. For example, vaccines are contraindicated if there is serious allergy to the vaccine or its components. Live vaccines should not be given to immune-deficient children. It is also important to check the expiry date and status of cold chain of every vaccine before administering it to a child.

Prevention of Immunization error-related reactions

The most common immunization error related reaction (programme error) is an infection as a result of non-sterile injection. The infection can manifest as a local reaction (e.g. suppuration, abscess), systemic effect (e.g. sepsis or toxic shock syndrome), or blood-borne virus infection (e.g. HIV, hepatitis B or hepatitis C). To avoid immunization error-related reactions (programme errors):

- ◆ vaccines must only be reconstituted with the diluent supplied by the manufacturer for the index vaccine,
- ◆ reconstituted vaccines must be discarded at the end of each immunization session / or within 6 hours of reconstitution and never retained,
- ◆ all precautions should be taken to avoid contamination of open vials during transport and handling,
- ◆ no other drugs or substances should be stored in a vaccine refrigerator,
- ◆ immunization must be carried out by an adequately trained personal and whole process must be closely supervised to ensure proper procedures are being followed,
- ◆ penta/DPT/DT vials **should not** be frozen during storage or especially during transport from the MOH office to the field immunization clinics,
- ◆ penta/DPT/DT vials should be well shaken before administering to the recipient,
- ◆ the correct dose and the correct route for each vaccine must be adhered to (e.g. Penta/DPT/DT should be given deep IM and not subcutaneously),
- ◆ Sterile procedures must be followed during administration.

Table 5: Case definitions and treatment for AEFI

Adverse event	Case definition	Treatment	Vaccines
Acute flaccid paralysis (vaccine associated paralytic poliomyelitis)	Acute onset of flaccid paralysis within 4 to 30 days of receipt of oral poliovirus vaccine (OPV), or within 4 to 75 days after contact with a vaccine recipient and neurological deficits remaining 60 days after onset, or death.	No specific treatment available, supportive care	OPV
Anaphylactoid reaction (acute hypersensitivity reaction)	Exaggerated acute allergic reaction, occurring within 2 hours after immunization, characterized by one or more of the following: <ul style="list-style-type: none"> • Wheezing and shortness of breath due to bronchospasm • Laryngospasm/laryngeal oedema • One or more skin manifestations, e.g. hives, facial oedema, or generalized oedema. <p>Less severe allergic reactions do not need to be reported.</p>	Self-limiting, anti-histamines may be helpful.	All
	Severe immediate (within 1 hour) allergic reaction leading to circulatory failure with or without bronchospasm and/or laryngospasm/laryngeal oedema	Adrenaline injection (Given in latter part of this chapter)	All
Arthralgia	Joint pain usually including the small peripheral joints. Persistent if lasting longer than 10 days, transient : if lasting up to 10 days.	Self-limiting; analgesics	Rubella, MMR
Brachial neuritis	Dysfunction of nerves supplying the arm/shoulder without other involvement of nervous system. A deep steady, often severe aching pain in the shoulder and upper arm followed within days by weakness and wasting in arm/shoulder muscles. Sensory loss may be present, but is less prominent. May present on the same or the opposite	Symptomatic only; analgesics	Tetanus

	side to the injection and sometimes affects both arms.		
	Widespread infection occurring within 1 to 12 months after BCG vaccination and confirmed by isolation of Mycobacterium bovis BCG strain. Usually in immunocompromised individuals.	Should be treated with anti-tuberculous regimens including isoniazid and rifampicin.	BCG
Encephalopathy	Acute onset of major illness characterized by any two of the following three conditions: Seizures Severe alteration in level of consciousness lasting for one day or more Distinct change in behaviour lasting one day or more. Needs to occur within 48 hours of DTP vaccine or from 7 to 12 days after measles or MMR vaccine, to be related to immunization	No specific treatment available; supportive care	Measles, Pertussis Measles, Pertussis
Fever	The fever can be classified (based on rectal temperature) as mild (38 to 38.9 °C), high (39 to 40.4 °C) and extreme (40.5 °C or higher). Fever on its own does not need to be reported.	Symptomatic; paracetamol	All
Hypotonic, hyporesponsive episode (HHE or shock-collapse)	Event of sudden onset occurring within 48 (usually less than 12) hours of vaccination and lasting from one minute to several hours, in children younger than 10 years of age. All of the following must be present. <input type="checkbox"/> Limpness (hypotonic) <input type="checkbox"/> Reduced responsiveness (hyporesponsive) <input type="checkbox"/> Pallor or cyanosis – or failure to observe/recall	The episode is transient and self-limiting, and does not require specific treatment. It is not a contraindication to further doses of the vaccine.	Mainly DTP, rarely others
Injection site abscess	Fluctuant or draining fluid-filled lesion at the site of injection. Bacterial if evidence of infection (e.g. purulent, inflammatory signs, fever, culture), sterile abscess if not.	Incise and drain; antibiotics if bacterial.	All
Lymphadenitis	Either at least one lymph node	Heals	BCG

(includes suppurative lymphadenitis)	enlarged to >1.5 cm in size (one adult finger width) or a draining sinus over a lymph node. Almost exclusively caused by BCG and then occurring within 2 to 6 months after receipt of BCG vaccine, on the same side as inoculation (mostly axillary).	spontaneously (over months) and best not to treat unless lesion is sticking to skin. If so, or already draining, surgical drainage and local instillation of anti-tuberculous drug. Systemic treatment with anti-tuberculous drugs is ineffective.	
Osteitis/ Osteomyelitis	Inflammation of the bone with isolation of <i>Mycobacterium bovis</i> BCG strain.	Should be treated with anti-tuberculous regimens including isoniazid and rifampicin.	BCG
Persistent inconsolable screaming	Inconsolable continuous crying lasting 3 hours or longer accompanied by high-pitched screaming.	Settles within a day or so, analgesics may help.	DTP, Pertussis
Seizures	Occurrence of generalized convulsions that are not accompanied by focal neurological signs or symptoms. Febrile seizures: if temperature elevated >38 °C (rectal) Afebrile seizures: if temperature normal	Self-limiting; supportive care; paracetamol and cooling if febrile; rarely anticonvulsants	All, especially pertussis, measles
Sepsis	Acute onset of severe generalized illness due to bacterial infection and confirmed (if possible) by positive blood culture. Needs to be reported as possible indicator of programme error.	Critical to recognize and treat early. Urgent transfer to hospital for parenteral antibiotics and fluids	All
Severe local	Redness and/or swelling centred at	Settles	All

reaction	<p>the site of injection and one or more of the following:</p> <ul style="list-style-type: none"> <input type="checkbox"/> Swelling beyond the nearest joint <input type="checkbox"/> Pain, redness, and swelling of more than 3 days duration <p>Requires hospitalization.</p> <p>Local reactions of lesser intensity occur commonly and are trivial and do not need to be reported.</p>	<p>spontaneously within a few days to a week. Symptomatic treatment with analgesics. Antibiotics are inappropriate.</p>	
Thrombocytopenia	<p>Serum platelet count of less than 50,000/ml leading to bruising and/or bleeding</p>	<p>Usually mild and self-limiting; occasionally may need steroid or platelets.</p>	MMR
Toxic shock syndrome (TSS)	<p>Abrupt onset of fever, vomiting and watery diarrhoea within a few hours of immunization. Often leading to death within 24 to 48 hours. Needs to be reported as possible indicator of programme error.</p>	<p>Critical to recognize and treat early. Urgent transfer to hospital for parenteral antibiotics and fluids.</p>	All

Sources

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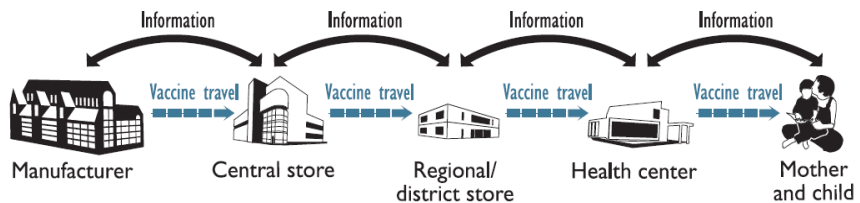
Introduction

The “cold chain” is the name given to a system of people, equipment and devices in place to ensure that “correct quantities of potent vaccine” are procured, stored and transported in correct temperature, until it reaches the recipients, from the time of production.

All vaccines lose their potency when exposed to higher temperatures than recommended. Some vaccines lose their potency when they are exposed to sub zero temperature. Therefore use of potent vaccine stored and transported in correct temperature, remains an integral part of the success of the immunization programme. High levels of immunization coverage become meaningless if the vaccines used are not potent.

Figure 1 illustrates the entire cold chain system. There are many steps between the manufacturer of the vaccine and recipients in need of immunization. Vaccine must stay at the correct temperature throughout the entire cold chain system: when it is transported, when it is stored in a refrigerator/ cold room, and in a vaccine carrier until it is used at an immunization session.

Figure 14 :Cold chain system



The three essential elements of the vaccine cold chain system are:

- ◆ persons who manage vaccine distribution,
- ◆ equipments used to store and transport vaccine,
- ◆ devices used to monitor temperature.

Health staff managing the immunization programme remain an extremely important link of the cold chain. Even if the finest and modern equipments and devices are available, the cold chain will not be effective, if persons who handle them are not using these equipments and devices properly.

The basic cold chain equipment includes:

- ◆ cold rooms and refrigerators used for vaccine storage,
- ◆ freezers used to freeze ice packs,

- ◆ cold boxes, vaccine carriers, and cold packs used for vaccine transport,
- ◆ thermometers, Vaccine Vial Monitors (VVM), data loggers and freeze tags used for temperature monitoring,
- ◆ vehicles used for transportation of vaccines.

Vaccine Stock Management

In the national EPI vaccine handling occurs at four main levels:

- ◆ central (national) level at the Epidemiology Unit,
- ◆ regional (district) level at the RMSDs,
- ◆ divisional level at Medical Officer of Health (MOH) and medical institutions,
- ◆ immunization clinics.

1. Central level [Epidemiology Unit] is responsible for,

- ◆ Indent of vaccines

The required stocks of vaccine are estimated annually and procurement process commenced one year ahead. The requirements are decided based on the target population, previous usage pattern, wastage rates and any special immunization activities planned and any new vaccines to be included into the schedule.

- ◆ Receipt of vaccine

All vaccines are imported from overseas manufacturers and the State Pharmaceutical Corporation (SPC) staff receives the stocks on arrival at the Katunayaka airport and transfers them to the Epidemiology Unit in cooler trucks. Prior to transfer to the Epidemiology Unit, SPC staff checks the consignment for the maintenance of cold chain during international transport and in agreement with the invoice and packing details. Vaccine on arrival at the Epidemiology Unit, standard Vaccine Arrival Report is filled for each consignment and any discrepancies are brought to the notice of the SPC, Ministry of Health and the manufacturer.

- ◆ Storage of vaccine

At the Epidemiology Unit all killed vaccines are stored in plus cold rooms at + 2°C to + 8°C temperature and all live vaccines are stored at -20°C temperatures.

- ◆ Distribution of vaccine

Vaccine stocks are distributed to Regional Medical Supplies Divisions (RMSD) once in every two months.

2. Regional Medical Supplies Division (RMSD)

Indent of vaccines

RMSD is supposed to make vaccine stock request from the Epidemiology Unit based on the district need.

Officer in charge of the RMSD should obtain the monthly stock return forms from all institutions to which vaccines are distributed in the RDHS division, before the 5th of the month. These returns should be checked for the following:

- ◆ the stocks requested are within reasonable limits and are adequate to immunize the target recipients in each MOH division/Institution,
- ◆ the stocks requested are adequate to maintain one month's buffer stock at the MOH/institution level,
- ◆ the requested quantity of vaccine will not exceed the two months stock at the MOH/institution level,
- ◆ guidelines given to prepare the requisition have been followed.

The return could be adjusted in consultation with the MOH/Head of the institution/ RE if necessary and the consolidated return for the RMSD prepared.

“Maximum stock” refers to the amount of any vaccine which should be in the store at the start of a new supply period. This should be three months stock of each vaccine at the RMSD level.

The quantity of vaccine to be ordered should be calculated as follows: The quantity of different vaccines currently in stock according to the vaccine stock ledger should be noted. This should be checked with the actual stocks in hand (these stocks should be the same). The formula below will determine the quantity of vaccine or supplies to be ordered for the next supply period.

$$\boxed{\text{Quantity to order}} = \boxed{\text{Maximum Stock}} - \boxed{\text{Current Stock}}$$

However this should be compared with the total quantity ordered by the MOOH /institutions in the area and average number of each vaccine doses used during the past 12 months and could be adjusted if necessary (e.g. vaccines for special immunization programmes).

The consolidated return should be forwarded to the Epidemiologist by the 5th of every month in consultation with the RDHS/RE. Return should be sent to the Epidemiology Unit every month whether stocks are requested or not.

Receipt of vaccine at RMSD level

Epidemiology Unit will give notice of the delivery of vaccines by letter and telephone to the RDHS/RE/RMSD. The officer in charge of the RMSD should ensure that he himself receives the stocks. If not, a responsible officer should be identified to receive the stocks.

The following should be checked before accepting the stocks:

- ◆ vaccine has been delivered on time,
- ◆ the quantity of vaccine, diluents and supplies are correct according to the invoices,
- ◆ expiry date and batch numbers of vaccines and diluents,
- ◆ the vials of vaccine and diluents are not damaged i.e. broken vials, labels separated from the vials,
- ◆ vaccine has not been exposed to harmful temperatures en-route by observing:
 - vaccine vial monitors – Figure 21 ,
 - cold chain monitors if accompanying the vaccine and/or the ice packs are not melted completely and
 - killed vaccines are not frozen

Vaccine arrival report should be completed by the OIC/RMSD according to the instructions given by Epidemiology Unit. If no problems are detected, stocks should be accepted. If any problem is detected, it should be immediately informed to the officer accompanying the vaccine stocks from the Epidemiology Unit.

- ◆ The stocks should be taken into the relevant vaccine stock ledger.
- ◆ The invoices should be filed .
- ◆ The balance of stocks should be updated immediately.

Possible problems that can be anticipated at RMSD level are:

- ◆ short expiry date,
- ◆ stocks in excess/short of order,
- ◆ breach in cold chain.
 - Any problem detected should be discussed with the superior.
 - If a superior is not available, the stocks or part of the stocks of vaccine could be accepted.
 - For the stocks not accepted, reasons should be indicated by a note brought to the notice of the superior and Epidemiology Unit as soon as possible.

Distribution of vaccines to MOOH

Vaccines should be delivered to the MOOH and institutions by the RMSD after prior notice by telephone or letter. Vaccine stocks should be distributed to Medical Officers of Health (MOOH) and institutions in the RDHS division every month.

The vaccines should be distributed packed in cold boxes. The required number of conditioned cold packs identified for each cold box should be used to ensure the cold life of the vaccines.

Care should be taken to ensure that liquid vaccines e.g. DTP, TT, DT, aTd, Hep B, Penta, JE (killed) and freeze dried live JE are not placed against the cold packs to avoid any possibility of freezing.

The cold box and conditioned cold packs should be ready and taken close to the cold room/refrigerator/freezer before taking out the vaccines for packing. The shortest possible route should be taken to reach the MOH/institution avoiding any undue stoppages/delays en-route. Activated data loggers and freeze tags may be used in the packed cold boxes to monitor the maintenance of cold chain during transport.

Before leaving MOH office, the officer from the RMSD should ensure that:

- ◆ vaccines are received by a responsible officer ,
- ◆ stocks are transferred to the refrigerators/freezers immediately,
- ◆ Relevant stock ledgers and registers are updated.

Medical Officer of Health/Institution conducting immunization

Indent of vaccine

Medical Officers of Health and institutions should send the vaccine stock returns to the RMSD before the 5th of the month. The return should be sent whether stocks are requested or not.

Preparation of stock return by MOH/Institution

In general, the amount of vaccine expected to be used during the following month, should be based on the average monthly usage. However, to ensure that:

- ◆ the stocks requested are within reasonable limits and are adequate to immunize the target recipients in each MOH division/Institution,
- ◆ the stocks requested are adequate to maintain one month buffer stock at the MOH division/institution level,
- ◆ the requested quantity of vaccine will not exceed the two months stock at the MOH division/institution level ,

- ◆ guidelines given to prepare the request have been followed,
- ◆ if there is a seasonal variation in vaccine demand, the quantity should be based on the experience in the previous year,
- ◆ if activities greatly increasing immunization coverage e.g. a SMI, special immunization programme are planned, a larger quantity of vaccine should be included in the stock return. This should be indicated in the return form for the benefit of the RDHS/RE/OIC-RMSD.

At the MOH office/Institution the maximum stock (one month buffer stock plus current month stock) is equal to the amount of **average vaccine usage for two months**.

The quantity of vaccine to be ordered should be calculated as follows:

The quantity of different vaccines currently in stock according to the vaccine stock leader should be noted. This should be checked with the actual stocks in hand (these stocks should be the same). The formula below will determine the quantity of vaccine or supplies to be ordered for the next supply period.

$$\boxed{\begin{array}{c} \text{Quantity to} \\ \text{order} \end{array}} = \boxed{\begin{array}{c} \text{Maximum} \\ \text{Stock} \end{array}} - \boxed{\begin{array}{c} \text{Current} \\ \text{Stock} \end{array}}$$

If extra stocks are needed add this amount. Indicate the reason for the order for extra stocks for the benefit of the OIC/RMSD.

Receipt of vaccine at the MOH office

MOH/Officer in charge of the institution should identify an officer (who is trained in handling vaccines and management of cold chain) to receive vaccine stocks and to maintain cold chain. The identified officer should be personally available to receive the stocks. Before accepting the stocks, they should be checked as given in section under RMSD.

Possible problems that could be anticipated at MOH level on receipt of vaccine are more or less same as at RMSD level.: please refer to the relevant section under RMSD.

Issuing and receiving vaccine to and from immunization clinics

The quantities taken to clinic should be entered in the vaccine movement register

- ◆ Unopened vaccine vials and open liquid vaccines should be transported back to the MOH office while maintaining the cold chain.
- ◆ The quantities returned should be noted in the vaccine movement register.
- ◆ The above details should be used to calculate vaccine usage/wastage by clinics.

Storage of vaccine and maintaining the cold chain

1. At RMSD level

Currently all RMSD have been provided with PLUS cold rooms. At RMSD level all vaccine could be stored at this plus cold room, including OPV (maximum up to three months period). All these cold rooms are equipped with two cooling machines to make sure continuous cold storage when one machine is failed. Further these cold rooms are equipped with auto start generators to provide uninterrupted electricity in power failure.

It is the responsibility of the RDHS to make sure that all these components are in good state of repair by arranging an annual maintenance contract with the local agent for these machines as per guidelines issued by the Epidemiology Unit.

However adequate number of refrigerators and freezers should be kept as a backup storage in the event of a cold room failure.

Temperature in the cold room should be maintained at +2°C to +8°C. All cold rooms are equipped with in built digital thermometers and 24 hour continued temperature recorders. Further they are provided with manual thermometers, data lodgers and freeze tags. It is the responsibility of the MOIC-RMSD to monitor the temperature and cold chain of vaccines, using the different monitoring devices provided at least twice a day. Findings of all thermometers, VVMs, freeze tags should be recoded twice a day on the cold chain monitoring sheets provided by the Epidemiology Unit. Data lodger should be read once in two weeks or when cold chain failure is detected. At the end of every two weeks, recordings of the data lodger should be printed out in triplicate. One copy should be filed at the RMSD, one copy should be send to RDHS/RE and the other copy should be forwarded to the Epidemiology unit with the Monthly vaccine stock return.

A separate freezer should be used for freezing of ice packs at the RMSD.

All space in the cold room/refrigeration equipment cannot be used for vaccine storage purposes. Spacing between the stored vaccine / diluents stacks and cold packs is needed for proper circulation of cold air and uniform cooling. As a rule about 60% of the internal space is used for vaccine, diluents and cold packs storage. The remaining, 40% is left unfilled stacking the vaccines, diluents and ice packs in rows at distances of about 2 cm from one another and walls.

2. At MOH/Institution level

At MOH/institution level all types of vaccines including OPV should be stored in an ice lined refrigerator or ordinary refrigerator which are identified for vaccine storage. Except vaccine and diluents no other drugs or any other pharmaceutical or non pharmaceutical products should be stored in a vaccine refrigerator.

Storage of vaccines in ordinary front-loading refrigerator

Depending on the make and the model, temperature inside the refrigerator may be varying from coolest to warmest at different shelves. Hence as a rule live vaccines should be stored in the coolest part of the refrigerator and killed or inactivated vaccines at the warmest part of the refrigerator.

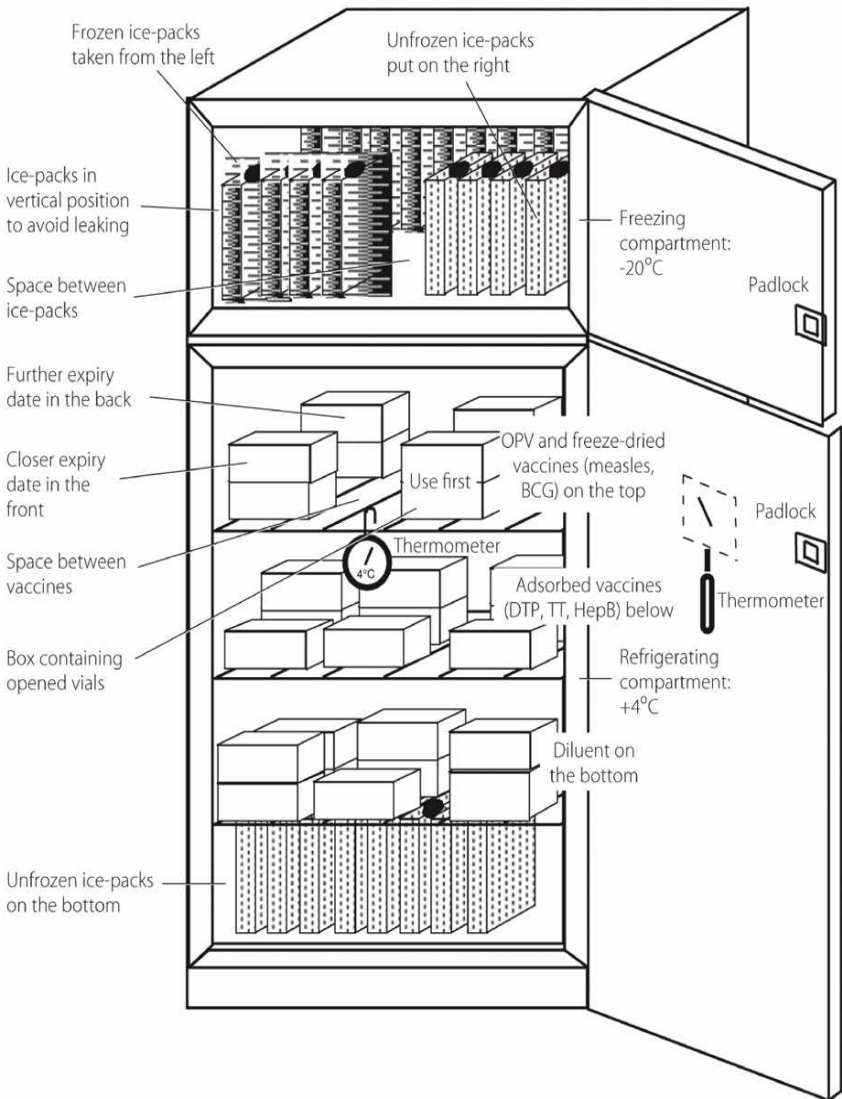
In an ordinary front loading refrigerator, cooling effect starts from the top (freezer compartment being up) of the refrigerator. Therefore, all the live vaccines (except live JE); OPV, Measles, Rubella, Measles-Rubella (MR), Measles-Rubella-Mumps (MMR), should be stored in the top shelves of the refrigerator as indicated in figure 15. This is because, live vaccines will not be damaged by freezing even if temperature reaches minus in this part of the refrigerator accidentally.

Killed or inactivated vaccines should be stored in the warmest/lower part of the refrigerator to prevent possible accidental freezing.

No vaccines should be stored in the door or the vegetable basket of the refrigerator.

Storage space in the door and the vegetable basket of a domestic refrigerator can be used for keeping reasonable quantities of salt water filled cold packs or water bottles to act as lining to provide longer hold over time upon power supply interruptions.

Fig. 15: Storage of vaccines in ordinary front-loading refrigerator



Storage of vaccines in ice-lined top-loading refrigerator

Ice-lined top-loading refrigerators are purposely built refrigerators for vaccine storage. It has lining space filled with water within the walls of the refrigerator and become lining of ice in operation. During power failure this lining of ice will increase the cold holdover time considerably depending on the amount of ice formed.

In a top loading ice lined refrigerator, coolest is the bottom part of the refrigerator. Warmest is top/upper part of the refrigerator. Hence when storing vaccines, live vaccines should be stored in the bottom of the refrigerator and killed/inactivated vaccines should be stored in the upper part of the refrigerator as indicated in the figure 16



Figure 16: Ice-lined refrigerator

As in the case of cold rooms or refrigerators, all the space in the refrigerator compartment cannot be used for vaccine storage purposes. Spacing between the stored vaccine / diluents stacks and cold packs is needed for proper circulation of cold air and uniform cooling. As a rule about 60% of the internal space is used for the vaccine, diluents and cold packs storage. Rest, 40% is left unfilled stacking the vaccines, diluents and ice packs in rows at distances of about 2 cm from one another and walls.

The cartons of vaccine should,

- ◆ be stored to ensure air circulation among the piles of vaccine,
- ◆ be identified by date of arrival and date of expiry,
- ◆ indicate the quantity in each carton.

Storage of vaccines returned from immunization clinics

Stocks of vaccine that have been taken to clinics and brought back unused (unopened vials), should be stored separately from the bulk stocks in a separate box marked as, “ returned unopened vials”. Returned opened vials should be kept in a separate box marked as “returned open vials”. These two boxes should be kept in the 2nd shelf of the refrigerator. Returned open and unopened OPV vials also should be kept in the same box. These returned unopened vials should be taken to the very next clinic and used before using the bulk stocks.

With freeze-dried vaccines diluents are provided for reconstitution. The vaccine should always be reconstituted with the diluent provided by the manufacturer for the same batch of vaccine. Diluent can be stored at +2°C to +8°C or at room temperature but should not be frozen. If stored at room temperature, they should be cooled to +2 to +8°C, 24 hours before use/reconstitution to avoid thermal shock to the vaccine, which may reduce its potency.

Adjusting temperatures inside the refrigerator

Temperatures inside a refrigerator can be adjusted by turning the “thermostat switch” provided for increasing or decreasing cooling of the refrigerator. Increasing number or clockwise turning of the thermostat will result in higher cooling. Turning thermostat to lower number or anticlockwise will result in less cooling. Thermostat can thus be adjusted as required in order to maintain the required inside temperature of around +4°C (average between +2°C to +8°C) within the refrigerator. Hence thermostat has to be adjusted with variation of ambient temperature and with vaccine quantities and cold packs stored.

The temperature inside a refrigerator depends on ambient temperature, duration and frequency of door opening, proper door closing (sealing with door gasket), and continuity of electric power supply, frosting ice in the freezer compartment, the total load vaccines and amount of cold packs/bottles.

If the temperature goes above +8°C:

- ◆ inside temperature could be decreased by turning the temperature control switch (Thermostat) to a lesser number or anticlockwise,
- ◆ more bottles of water (or ice packs filled with water) should be stored in every spare space in the refrigerator, except for 40 % of the volume which is needed for air circulation. This helps to stabilize the temperature and prevent wide fluctuations during the day,
- ◆ ensure that the door of the refrigerator/freezer is opened as few times as possible.

If the temperature is maintained below 0°C

More bottles of water (or ice packs filled with water) should be stored in every spare space in the refrigerator, except for 40 % of the volume which is needed for

This helps to stabilize the temperature and stop it from fluctuating widely during the day.

- ◆ Inside temperature could be increased by turning the temperature control switch button (thermostat) to a higher number or clock wise.
- ◆ Windows or ventilators of the room should be kept closed at night to keep the store-room warmer if necessary.
- ◆ If these actions do not ensure that the internal temperature is maintained correctly, the refrigerator should be replaced.

If it is found that the temperature may remain high or low for long, the vaccine should be shifted to another refrigerator or cold boxes with cold packs as necessary. The storage unit can be kept under adjustment / observation for a day and then the decision for shifting the vaccine back can be taken.

- ◆ Bottles of water (or ice packs filled with water) should be stored in the refrigerator to keep the refrigerator cool specially if there are frequent interruptions to energy/power supply. Bottles of water will help keep the refrigerator cool if energy/power supply fails or the refrigerator breaks down.
- ◆ The cartons of vaccine should be stored to ensure air circulation among the piles of vaccine.
- ◆ The cartons should be identified by date of arrival and date of expiry and the quantity in each carton.
- ◆ The arrangement of the stocks should be such that those with a shorter expiry date are delivered before those with longer expiry dates.

Maintenance of cold rooms, refrigerators and freezers

For better access and ease of monitoring the cold chain cold rooms, refrigerators and freezers used in vaccine storage at any given health facility should be installed in one room or adjacent rooms. One person should be identified and assigned with the responsibility of day to day vaccine receipts and issues along with refrigerator temperature recording and cold chain maintenance through ensuring the following:

- ◆ the room is well ventilated, preferably fitted with an exhaust fan,
- ◆ each refrigerator/freezer is protected from any outside heat,
- ◆ drays of the sun do not fall on the refrigerator/freezer,
- ◆ refrigerators should be kept on level floor and are firm on four legs,
- ◆ refrigerators should be kept away from walls or other units at a distance of minimum 10 cm,
- ◆ each refrigerator/freezer should be plugged directly into the points, switches if any should be taped in “ on position” ensuring that there is no possibility of their disconnection or switching off,

- ◆ refrigerator/freezer doors and lids are kept firmly closed,
- ◆ each refrigerator/freezer is defrosted regularly and kept clean. Whenever a layer of ice measuring several millimeters (5 at most) forms on the freezer compartment, the refrigerators should be defrosted,
- ◆ each refrigerator/freezer has a maintenance chart - Refrigerator Record,
- ◆ any problems should be brought to the notice of the relevant officers immediately. A note should be prominently displayed as to whom to be contacted,
- ◆ an alternate place to store vaccine during an emergency (an emergency plan) should be identified and prominently displayed. This place should be identified at the onset in consultation with the RDHS/RE/MO (MCH)/MOH depending on the stores involved ,
- ◆ inventory of equipment is checked annually,
- ◆ have a maintenance agreement with a prequalified cold room/refrigerator repair/maintenance company for preventive maintenance and repair .

Maintenance of cold chain at MOH level

- ◆ A responsible person should be identified to be in charge of the vaccine management and maintenance of cold chain and to maintain all records pertaining to it/them. In the event of this person being absent, a second and a third person should be identified.
- ◆ These persons should be made known to all relevant people.
- ◆ Immediate action should be taken to correct any problems detected by the identified person/s.
- ◆ Any problem should be discussed with superior officers (MOH/RE/MO (MCH)) and suitable action taken.
- ◆ Possible common problems and emergency action to be taken should be noted and prominently displayed e.g. interruption to electricity etc.

Transport of vaccines to the field clinics

- ◆ Vaccine stocks should be distributed to the clinic centers packed in vaccine carriers with cool packs.
- ◆ Vaccine carriers should be used even when the clinic is held in a room adjoining the storage point.
- ◆ The correct number of cold packs should be used to maintain the cold life of the vaccine during transport to and from the clinic and duration of the clinic.
- ◆ The vaccine carrier should be taken close to the refrigerator while packing it.

- ◆ The vaccine should be packed immediately after removal from the refrigerator ,
- ◆ The vaccine carriers should be in good condition i.e.
 - the walls are not cracked ,
 - handles are not broken,
 - clasps of the lid are not broken,
 - lid closes tightly ,
 - each cold box and vaccine carrier has the full set of ice packs,
 - they are washed, dried and kept open for complete drying after each use,
 - inventory is checked annually,
 - any problems brought to the notice of relevant officers.

Conditioning of “cold packs” before use in vaccine carriers

The proper use of ice packs is essential for maintaining the potency of vaccines. It is essential to “condition” ice packs to prevent freeze-sensitive vaccines from freezing during transport. To condition an ice pack, remove it from the freezer compartment and keep it at room temperature until the ice within it starts to melt. When you shake the ice pack and can hear the water inside, it is ready to be loaded into the cold box or vaccine carrier. (figure 17). The time this takes varies depending on the ambient temperature; it can take over 20-30 minutes.



Figure 17 : Checking an ice pack

At the clinic centre

Unopened vials of vaccine should NOT be taken out of the vaccine carrier till ready for use. All open live vaccine (Measles, rubella, MMR,) vials should be kept in a container with contact ice cubes or inside the foam pad of the vaccine carrier. All the open killed/inactivated vaccine vials (DPT, Pentavalent, Hepatitis B, DT, aTd, TT) could be kept in the foam pad or on the clinic table and should not be in contact with ice. All the vaccine should be placed away from direct sun light.

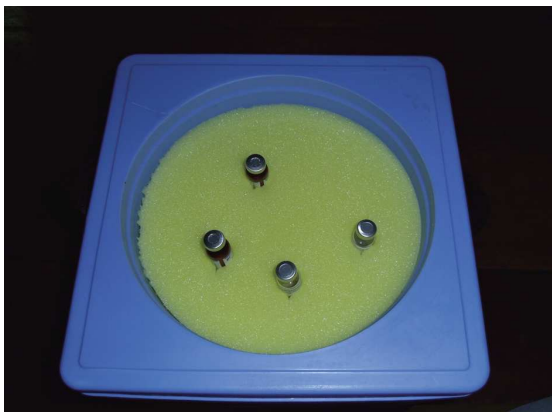


Figure 18: Keeping vaccine vials inside the foam pad

Packing of vaccines in cold boxes and vaccine carriers

- ◆ Ice packs should be removed from the freezer and kept outside for 20-30 minutes until the outer layer of ice in the ice pack gets melted and becomes water (conditioning of ice packs). Make sure that the outer layer of the ice has become melted before using inside a cold box, vaccine carrier or a day carrier to transport vaccines.
- ◆ Place ice packs in the vaccine carriers on all sides.



- ◆ Place the live vaccines and diluents at the bottom of the vaccine carrier
- ◆ Put all the killed vaccines into a plastic container, close the lid and keep the container on the live vaccines in the vaccine carrier.



- ◆ If cubes of ice are used they should be packed in a bag.
- ◆ Place cubes of ice on top.



- ◆ Take all precautions to prevent killed/inactivated vaccines from being frozen.
- ◆ Secure the lid tightly.

Supervision of the maintenance of cold chain

Supervising Officers should:

- ◆ observe as the vaccine stocks are received at the RMSD/MOH Office/immunization clinic,
- ◆ observe how vaccine is stored at RMSD/MOH office/institution/Immunization clinic,
- ◆ observe how vaccine is distributed from RMSD to MOH Office/institution,
- ◆ observe how cold chain is maintained at the RMSD/ MOH office and the institutions,
- ◆ observe on adequacy and maintenance of cold chain equipment,
- ◆ observe how vaccine is used at the clinic,
- ◆ observe on maintenance of records/returns at RMSD/MOH Office/institution.

Monitoring of temperature in the cold chain

1. Daily recording of temperature using thermometers

Keeping a record of temperature changes in the vaccine cold room/refrigerator is critically important. Person in-charge of cold chain should record the temperature of their vaccine refrigerator twice a day in the temperature record provided by the Epidemiology Unit.

When they visit the MOH office/Institutions, district- and higher-level managers and supervisors should review these charts to emphasize the importance of maintaining vaccines in appropriate temperatures. Recording thermometers that automatically make such recordings also are available.

Different types of thermometers and thermo-recorders are used to monitor vaccine temperatures (figure 19). Officers' in-charge of vaccines should be familiar with the use of these devices.

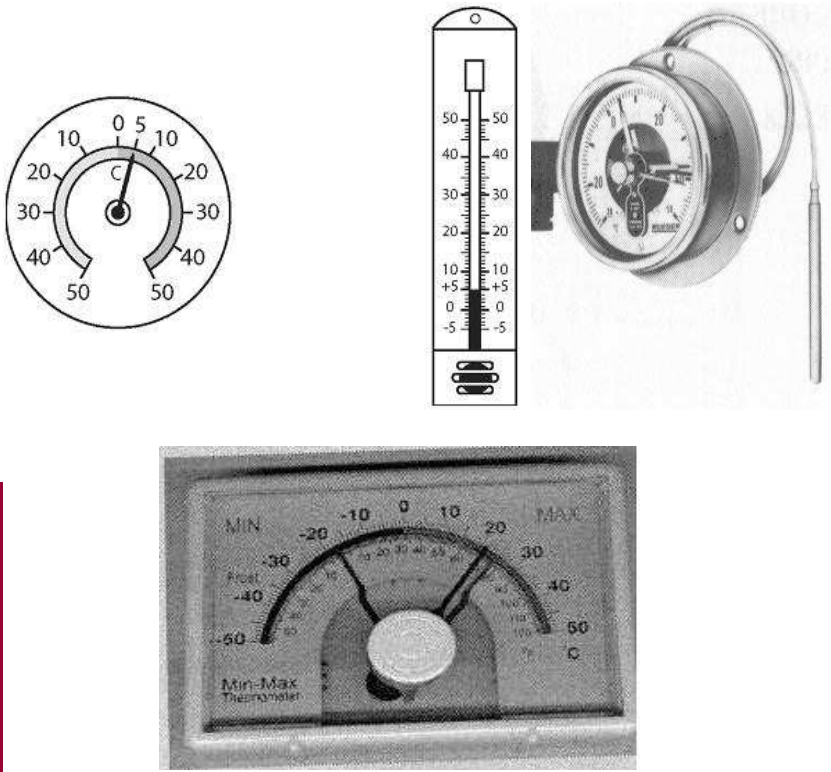


Figure 19: Different types of thermometers

2. Using the VVM to monitor the quality of vaccine vials

With the invent of the vaccine vial monitor (VVM) cumulative heat exposure of a vaccine vial can now be monitored with the help of the VVM. which can be found on all WHO prequalified vaccines.

A heat sensitive square within a circle changes colour under the combined influence of heat and time. If, after exposure to heat for a certain period of time, the square reaches the same colour of the circle or becomes darker as shown below, the vial should be discarded.

The VVM allows the user to see at any time if the vaccine vial can still be used in spite of possible cold chain interruptions (figure 21). If necessary, health staff and management can then take the required corrective measures.

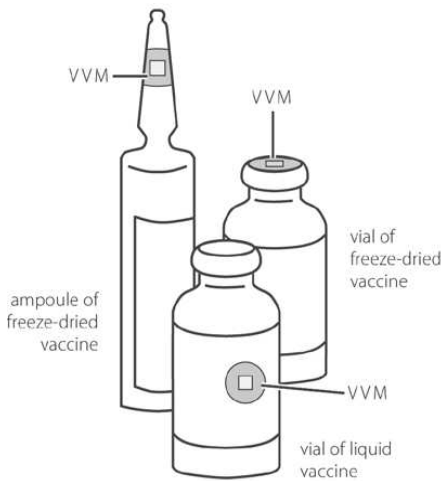


Figure 20 : Vaccine vial monitor (VVM)

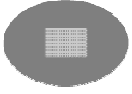
Important points on use of VVMs

- ◆ Under circumstances where vaccines could have been exposed to excessive heat during shipment or storage, the VVM will always indicate whether or not the vaccine is safe for use.
- ◆ The VVM will only apply to the vaccine in the vial on which it appears. It cannot be used as a proxy for other vaccines; they may have different temperature sensitivities and storage history.
- ◆ The VVM is a useful indicator when conducting outreach activities. Even under intermittent cold-chain conditions vaccines can continue to be used according to the VVM status. A VVM will not, however, indicate whether a freeze-sensitive vaccine has been frozen.
- ◆ The expiry date of a vial has priority over the VVM. If the expiry date is reached, the vial should be discarded even if the VVM suggests the vial can still be used.
- ◆ All health workers must know how to interpret a VVM (see Figure 20).

There are currently, four types of VVM in use – types 2, 7, 14 and 30. Each number refers to the number of days the VVM takes to reach the discard point if it is kept at +37 °C. Various types of VVMs are assigned to different vaccines according to their heat sensitivity – for example, VVM type 2 is assigned to OPV which is a very heat-sensitive vaccine, while VVM type 7 is assigned to DTP-HepB-Hib which is much less heat sensitive.



Inner square lighter than outer circle.
If the expiry date has not been passed, USE the vaccine.



At a later time, inner square still lighter than outer circle. ***If the expiry date has not been passed, USE the vaccine.***



Discard point:
Inner square matches colour of outer circle.
DO NOT use the vaccine. Inform your supervisor.



Beyond the discard point:
Inner square darker than outer circle.
DO NOT use the vaccine. Inform your supervisor.

Figure 21: Interpretation of the Vaccine Vial Monitor (VVM)

3. Use of freeze tags to monitor exposing vaccine to freezing

Freeze Tag is an irreversible temperature indicator that shows if a product, such as vaccine has been exposed to freezing temperatures. It consists of an electronic temperature measuring circuit with associated LCD-display. If the indicator is exposed to a temperature below $0^{\circ}\text{C} \pm 0.3^{\circ}\text{C}$ for more than $60\text{min} \pm 3\text{min}$ the display will change from the “good“ status into the “alarm“ status. A small blinking dot in the bottom right hand corner of the LCD display indicates that the device is functioning. The indicator is used to warn of freezing and is packed with DPT and its combinations, TT as well as with Hepatitis B and other freeze sensitive vaccine. Shelf life is around 5 years.



Figure 22 : Freeze tag

4 . Electronic data lodgers

Electronic data lodger is a portable, self-contained, user-programmable, temperature recorder for use with goods sensitive to temperature. As a "reusable cold chain monitor", it gives a complete history and is suitable for use in vaccine refrigerators, vaccine shipments and cold chain studies.



Figure 23 : Electronic data lodgers

Recorded data can be downloaded, viewed and stored using freely available Windows software "Data Analyzer" via a data lodgers interface connected to the computer's USB or COM port connection. Currently data lodgers are provided to all RMSD and all MOH offices.

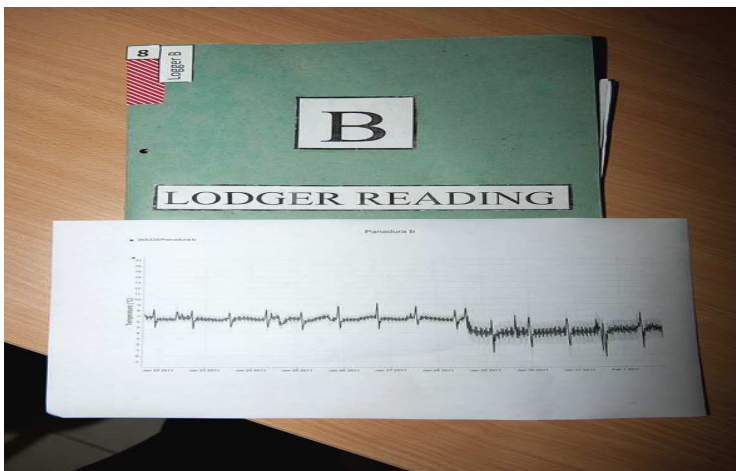


Figure 24: Data lodger reading

The shake test

The shake test is used to determine if the vaccine has been frozen.

During the process of freezing, vaccine tends to flocculate (i.e., virus particles stick together to form larger clumps). When a vial of vaccine which has been frozen and then thawed is shaken and then allowed to sediment, it will sediment more quickly than the same vaccine from the same manufacturer which has not been frozen. Figure 25 gives a comparison between the sedimentation rates of a frozen and a never frozen DPT vaccine.

The shake test is best conducted using a vial of vaccine which you have frozen solid yourself and do not intend to use. This vial can be used as a frozen “control” against which to compare vaccines in doubt. Whenever the “control” vial sediments significantly faster than the test vial, then the test vial is acceptable. If the sedimentation rates are the same, however, then the test vial should not be used. Remember, the shake test can only be conducted on “test” and “control” vials from the same manufacturer.

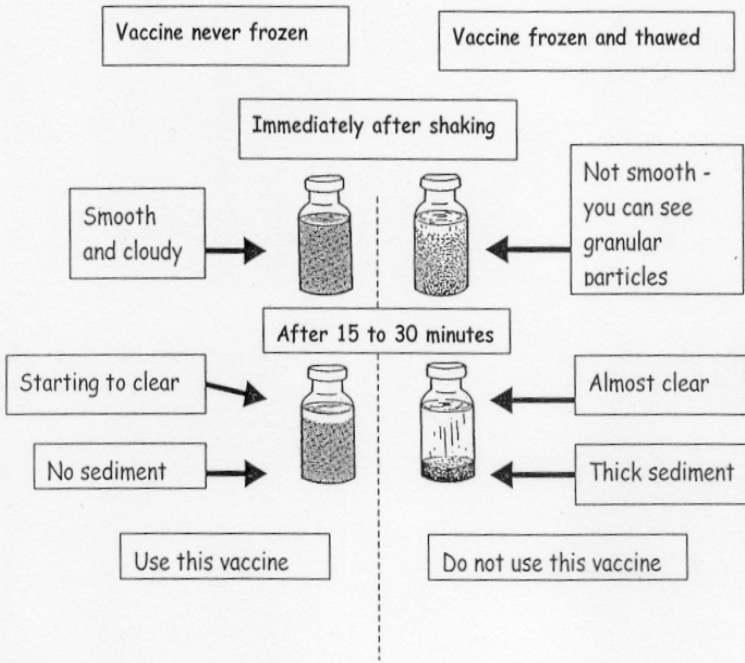


Figure 25: Shake test

Sources

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Introduction

In the modern era, vaccination related to international travel is of great importance. For travellers, vaccination offers the possibility of avoiding numerous vaccine preventable diseases that may be contracted abroad. Hence at individual level, travellers gain from vaccination. Immunized travellers are also less likely to cause infections to other travellers or natives at the place of visit. They are also less likely to bring the infection to the country of their visit or to their native country on return from foreign travel. Therefore the community too benefits from individual Immunizations. Number of tourists arriving in Sri Lanka is high since it is a popular _tourist destination, and Sri Lanka sees a lot of out bound travel as well, especially for employment. Hence travel related vaccination is a priority area for consideration, especially in the Sri Lankan context.

Vaccination for Sri Lankans travelling abroad

Vaccination for Sri Lankans travelling abroad can be grouped into the following categories:

- ◆ vaccination in keeping with the National EPI vaccine schedule of the country of destination
- ◆ mandatory immunization required at the travel destination
- ◆ other recommended immunizations of potential importance

1. Vaccination in keeping with the National EPI vaccine schedule of the country of destination

Though the EPI vaccine preventable diseases are under control in Sri Lanka, the same may not be applicable in other parts of the world. Therefore travellers are advised to assess the current disease status in respect of EPI diseases in their travel destination. If there is a need, they are advised to be updated with routine immunization immediately as most vaccines take time to be effective. Ideally they should be given 4-6 weeks prior to travel. The EPI vaccine schedule of Sri Lanka is given in the EPI Chapter .

2. Mandatory immunization required at the travel destination

It is important for the traveller to consider if there are any mandatory vaccination requirements at the travel destination. The minimum gap between vaccination and travel, need to be maintained to ensure development of immunity. It is also important to consider the prerequisites relevant to vaccination that need to be fulfilled for embarking at the travel destination (e.g. need of a certificate, minimum duration required between vaccination and travel).

Such details need to be obtained and fulfilled on individual basis. The Consulate of the relevant country may offer some guidance. Once this information is obtained, it should be shared with the service provider (person immunizing the traveller), as the specific requirements may vary from one individual to another.

◆ **Yellow Fever Vaccination**

Yellow Fever is the only mandatory vaccination currently required under International Health Regulations (IHR). It is carried out for two reasons. It is carried out to protect the individual from yellow fever when the traveller goes to areas where there is a risk of yellow fever infection. It is also carried out to protect vulnerable countries from the yellow fever virus. Details of the vaccine are given in the chapter on yellow fever.

Travellers who are 9 months of age or above, visiting countries falling within the Yellow Fever endemic areas (some countries in Africa and South America) are required to be vaccinated at least 10 days prior to embarkation. The vaccine provides immunity for 10 years. The list of countries falling within the Yellow Fever endemic areas given below.

Africa: Angola, Burundi, Benin, Burkina Faso, Cameroon, Central African Republic, Chad, Congo, Democratic Republic of Congo, Equatorial Guinea, Ethiopia, Gambia, Gabon, Guinea, Guinea-Bissau, Ghana, Ivory Coast, Kenya, Liberia, Mali, Mauritania, Niger, Nigeria, Sao Tôme and Príncipe, Senegal, Sierra Leone, Somalia, Sudan, Rwanda, Tanzania, Togo, Uganda

South America: Argentina, Bolivia, Brazil, Colombia, Ecuador, French Guyana, Guyana, Paraguay Panama, Peru, Surinam, Trinidad and Tobago, Venezuela

◆ **Vaccination against Meningococcal Disease**

Vaccination against Meningococcal Disease is required by Saudi Arabia for pilgrims visiting Mecca and Medina annually. Pilgrims aged two years and older are required to show proof of vaccination against Meningococcal Meningitis A,C, W-135 and Y to obtain visa for entering Saudi Arabia for purposes of Hajj or Umrah.

In addition, Vaccination against meningococcal infections is recommended to travellers who are travelling to the 'meningitis belt' of sub-Saharan Africa.

Countries within the ‘meningitis belt’: Gambia, Senegal, Mali, Burkina Faso, Ghana, Niger, Nigeria, Cameroon, Chad, Central African Republic, Sudan, Uganda, Kenya, Ethiopia, Eritrea

Traveller should receive the meningococcal vaccine at least 10 days prior to departure and a booster dose every 3 years.

Details on vaccination against meningococcal disease are given in the chapter on meningococcal vaccine.

◆ **Polio Vaccination**

Some polio free countries may require for travellers from polio endemic countries to be immunized against polio in order to obtain an entry visa (e.g. Saudi Arabia). However since Sri Lanka does not fall into the polio endemic category this concern doesn't arise for Sri Lankans visiting other countries. Polio vaccination is described in the chapter on polio vaccine

3. Other recommended immunizations of potential importance

There is no uniform clear-cut vaccine schedule for travellers to adapt. Each schedule is individual and country based. Hence vaccinations recommended vary based on factors such as the traveller's age, present health condition, countries to be visited, duration and purpose of travel and activities proposed to be conducted during the visit.

Following vaccines are recommended for travellers, based on their travel purposes. Details of these vaccines are given in the respective chapters

◆ **Chickenpox Vaccine**

Chickenpox vaccine can be recommended to travellers who travel to countries with cold climates. These countries witness clustering of cases and periodical outbreaks. Preventing chickenpox is more important for older travellers as they are more likely to develop complications. Vaccination against chicken pox is described in the chapter on chickenpox vaccine.

◆ **Hepatitis A Vaccine**

Travellers expecting to travel to areas with poor sanitation and lack of safe water may get themselves vaccinated against Hepatitis A. Hepatitis A vaccination also needs to be considered if a traveller is planning to travel to Hepatitis A high or intermediate endemic areas. However, it should be noted that in addition to immunization, traveller should consume safe food and water wherever possible. Details on Hepatitis A Vaccination is given in the chapter on hepatitis A vaccine.

◆ Influenza Vaccine

Seasonal influenza vaccine is available in countries that experience influenza outbreaks during the winter season. These vaccines are prepared based on the prevalent strains that are causing influenza infection in the relevant geographical area. Therefore travellers are advised to seek clarification in this regard prior to travelling. The consulate of the relevant country may offer assistance required. More details on influenza vaccination is given in the chapter on influenza vaccine

◆ JE Vaccine

Immunization against JE should be considered when travelling to JE endemic areas, especially when travelling is undertaken to rural areas and when the stay is expected to be for a long (e.g. 1 month or more) period of time. Details on JE Vaccination is given in the chapter on JE vaccine.

◆ Rabies Vaccine

Pre travel (pre-exposure) rabies vaccination may be given to travellers who are travelling to Rabies endemic areas, especially if their proposed activities increase the risk of being exposed to wild or domestic animals. Vaccination before travel would simplify management of a subsequent exposure, since fewer doses are required and rabies immunoglobulin is not required. Vaccination against rabies is described in the chapter on rabies vaccine.

◆ Typhoid Vaccine

Typhoid vaccination could be considered for travellers who are expecting to travel to areas with poor sanitation and lack of safe water. It is also advised to vaccinate against typhoid infection when travelling to high typhoid endemic areas. As noted under Hepatitis A, the traveller should try to ensure consumption of hygienic food and water wherever possible in addition to immunization. Details on typhoid vaccination is given in the chapter on typhoid vaccine.

Vaccination for Travellers to Sri Lanka

1. Mandatory Vaccination requirement for travelling to Sri Lanka

Persons travelling to Sri Lanka are required to be vaccinated against yellow fever, if travelling from a country with risk of yellow fever transmission and are over 1 year of age. Therefore a yellow fever vaccination certificate is required from individuals falling into the above category. The list of countries falling within the yellow fever endemic areas is given above.

International certificate of vaccination

Based on the revision of IHR in 2005 by the World Health Assembly the previous “International certificate of vaccination or revaccination against yellow fever” has been replaced by “International certificate of vaccination or prophylaxis”. The model international certificate of vaccination or prophylaxis is given in figure 26.

Figure 26: Model International Certificate of Vaccination or prophylaxis

Model International Certificate of Vaccination or prophylaxis				
This is to certify that (name)				
Date of Birth Sex				
Nationality				
National Identification document (if applicable)				
Whose signature follows				
Has on the date indicated been vaccinated or received prophylaxis against (name of disease or condition)				
In accordance with the International Health Regulations				
Vaccine or prophylaxis	Date	Signature and professional status of supervising clinician	Manufacturer and batch no of vaccine or prophylaxis	Certificate valid from Until
<p>Note:</p> <p>This certificate is valid only if the vaccine or prophylaxis used has been approved by the World Health Organization</p> <p>This certificate must be signed in the hand of the clinician, who shall be a medical practitioner or other authorized health worker, supervising the administration of the vaccine or prophylaxis. The certificate must also bear the official stamp of the administrative centre; however, this shall not be an accepted substitute for the signature</p> <p>Any amendment of this certificate, or erasure, or failure to complete any part of it, may render it invalid</p> <p>The validity of this certificate shall extend until the date indicated for the particular vaccination or prophylaxis. This certificate shall be fully completed in English or French. This certificate may be completed in another language on the same document, in addition to either English or French</p>				

Official stamp of administrative centre

2. Vaccination recommended for travellers visiting Sri Lanka

In addition to routine EPI vaccines, travellers visiting Sri Lanka are recommended to take following vaccines as a precautionary measure as intermittent small scale outbreaks of following diseases are reported in Sri Lanka.

- ◆ **Hepatitis A vaccination** can be obtained prior to visiting Sri Lanka. As mentioned above, it is important to practice good sanitary practices for preventing Hepatitis A, in addition to immunization.
- ◆ **Japanese Encephalitis vaccination** is recommended for travellers who come from non endemic areas, especially if they are to visit the JE endemic areas of Sri Lanka. However, taking precautions against mosquito bites is also an important step for prevention.
- ◆ **Vaccination against Rabies** too can be obtained by travellers visiting Sri Lanka, as rabies is a endemic disease in the country.
- ◆ **Typhoid vaccination** can be obtained for travellers visiting Sri Lanka from non endemic areas. However, adhering to eating and drinking safe food is more important in preventing the disease.

Vaccination of immune-compromised travellers

Though the risk of contracting an infectious disease can be more in immune-compromised travellers, basic principles of vaccination still apply to these individuals. Risk and benefit should be carefully weighed when deciding on live vaccines to these individuals. In instances where a yellow fever vaccination certificate is required and it is contraindicated, a letter of deferral should be provided to the traveller instead.

Vaccination scheduling for last-minute travellers

Though not frequently discussed, it is a commonly occurring scenario for travellers to be last minute in preparing for their travel. Hence the ideal situation of consulting a Physician 2-3 months prior to the departure may not be very practical for most travellers. Therefore it is important to maintain the minimum time interval between doses for each vaccine. Doses given at less than minimum intervals can lessen the antibody response. Administration of a vaccine earlier than the recommended minimum time interval is discouraged. It should also be noted that if vaccination is done shortly before departure, the person may not have adequate immunity against the disease during the initial part of travel. Therefore it is appreciated if the service provider explains to the traveller as to how long it would take for optimum immunity to occur.

Point to consider when vaccination is required for travellers

A physician could be consulted, ideally 2 to 3 months prior to the proposed visit, to give sufficient time for completing immunization schedule and for optimum immunity on possible vaccinations

Traveller needs to contact the Counsel/Embassy of the place of visit and clarify regarding mandatory vaccination requirements and recommended vaccination at the place of visit. This information should be shared with the service provider

It should be noted that in addition to immunization, the traveller should also take other feasible primary preventive measures against the disease in question. For example in addition to JE vaccination, the traveller can use mosquito nets and mosquito repellents wherever possible.

The recommendations and requirements for vaccination may change from time to time. Hence it is advisable to obtain current information from print and electronic media including the internet.

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Present Notification System

History of the notification of communicable diseases in Sri Lanka dates back to late 19th century. The Quarantine and Prevention of Diseases Ordinance had been introduced in 1897 to implement the notification system on communicable diseases in the country. The Ordinance includes the List of Notifiable Diseases and states that all medical practitioners or persons professing to treat diseases and attending to patients suspected of any notifiable disease should notify the cases to the relevant public health authorities.

A medical officer notifying a case suspected with a notifiable disease should complete a Notification of a Communicable Disease Form (H 544). All such cases notified are entered in the Ward/OPD Notification Register. All wards i.e. medical, paediatric, surgical, obstetric/gynaecological and other specialty wards, should have Ward Notification Registers. Correct name and address of the patient, age and sex of the patient, the disease suspected, date of notification, to whom the case is referred to and special remarks are included in these ward notification registers.

Notification of a Communicable Disease Forms (H544) are posted daily to the respective MOH offices by a designated person in the hospital after entering them in an Institution Notification Register. Institution Notification Register is kept in the office of the Head of the Institution.

Notification of a patient with a notifiable disease initiates a regulated flow of activities in the field. All H544 forms received at the MOH offices are entered in the Notification Register of the MOH office and handed over to the relevant area Public Health Inspector (PHI) in whose area the notified patients reside in and may have contracted the disease. These cases are investigated personally by the relevant area PHI as soon as possible and ideally within 7 days of receipt of the notification form.

The house of the patient is visited by the PHI and relevant additional information is obtained from the patient, his/her medical records, his/her family and the environment. The probable diagnosis of the notified cases can be either clinically confirmed or discarded following these investigations. For confirmed cases, the PHI is responsible to carry out control and preventive measures related to the disease following the investigation. These include identification of the source of infection and contact tracing as well. Another form, Communicable Diseases Report Part I – H411 is completed for each case investigated and data from all confirmed cases are then entered in the Infectious Disease Register at the PHI's office.

Completed H 411 and H 544 forms are returned to the MOH office following this series of activities carried out by the PHI.

At the MOH office, details from the above forms on each case notified are used to update the Office Notification Register and if confirmed, entered in the MOH Office Infectious Disease Register (H700). Based on the Form 411 sent by the PHI, a form H411a is completed for each case confirmed.

A summary of notified diseases reported for the week from the MOH area is prepared every week at the MOH office. This is the Weekly Return of Communicable Diseases (WRCD) Form H 399. Data for completion of this form is collected from the Office Notification Register and the Infectious Disease Register. MOH is expected to verify each completed WRCD against the Office Notification Register, Infectious Disease Register and the previous week's WRCD. This form, signed personally by the Medical Officer of Health (MOH), should be posted to the Epidemiology Unit along with forms H 411a (for each confirmed case) by every Saturday with a copy of WRCD to the Regional Epidemiologist. An office copy of WRCD should be retained.

Data on communicable diseases received through WRCD from MOH areas in the country are entered daily in a central database at the Epidemiology Unit and consolidated at the end of every week. These consolidated data in the form of a summary report is published in the Weekly Epidemiological Report (WER), which is circulated to all health institutions in the country completing the feedback link in the national disease notification chain. Data on notified communicable diseases are also summarized quarterly in the Quarterly Epidemiological Bulletin published by the Epidemiology Unit. Both publications WER and the Quarterly Epidemiological Bulletin (QEB) are available at the official website www.epid.gov.lk.

Also, the Annual Health Bulletin published by the Medical Statistics Unit of the Ministry of Health publishes cumulative data on communicable diseases obtained from WRCD every year.

Special Investigations on Selected Communicable Diseases

Further to the field investigations during routine surveillance of communicable diseases, special investigations are carried out for certain selected diseases. Special investigations are aimed at obtaining more details than the data available through the routine preliminary field investigations for this group of diseases. Information targeted through special investigations includes patients' clinical presentation, laboratory investigations, final outcome and clinical conclusions. It also helps to select the confirmed cases out of the notified suspected cases.

Diseases that require special investigations are;

- ◆ Poliomyelitis/Acute Flaccid Paralysis (AFP)
- ◆ Diphtheria
- ◆ Pertusis
- ◆ Tetanus/ Neonatal tetanus (NNT)

- ◆ Measles
- ◆ Rubella/ Congenital Rubella Syndrome (CRS)
- ◆ Viral Hepatitis
- ◆ Encephalitis (including Japanese encephalitis)
- ◆ Leptospirosis
- ◆ Dengue
- ◆ Cholera
- ◆ Human Rabies
- ◆ Mumps
- ◆ Meningitis
- ◆ Chicken pox

Each disease in this group has a significance that warrants this type of detailed investigations. Out of these 15 diseases, Poliomyelitis/Acute Flaccid Paralysis (AFP), Diphtheria, Pertussis, Tetanus/NNT, Measles, Rubella/CRS, Japanese encephalitis, Hib meningitis, Mumps and Hepatitis B are all vaccine preventable diseases for which protection through immunization is presently offered in the Expanded Programme on Immunization of Sri Lanka (EPI) to the children of the country. Detection and investigation of every single case of vaccine preventable diseases is vital as these cases will indicate a need that necessitates further strengthening of the National Immunization Programme.

Poliomyelitis is a disease that is earmarked to be eradicated under a global programme and therefore it is mandatory that every single case is picked up. As for Measles, CRS, Rubella and Tetanus/Neonatal tetanus (NNT) which are selected to be eliminated from the country, discovery of even a single case is crucial for these elimination programmes.

It should be noted that this group of diseases is also primarily investigated in the field by the MOH staff following routine notification from hospitals similar to other notifiable diseases. For each case of the majority of the above listed diseases reported routinely to the Epidemiology Unit through the WRCD. Disease specific special investigation forms are available at all the MOH offices, to obtain further epidemiological and clinical details on the case.

Depending on the site of special investigations, MOH/MOH team (in field based special investigations) or the Infection Control Nursing Officer (ICNO) of the institution (in hospital based special investigations) is responsible for carrying out the special investigation procedure on clinically confirmed cases on discharge. Completed forms are sent back to the Epidemiology Unit. Special investigations data thus collected are entered into the central database of the Epidemiology Unit and analyzed separately.

Poliomyelitis/Acute Flaccid Paralysis

Case based surveillance in identified 67 sentinel sites for Acute Flaccid Paralysis has been in existence in the country since 1991. This comprehensive surveillance system based on World Health Organization (WHO) guidelines on Global Poliomyelitis Eradication Initiative is aimed at excluding poliomyelitis as a likely diagnosis from each case presenting to the sentinel sites with the relevant clinical presentation. These sentinel sites are hospitals where a Consultant Paediatrician is in place and consists of Base, General, Provincial and Teaching hospitals. Once a case is notified from a sentinel site, it is investigated at the institution by the hospital staff as well as in the field by the MOH team according to the guidelines of the global programme. Regional Epidemiologist is also involved in these investigations at the district level. Relevant returns are received by the Epidemiology Unit from all parties involved in the special investigation process: the institution, MOH office and the Regional Epidemiologist. (Refer *Eradication of Poliomyelitis: A Comprehensive Guide for Medical Officers 2nd Edition 2005*).

Diphtheria, Pertusis and Tetanus/ Neonatal tetanus (NNT)

For these vaccine preventable diseases which require special investigations, the follow up scrutiny is carried out by the MOH. Each case of these diseases notified from an institution to a MOH office is thereafter investigated and reported routinely to the Epidemiology Unit through the WRCD as a confirmed case, MOH should obtain further epidemiological and clinical details on the case through special investigation activities. MOH is responsible for investigating these confirmed cases (for the second time) and sending the completed special investigation forms to the Epidemiology Unit.

Measles, Congenital Rubella Syndrome and Rubella

Since 2005, these vaccine preventable diseases are being specially reported to the Epidemiology Unit through a weekly return from the same sentinel sites which have been identified for AFP surveillance. This is in addition to the routine reporting via the MOH office through WRCD to the Epidemiology Unit. Also, blood samples from reported cases are collected by the reporting site (e.g. Ward, OPD etc) and sent to the Medical Research Institute (MRI) for laboratory diagnosis.

Special investigations for confirmed cases of these diseases take place in the field by the MOH and completed special investigation forms are sent to the Epidemiology unit.

Viral Hepatitis, Chicken pox and Leptospirosis, Mumps

All cases of Viral Hepatitis, chicken pox, leptospirosis and mumps notified to MOH offices from institutions are investigated routinely as well as specially by these MOH teams. Completed special investigation forms for these cases are sent to the Epidemiology Unit by the MOH offices.

Encephalitis (including Japanese encephalitis), Meningitis, Cholera and Human Rabies

All suspected cases of the above diseases are notified from institutions to a MOH office, thereafter investigated by the MOH team and reported routinely to the Epidemiology Unit through the WRCD.

In addition, it is a responsibility of the MOH to carry out the special investigation procedures for confirmed cases of these diseases personally by visiting them on discharge from the hospital. Duly completed special investigation forms are sent to the Epidemiology Unit by the MOH offices.

Dengue fever

All suspected dengue fever cases are notified from institutions to a MOH office, thereafter investigated by the MOH team and reported routinely to the Epidemiology Unit through the WRCD.

In addition, it is the responsibility of the ICNO of the reporting institution to carry out the special investigation procedure on clinically confirmed patients on discharge. Duly completed special investigation forms are sent to the Epidemiology Unit by the ICNOO.

Frequently Asked Questions (FAQs) about immunization

01. What is the new national immunization schedule for EPI vaccines?

The new schedule is given in Chapter on EPI.

02. What are the main changes incorporated to the new schedule compared to the previous one?

a. Change of age of administration of Live JE vaccine from the previous schedule of “on completion of 1 year” to “on completion of 9 months “ in current schedule

b. Change of age administration of 1st dose of Measles Vaccine from the previous schedule of “on completion of 9 months” to “on completion of 1 year” with the administration of the 1st dose of MMR in current schedule

c. Administration of Measles Rubella (MR) Vaccine in the previous schedule at “on completion of 3 years” will be replaced by the 2nd Dose of MMR vaccine in the new schedule.

d. MMR vaccine could be offered to females in child bearing age (16 – 44 years) as a rubella containing vaccine instead of Rubella Vaccine.

02. From when has the current immunization schedule been in operation in Sri Lanka?

The new schedule has been in operation from the 1st October 2011.

03. Why is combination preparation of Measles-Mumps-Rubella (MMR) vaccine given on completion of one and three years?

Previously 1st dose of measles vaccine was given at the age of 9 months and 2nd dose given with rubella (MR) at 3 years and no mumps vaccine was given in the national immunization programme. At the time of introduction of measles vaccine into the national immunization programme in 1984, measles transmission in Sri Lanka was high and risk of infection with measles of children age between 9 months and 12 months was high among a proportion of children, whose passively transmitted maternal antibody levels had already waned. However, by the end of 2010, measles transmission in Sri Lanka has already reached elimination levels and risk of transmission of measles between 9 months and 12 months is

Available evidence from national surveillance data has indicated that mumps is increasing in the country. Giving mumps vaccine at early childhood can also prevent mumps complications, particularly among adults.

Hence, it is decided to give the first dose of MMR vaccine containing antigens of measles, mumps and rubella on completion of one year. However, as of many other live vaccines, vaccine efficacy of MMR vaccine is not 100%. Hence, there may be a small proportion of children who will not develop adequate antibodies (vaccine failures) to protect against measles, mumps and rubella. Immunizing them again at 3 years of age will give an additional opportunity to protect these children against these three vaccine preventable diseases and also children who were also not immunized with these vaccines previously. In addition, by immunizing both males and females at early ages, congenital rubella as well as rubella can be controlled in the country.

04. Why is live Japanese encephalitis vaccine given on completion of 9 months?

Vaccination against Japanese encephalitis (JE) was started in 1988, focusing high risk districts in the country. However, national disease surveillance data indicated that all districts are now endemic with the disease and therefore island-wide immunization is necessary. Until the recent past, inactivated JE vaccine was used in Sri Lanka and in 2009 live JE vaccine was introduced into the programme.

A study conducted by the Epidemiology Unit also has indicated adequate high immunogenicity by administration of a single dose of live JE vaccine at the age of 9 months. Available evidence from other countries too have indicated that after 5 years of administration of a single dose of live JE vaccine, the protective efficacy is as high as 96%.

Shifting of 9 months measles vaccination to 1 year MMR vaccination has created a time gap in the national immunization schedule between 6 months (following

the third dose of Pentavalent and OPV vaccinations) to one year. Introducing JE vaccine at 9 months will also avoid this time gap and give an opportunity to the public health staff to closely monitor the health status and development of the infant, until the next immunization of MMR at one year.

05. If the child has been previously vaccinated with inactivated JE vaccine, is it a problem to administer live JE vaccine, if the need has arisen?

No. There is no barrier to shifting inactive JE vaccine to live JE vaccine or vice-versa to complete either vaccine schedule. However, the new immunization schedule is limited only to use live JE vaccine.

06. Why is adult Tetanus-diphtheria vaccine (aTd) given to children at school (10-15 years)?

Outbreaks of diphtheria in adolescents and adults have been reported during the last few years in some Asian and European countries due to the waning of immunity against diphtheria over the years. Re-immunizing them using the adult diphtheria-tetanus combination vaccine can protect these adolescents and young adults, by boosting their immunity against diphtheria and tetanus.

07. Is it acceptable for child to have so many vaccines at once?

Yes. Studies show that kid's bodies (even infants) can handle many shots at once.

Having several vaccines at once is safe, even for a newborn. Combination vaccines protect your child against more than one disease with a single shot.

08. What is combination vaccine?

Combination vaccines are developed to protect against more than one infection (e.g.: DTP-HepB-Hib, MMR). With the invent of combination vaccines, number of injections required to immunize against several diseases are reduced and the number of clinic visits to complete the recommended immunization schedule is also minimized.

Polyvalent vaccines against multiple strains or serotypes of the same infection against are not considered to be combination vaccines (e.g.: OPV). The term “combined vaccines” may also be used to describe the mixture of two separate vaccines in a single vial prior to administration or vaccines that are separately manufactured but combined into one product during the final packaging stages.

Health care workers should never combine products that are intended for separate administration.

09. Haven't we got rid of most of these diseases in this country?

Thanks to vaccines, most diseases prevented by vaccines are no longer common in this country. Even the few cases we have, could very quickly become **tens** or hundreds of thousands of cases if we stopped vaccinating.

It's not uncommon to have measles outbreaks, whooping cough outbreaks and other diseases when vaccination rates drop. Kids that are not fully vaccinated can become seriously sick and spread it through a community.

10. Will the schedule need to be restarted after a long break – for example, if a child has received only one injection of Pentavalent (DPT-HepB-Hib) vaccine, or one dose of Oral Poliomyelitis Vaccine (OPV) in the 1st year, is there a need to start the whole schedule again?

There is no need to repeat doses that have already been given. The vaccine schedule can safely and effectively be continued as if there had been no delay. The usual intervals between further doses should be maintained or reduced to a minimum of 4 weeks interval in the case of the last two doses of pentavalent vaccine. The immune system does not forget the past immune memory.

11. What if a dose was missed?

The immunization course should be resumed. No extra doses need be given.

12. What happens to the rest of the vaccination schedule when an adverse event occurs after the administration of a vaccine?

Mild local reactions are not a reason to avoid giving further doses of vaccine. However, if the reaction is severe, it may be appropriate to omit further doses of the same vaccine. If there has been a severe reaction to Pertussis containing vaccines, it may be necessary to use a preparation without pertussis vaccine (DT) instead of Penta (DTP-HepB-Hib) or Triple antigens (DTP). Such reactions should be reported to the Medical Officer of Health.

13. Should premature babies have their vaccinations delayed?

Babies born prematurely should receive BCG when they are fit to be discharged from the hospital. They should also receive their 1st dose of Pentavalent (DTP-HepB-Hib) and OPV, two months after birth, unless they are seriously ill.

14. Should vaccination be postponed if a child has a cold or a chest infection?

Babies with minor coughs and colds without fever, or those receiving antibiotics in the recovery phase of an acute illness, can be immunized safely and effectively. Vaccination should only be postponed if a child is seriously ill or has high fever. In such cases, vaccination should be arranged for a week or two later.

15. Is acellular pertussis (aP) vaccine safer than whole cell pertussis vaccine?

Both vaccines have excellent safety records and severe reactions are rare. Whole cell pertussis vaccine is more reactogenic and therefore minor and local reactions may be common than acellular vaccine. However, wholecell pertussis vaccine has demonstrated high immunogenic response, which is very important to protect the child against pertussis and disease control.

16. Should children be given a particular vaccine if they have already had that disease? For example, is a past history of measles, rubella or whooping

cough a contraindication to vaccination?

It is safe to immunize against these diseases even if there is a history of prior infection. Vaccination boosts the immunity of an individual who is already immune to measles and it carries no risk. In addition, diagnosis of measles and rubella without laboratory confirmation is very unreliable; so children who appear to have had these diseases should certainly be immunized with measles, MR or MMR vaccine.

17. What are the advantages of Injectable Polio Vaccine (IPV) over Oral Polio Vaccine (OPV)?

IPV does not cause vaccine associated paralytic poliomyelitis (VAPP), since it is an inactivated vaccine. VAPP associated with OPV is extremely rare (1cases per ~ 2 million doses administered). OPV has many advantages than IPV as it will lead to develop herd protection among the community and also avoid all injection related adverse reactions. The National immunization programme recommends the administration of OPV as it is more appropriate to Sri Lankan epidemiological settings.

18. Should a child be immunized if the child's mother is pregnant?

There is no problem with routine vaccine administration to a child whose mother is pregnant. In fact, measles/MR/MMR vaccine given to the child of a pregnant mother will reduce the risk of her being infected by her offspring if she is not immune. Measles, MR and MMR vaccine viruses are not infectious.

19. What if a child has a chronic disease?

In general, children with chronic diseases should be immunized as a matter of priority. Care is needed however, in situations where the child's illness, or its treatment, may result in impaired immunity.

20. What if a child has had a history of fit or has epilepsy?

Stable neurological disease is not a reason to avoid giving pertussis containing vaccines. A child may develop fever after administration of any vaccine; parents should be warned of this and advised to give the child age specific dose of paracetamol. A family history of fits or epilepsy is not a reason to avoid vaccination. You may also consult the family doctor.

21. Should allergic children be immunized?

Asthma, eczema, hay fever and allergies are not contraindications to any vaccine. An important exception is genuine severe egg allergy. A history of an anaphylactic reaction to egg (generalized hives, swelling of the mouth or throat, difficulty in breathing, wheeze, low blood pressure, or shock) is generally a contraindication to influenza and yellow fever vaccines.

Measles/MR/MMR vaccine viruses are not cultured in eggs and the vaccine does not contain egg protein, so these vaccines can be given safely to those with history of allergy to eggs. However, history of allergy to beef is a contraindication to gelatine containing vaccines.

It is important to note, that history of *severe* allergic reactions to food or any other product is not necessarily a contraindication to vaccination. However, when there is any doubt, it is advised to consult a pediatrician or the Epidemiology Unit and such a child should be immunized in an appropriate setting where emergency management can be provided.

22. Isn't natural immunity better than vaccine induced immunity?

While vaccine-induced immunity may diminish with time, 'natural' immunity, acquired by catching the disease, is usually lifelong. The problem is that the wild or 'natural' disease can kill or leave a child permanently handicapped. Children or adults can be re-immunized if their immunity from the vaccines falls to a low level. Vaccines are many times safer than the diseases they prevent.

23. Can too many vaccines overload the immune system?

There is no evidence that this occurs in standard vaccination programmes. All children and adults confront enormous numbers of antigens (substances that provoke a reaction from the immune system) each day, and the immune system responds to each of the antigens in various ways to protect the body. Vaccine antigens have an advantage over their corresponding wild antigens in that the immune response (such as making antibodies) to the wild antigens is usually evident only after a notable illness has occurred. With vaccine antigens, however, the 'illness', if it does occur, is usually insignificant.

24. How can you help a child's immune system function effectively so that it can fight off infections?

Eating, sleeping and exercising adequately will help keep the child's immune system functioning well. Vaccination has an important role to play in protecting children from specific diseases.

25. Is it true that vaccinated children may still contract a disease?

Yes. It is possible, since no vaccine is 100% effective. A small proportion of those who are vaccinated will remain susceptible to the disease. However, in cases in which illness does occur in vaccinated individuals, the illness is usually much less severe than in those who have not been vaccinated.

26. Haven't diseases like polio, tetanus, whooping cough and diphtheria already disappeared from most parts of Sri Lanka? So, do we need to keep immunizing children against these diseases?

These diseases are much less common now, but the bacteria and viruses that cause them are still present. The potential problem is kept in check by routine vaccination programmes. In countries where vaccination rates have declined, the vaccine preventable diseases have reappeared.

27. Do breast-fed children need a different vaccination schedule?

No. Breast-fed children should be vaccinated according to the standard schedule. Breast milk contains small amounts of antibodies, but these do not interfere with the immunization process.

28. Does vaccination cause allergies?

Some children are allergic to particular components of vaccines. However, vaccination does not provoke the development of a general allergic tendency.

29. What if a baby vomits the oral polio vaccine?

It is quite safe to repeat the dose.

30. Should a child with diarrhoea receive Oral Polio Vaccine?

Yes. Oral polio vaccine should be given and an additional dose should be given at the next clinic session i.e. soon after the child has recovered.

31. Are any other vaccines available in Sri Lanka?

Yes. Pneumococcal, Rota virus , Varicella (chickenpox), HPV vaccines and several other vaccines are available in Sri Lanka only in the private sector. Decisions about administering these vaccines to children should be taken after consulting your family doctor.

32. What immunizations do you give to a child with no immunization records?

If there is no satisfactory verbal or written record of immunization, the child should be given immunizations from then on as if they were never immunized previously.

33. For how long after a significant febrile illness should vaccination be delayed?

Vaccination should be delayed until the child has recovered.

34. Does immunization cause asthma?

No. There is no evidence that immunization causes or worsens asthma. It is especially important that children with asthma be immunized like other children, as catching a disease like whooping cough can make an asthma attack worse.

35. How do vaccines differ from other pharmaceutical agents?

A vaccine is “**a biological preparation**” that improves immunity to a particular disease. A vaccine typically contains an agent that resembles a disease-causing microorganism, and is often made from weakened or killed forms of the microbe, its toxins or one of its surface proteins. In contrast a drug is a [chemical substance](#).

When compared to drugs, vaccines are delicate substances that lose potency if they are exposed to temperatures that are **too warm or too cold**. It is useless to vaccinate a child if the vaccine that was used is exposed to high or low temperature than recommended.

The “cold chain” is the name given to a system of people, equipment and devices which ensures that potent vaccine reaches the recipients from the point of production through the correct storage temperature range.

36. How does the national immunization programme ensure vaccines used in it are potent?

Most vaccines used in the national programme are equipped with VVM. Vaccine Vial Monitor (VVM) appeared on vaccine vials has been developed and used to monitor maintenance of the cold chain; damaging vaccine due to heat exposure. However, it does not indicate any exposure to freezing, which is a limitation of the VVM.

New electronic devices such as data lodger, tiny tag, freeze tag are available to monitor the freeze damage to vaccine and are available at all vaccine storage sites

of the national immunization programme.

37. Are Vaccines Safe?

Vaccines are held to the highest standard of safety. The Sri Lankan immunization programme currently has the safest, most effective vaccine supply in history.

Years of testing are required by law before a vaccine can be licensed. Once in use, vaccines are continually monitored for safety and effectiveness. However, like any medication, vaccines can cause side effects.

Before vaccines are licensed, regulatory agencies of the country of origin requires testing to ensure safety. This process can take 10 years or longer. Once a vaccine is in use, the Epidemiology Unit of the Ministry of Health monitors its adverse events (health problems after vaccination) through the [Adverse Event Following Immunization Surveillance System \(AEFISS\)](#). Any hint of a problem with a vaccine prompts further investigations by the Independent Expert Committee. If it finds a vaccine causing a side effect, Ministry of Health will initiate appropriate action in collaboration with the WHO that may include the changing of vaccine labels or packaging, distributing safety alerts, inspecting manufacturers' facilities and records, withdrawing recommendations for the use of the vaccine, or revoking the license of the vaccine.

38. What is WHO prequalification of vaccines?

WHO provides services to UNICEF and other UN agencies that purchase vaccines to determine the acceptability, in principle, of vaccines from different sources for supply to these agencies. There is an established procedure used by the WHO for initial evaluation of candidate vaccines. Re-assessment at regular intervals ensures the continuing quality of vaccines being supplied.

Countries, where national regulatory authority and national laboratory services are not available or lack capacity to make comprehensive evaluation of vaccine quality will use WHO prequalification as an alternative indicator to assure vaccine quality.

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