This Edition
is
Dedicated
to the
Memory
of
Dr Desmond Fernando
MBBS, FCGP, FAAFP
Family Physician
Who was a great supporter of these Guidelines
and
contributed chapters
to the first four editions
TABLE OF CONTENTS

Chapter No | Contents | Page No
---------|----------|--------
Preface   |          | 1      
Introduction |          | 4      
Abbreviations |          | 8      
Precautions before vaccination |          | 14     

Chapter 1 | Immunological basis of vaccination | 16     
Dr Rajiva de Silva

Chapter 2 | BCG | 25     
Prof. Anura Weerasinghe

Chapter 3 | Cholera vaccine | 29     
Dr Risintha Premaratne

Chapter 4 | Diphtheria, tetanus and pertussis vaccine | 33     
Dr Ananda Amarasinghe

Chapter 5 | Haemophilus influenzae type b vaccine | 41     
Dr Ranjan Wijesinghe  
Dr Ranjith Baturuwantudawe

Chapter 6 | Hepatitis A vaccine | 46     
Dr Geethani Galagoda

Chapter 7 | Hepatitis B vaccine | 51     
Prof. Jennifer Perera

Chapter 8 | Human papilloma virus vaccine | 59     
Dr Kanishka Karunaratne

Chapter 9 | Influenza vaccine | 64     
Dr Jude Jayamaha

Chapter 10 | Japanese encephalitis vaccine | 69     
Dr Omala Wimalaratne

Chapter 11 | Measles vaccine | 75     
Dr Paba Palihawadana  
Dr Deepa Gamage

Chapter 12 | Measles, mumps and rubella vaccine | 79     
Dr Prasanna Siriwardena

Chapter 13 | Meningococcal vaccine | 86     
Prof. Jennifer Perera

Chapter 14 | Pneumococcal vaccine | 91     
Prof. Sanath Lamabadusuriya

Chapter 15 | Poliomyelitis vaccine | 97     
Dr Paba Palihawadana  
Dr Deepa Gamage

Chapter 16 | Rabies vaccine | 102    
Dr Omala Wimalaratne

Chapter 17 | Rotavirus vaccine | 112    
Dr Geethani Galagoda

Chapter 18 | Tetanus vaccine | 117    
Dr Kanthi Nanayakkara

Chapter 19 | Typhoid vaccine | 123    
Dr Enoka Corea
<table>
<thead>
<tr>
<th>Chapter No</th>
<th>Contents</th>
<th>Page No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapter 20</td>
<td>Varicella vaccine</td>
<td>127</td>
</tr>
<tr>
<td></td>
<td>Prof. Sirimali Fernando</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dr Neelika Malavige</td>
<td></td>
</tr>
<tr>
<td>Chapter 21</td>
<td>Yellow fever vaccine</td>
<td>133</td>
</tr>
<tr>
<td></td>
<td>Prof. Anura Weerasinghe</td>
<td></td>
</tr>
<tr>
<td>Chapter 22</td>
<td>Immunisation of HIV infected persons</td>
<td>137</td>
</tr>
<tr>
<td></td>
<td>Dr Geethani Galagoda</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dr Lilani Rajapakse</td>
<td></td>
</tr>
<tr>
<td>Chapter 23</td>
<td>Immunisation of the elderly</td>
<td>144</td>
</tr>
<tr>
<td></td>
<td>Dr Kanthi Nanayakkara</td>
<td></td>
</tr>
<tr>
<td>Chapter 24</td>
<td>Passive immunization</td>
<td>148</td>
</tr>
<tr>
<td></td>
<td>Dr Neelika Malavige</td>
<td></td>
</tr>
<tr>
<td>Chapter 25</td>
<td>Adverse events following immunization</td>
<td>154</td>
</tr>
<tr>
<td></td>
<td>Dr Ananda Amerasinghe</td>
<td></td>
</tr>
<tr>
<td>Chapter 26</td>
<td>Management of anaphylaxis</td>
<td>159</td>
</tr>
<tr>
<td></td>
<td>Prof Rohini Fernandopulle</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dr Shalini Sri Ranganathan</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dr Rajiva de Silva</td>
<td></td>
</tr>
<tr>
<td>Chapter 27</td>
<td>Immunisation for international travel</td>
<td>178</td>
</tr>
<tr>
<td></td>
<td>Prof. Jennifer Perera</td>
<td></td>
</tr>
<tr>
<td>Chapter 28</td>
<td>Immunisation in special clinical circumstances</td>
<td>186</td>
</tr>
<tr>
<td></td>
<td>Dr Naomal Gunaratne</td>
<td></td>
</tr>
<tr>
<td>Chapter 29</td>
<td>The storage and transport of vaccines</td>
<td>194</td>
</tr>
<tr>
<td></td>
<td>Prof. Jennifer Perera</td>
<td></td>
</tr>
<tr>
<td>Chapter 30</td>
<td>General information on vaccines</td>
<td>206</td>
</tr>
<tr>
<td></td>
<td>Dr Kanthi Nanayakkara</td>
<td></td>
</tr>
<tr>
<td>Chapter 31</td>
<td>Frequently asked questions</td>
<td>212</td>
</tr>
<tr>
<td></td>
<td>Dr Prasanna Siriwardena</td>
<td></td>
</tr>
</tbody>
</table>

**ANNEXES**

Annex I National Immunization Programme of Sri Lanka

Annex II Vaccines outside National Immunization Programme of Sri Lanka

Annex III Recommendations for route and site of immunization

Annex IV Notification form for adverse events following immunization

Annex V Anaphylaxis event record
PREFACE

As the current President of the Sri Lanka Medical Association (SLMA) it is my privilege to write a foreword to the 5th Edition of one of the most extensively consulted and widely sought after technical publications of the SLMA, “SLMA Guidelines and Information on Vaccines”. First of all on behalf of the Council and the Members of the SLMA I must compliment the team led by Dr. Lucian Jayasuriya and Professor Jennifer Perera for assiduously accomplishing another painstaking revision and update of the 4th edition of this valuable publication. They have given their time and expertise voluntarily and unreservedly in order to provide the essential knowledge and information to the health and medical practitioners to control, reduce and eliminate vaccine preventable diseases in Sri Lanka. Dr. Jayasuriya in particular deserves the highest credit for having steered this process with a missionary zeal since its inception in 2001.

The editors have ensured that the book is very comprehensive and eminently practical by including expert guidance on immunization related issues such as surveillance and prevention of adverse reactions, management of anaphylaxis, immunization for international travel and in special circumstances, and the exceedingly practical aspects of storage and transport of vaccines.

Sri Lanka has over the years been able to prevent thousands of deaths through more equitable access to existing vaccines for all the people of the country. While maintaining these significant achievements, Sri Lanka also needs to maintain the routine immunization coverage targets, further accelerate control of vaccine-preventable diseases and introduce new and improved vaccines as best as possible and in a self-sustaining manner. Sri Lanka, in the coming decade, should also be able to engage with technical partners and spur research and development for the next generation of vaccines and technologies.

The Global Vaccine Action Plan (GVAP) – endorsed by the 194 Member States of the World Health Assembly in May 2012 – is a framework to prevent millions of deaths by 2020 through more equitable access to existing vaccines for people in all communities. WHO has determined that if these immunization-specific goals are achieved, hundreds of millions of cases and millions of future deaths will be averted by the end of the decade, billions of dollars of productivity will be gained, and immunization will contribute to exceeding the Millennium Development Goal 4 target for reducing child mortality (and the target that succeed it post-2015). This general scenario is applicable to Sri Lanka too and hence we should strive to gain the maximum benefits from immunization.

Ever since vaccines were firstly used against smallpox, adverse events following immunization have been reported. As immunization programmes expand to reach even the most remote communities in the country, it is likely that many more events will be temporally linked with vaccine administration. Furthermore, the profound shift in the general public and media interest in adverse events may lead to undue concerns and allegations which may at least temporarily jeopardize immunization programmes. We know that the familiar vaccines, well-tested over decades, have not changed – but the perception regarding their safety may have shifted somewhat and claims may be made against both the old and the newly-introduced vaccines. Sri Lanka, with the WHO assistance has always been on the alert to guarantee vaccine safety for the last 30 years and will continue to do so with the introduction of safer technologies, and the prevention, early detection and management of adverse events.

Traditional EPI vaccines are considered to be among the most efficient uses of scarce health care resources. Today, there are many under-used and new vaccines available and we will have many newer vaccines in the years to come. In the short to medium term, it is likely that these vaccines probably will not cost the few cents per dose the traditional vaccines do, at least at the start, but will probably be relatively more expensive vaccines. How should countries like ours respond in this milieu, in order to ensure that our population is not denied the benefits of such life-saving technology? We will need to obtain complete information, among other things, on their relative cost-effectiveness, interpretability and transferability of the analyses and the comparability of economic...
evaluations of vaccination programmes. I believe the authors and the editors of this book will pay some attention, provide leadership and engage and address some of these practical aspects of the introduction of new vaccines to our national programme. We will need to judiciously introduce newer vaccines into our programmes in a sustainable way.

Finally, the SLMA, while presenting this book for the benefit of all the health professionals of Sri Lanka, is of the firm belief that it will make a useful contribution to the reduction and elimination of vaccine preventable communicable diseases from Sri Lanka. I sincerely thank GlaxoSmithKline for their continued collaboration with the SLMA in the production and the publication of this edition. Their support has been invaluable.

Dr Palitha Abeykoon
President
Sri Lanka Medical Association

INTRODUCTION

Edward Jenner demonstrated the value of immunization against smallpox in 1792. Nearly 200 years later, in 1977, smallpox was eradicated from the world through the widespread and targeted use of the vaccine. The global vaccine scene has changed drastically during the past two decades. The most obvious sign of change is a wave of production of new vaccines that began during the last two decades and continues to date. The new vaccines represent a major advance in the science of discovery as well as in production technologies. This period witnessed the production of several conjugate vaccines, *Haemophilus influenzae* type b (Hib) pneumococcal and meningococcal vaccines. The other major development has been in the successful production of combined vaccines which reduces the number of injections without compromising on the efficacy of individual vaccines. The next step forward was utilization of a new technology, genetic recombination e.g. for the production of influenza, rotavirus and human papillomavirus (HPV) vaccines. Vaccines have been useful in preventing malignancies. The hepatitis B virus vaccine prevents chronic liver disease which in some, results in liver cancer. The human papillomavirus vaccine is targeted to prevent cervical cancer, in which the aetiology is confined to persistent HPV infection. This wave of new vaccines also correlated with new pricing policies, such as tiered pricing to make vaccines more affordable for developing countries. Along with these changes, the formation of the Global Alliance for Vaccines and Immunization (GAVI) and the dedication of new streams of funding led to an emphasis on global vaccination efforts. Thus a number of these new vaccines are already registered for use in Sri Lanka.

With regard to childhood immunization programmes, the World Health Organization (WHO) established the Expanded Programme on Immunization (EPI) in 1974. Through the 1980s, WHO and UNICEF worked together to achieve universal childhood immunization of the six EPI vaccines (BCG, OPV, diphtheria, tetanus, pertussis, and measles) and as a result the current global immunization coverage is over 80%.
New vaccines, pneumococcal conjugate vaccine and rotavirus vaccine against the leading causes of child deaths, pneumonia and diarrhoea, offer new hope.

Vaccination against smallpox was introduced in Sri Lanka under the Vaccination Ordinance as early as 1886. Subsequently BCG was introduced in 1949 and DPT in 1961. This was closely followed by OPV in 1962. Sri Lanka launched the EPI in 1978 and measles vaccination was included into the EPI in 1984. Sri Lanka’s immunization programme is widely recognized as one of the strongest performers in the region and is among the best in the world. It has effectively controlled or eliminated all traditional childhood vaccine preventable diseases through outstanding levels of sustained infant immunization coverage. Throughout the last decade, immunization coverage of infants in Sri Lanka against the six diseases has exceeded 99% as per WHO fact sheet of 2013. In addition the state sponsored, national infant immunization programme introduced the Hep B vaccine in 2003 which was administered simultaneously with the DPT vaccine. Subsequently with the introduction of the *Haemophilus influenzae* type b (Hib) vaccine in 2008, the pentavalent vaccine (DTwP–Hep B – Hib) replaced the DTP and hepatitis B vaccines requiring only a single injection to administer all five vaccines. The introduction of the live Japanese encephalitis (JE) vaccine in 2011 has reduced the number of doses required for effective prevention of JE. The MMR vaccine has been introduced to the childhood immunization programme in 2011 and has replaced the measles and measles-rubella vaccines and is expected to reduce the morbidity due to deafness, a serious complication of mumps virus infection.

The Communicable Diseases Committee of the Sri Lanka Medical Association reviewed the first edition of this book written by several specialists. It was titled “Guidelines for the use of non EPI vaccines” and was published in 2001. The second edition published in 2004, included the EPI vaccines and was named the “SLMA guidelines on vaccines”. The third edition was published in 2008 and was titled “SLMA guidelines and information on vaccines” and the fourth edition was launched 2011. The revision of the fifth edition of the book was commenced in November 2013. In addition to the updated information on vaccines included in the previous edition, the revised edition contains two new chapters. The first is devoted to provide information on ‘Vaccination of the Elderly’ in the current context where the proportion of people over 60 years is expected to account for 17% of the population by the year 2020. The chapter on “Immunology of vaccination” will enable understanding the rationale behind vaccination schedules, dosing intervals and simultaneous use of multiple vaccines etc. The form used for reporting adverse events following immunization and anaphylaxis events has been revised by the National Immunization Programme to make it more user friendly and has been included in the appendix of the new edition.

These guidelines are intended to provide assistance to practitioners and represent a consensus opinion arrived at, by committee members and authors of chapters based on current evidence. As new information becomes available this edition will be revised. I am grateful to authors of the chapters and the core group who reviewed them, for their dedicated efforts to formulate the revised guidelines. I thank GlaxoSmithKline for their sponsorship during the preparation of the manuscript and for its publication.

This year’s theme of the Sri Lanka Medical Association is “Globalising the Paradox of Sri Lanka’s Health Achievements and Challenges”. Sri Lanka has achieved much in terms of health in spite of numerous challenges such as the thirty year old war and a low GDP. Infectious diseases including vaccine preventable diseases have been controlled to a large extent and currently take second place to non-communicable diseases. High immunization coverage throughout the island has largely contributed to achieving zero or low prevalence rates with regard to vaccine preventable diseases. This has been possible due to availability of effective vaccines and trained staff, government policy on financial commitment and good programme management. The Vaccination Policy that was launched in April 2014 is expected to improve and facilitate the
existing processes towards better delivery of services with regard to immunization.

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

Professor Jennifer Perera  
Chairperson,  
SLMA Communicable Diseases Committee

<table>
<thead>
<tr>
<th>ABBREVIATIONS</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC</td>
<td>airway, breathing, circulation</td>
</tr>
<tr>
<td>ACIP</td>
<td>Advisory Committee on Immunization Practices</td>
</tr>
<tr>
<td></td>
<td>(of the Centers for Disease Control and Prevention)</td>
</tr>
<tr>
<td>AE</td>
<td>accident &amp; emergency</td>
</tr>
<tr>
<td>AEFI</td>
<td>adverse events following immunization</td>
</tr>
<tr>
<td>AFP</td>
<td>acute flaccid paralysis</td>
</tr>
<tr>
<td>AIDS</td>
<td>acquired immunodeficiency syndrome</td>
</tr>
<tr>
<td>APC</td>
<td>antigen presenting cell</td>
</tr>
<tr>
<td>ARSN</td>
<td>Asian Rotavirus Surveillance Network</td>
</tr>
<tr>
<td>ARV</td>
<td>anti-rabies vaccine</td>
</tr>
<tr>
<td>aTd</td>
<td>adult tetanus and diphtheria vaccine</td>
</tr>
<tr>
<td>BCG</td>
<td>Bacillus Calmette- Guerin</td>
</tr>
<tr>
<td>CCID&lt;sub&gt;50&lt;/sub&gt;</td>
<td>cell culture infective dose&lt;sub&gt;50&lt;/sub&gt;</td>
</tr>
<tr>
<td>CDDA</td>
<td>Cosmetics, Devices &amp; Drugs Regulatory Authority</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control</td>
</tr>
<tr>
<td>CD4</td>
<td>cluster of differentiation 4</td>
</tr>
<tr>
<td>CD8</td>
<td>cluster of differentiation 8</td>
</tr>
<tr>
<td>CHDR</td>
<td>Child Health Development Record</td>
</tr>
<tr>
<td>CMVIG</td>
<td>cytomegalovirus immunoglobulin</td>
</tr>
<tr>
<td>CRS</td>
<td>congenital rubella syndrome</td>
</tr>
<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
</tr>
<tr>
<td>DTP</td>
<td>diphtheria, tetanus and pertussis vaccine</td>
</tr>
<tr>
<td>DTaP</td>
<td>diphtheria, tetanus and acellular pertussis vaccine</td>
</tr>
<tr>
<td>DTwP</td>
<td>diphtheria, tetanus and whole cell pertussis vaccine</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>DTP-HepB</td>
<td>diphtheria, tetanus, pertussis and hepatitis B vaccine</td>
</tr>
<tr>
<td>DTaP-HepB</td>
<td>diphtheria, tetanus, acellular pertussis and hepatitis B vaccine</td>
</tr>
<tr>
<td>DTP-HepB-Hib</td>
<td>diphtheria, tetanus, pertussis, hepatitis B and <em>Haemophilus influenzae</em> type b vaccine</td>
</tr>
<tr>
<td>DTaP-HepB-Hib-IPV</td>
<td>diphtheria, tetanus, acellular pertussis, hepatitis B, <em>Haemophilus influenzae</em> type b and inactivated polio vaccine</td>
</tr>
<tr>
<td>DTP-Hib</td>
<td>diphtheria, tetanus, whole cell pertussis and <em>Haemophilus influenzae</em> type b vaccine</td>
</tr>
<tr>
<td>DT</td>
<td>diphtheria and tetanus vaccine</td>
</tr>
<tr>
<td>dTpa</td>
<td>reduced antigen diphtheria, tetanus and acellular pertussis vaccine</td>
</tr>
<tr>
<td>ELISA</td>
<td>enzyme linked immunosorbent assay</td>
</tr>
<tr>
<td>EPI</td>
<td>Expanded Programme of Immunization</td>
</tr>
<tr>
<td>ERIG</td>
<td>equine rabies immunoglobulin</td>
</tr>
<tr>
<td>ETU</td>
<td>emergency treatment unit</td>
</tr>
<tr>
<td>FA</td>
<td>fluorescent antigen</td>
</tr>
<tr>
<td>FHA</td>
<td>filamentous haemagglutinin</td>
</tr>
<tr>
<td>GAVI</td>
<td>Global Alliance on Vaccination and Immunization</td>
</tr>
<tr>
<td>GBS</td>
<td>Guillain Barre Syndrome</td>
</tr>
<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>HAV</td>
<td>hepatitis A virus</td>
</tr>
<tr>
<td>HBV</td>
<td>hepatitis B virus</td>
</tr>
<tr>
<td>HBIG</td>
<td>hepatitis B immunoglobulin</td>
</tr>
<tr>
<td>HBSAb</td>
<td>hepatitis B surface antibody</td>
</tr>
<tr>
<td>HBSAg</td>
<td>hepatitis B surface antigen</td>
</tr>
<tr>
<td>HCW</td>
<td>health care worker</td>
</tr>
<tr>
<td>HDV</td>
<td>hepatitis D virus</td>
</tr>
<tr>
<td>HDV</td>
<td>hepatitis D virus</td>
</tr>
<tr>
<td>HDC</td>
<td>human diploid cell</td>
</tr>
<tr>
<td>HDCV</td>
<td>human diploid cell vaccine (for rabies)</td>
</tr>
<tr>
<td>Hep B</td>
<td>hepatitis B</td>
</tr>
<tr>
<td>HHE</td>
<td>hypotonic hyporesponsive episode</td>
</tr>
<tr>
<td>Hib</td>
<td><em>Haemophilus influenzae</em> type b</td>
</tr>
<tr>
<td>HibMenC</td>
<td>Hib &amp; <em>Neisseria meningitidis</em> sero group C vaccine</td>
</tr>
<tr>
<td>Hib-PRP</td>
<td><em>Haemophilus influenzae</em> type b conjugated polysaccharide vaccine</td>
</tr>
<tr>
<td>PRP-CRM 197</td>
<td>Non toxic mutant diphtheria toxin</td>
</tr>
<tr>
<td>PRP-D</td>
<td>with diphtheria toxoid</td>
</tr>
<tr>
<td>PRP-T</td>
<td>with tetanus toxoid</td>
</tr>
<tr>
<td>PRP-OMP</td>
<td>with meningococcal outer membrane protein</td>
</tr>
<tr>
<td>HbOC</td>
<td><em>Haemophilus b</em> oligosaccharide</td>
</tr>
<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>HAV</td>
<td>hepatitis A virus</td>
</tr>
<tr>
<td>HBV</td>
<td>hepatitis B virus</td>
</tr>
<tr>
<td>HBIG</td>
<td>hepatitis B immunoglobulin</td>
</tr>
<tr>
<td>HBSAb</td>
<td>hepatitis B surface antibody</td>
</tr>
<tr>
<td>HBSAg</td>
<td>hepatitis B surface antigen</td>
</tr>
<tr>
<td>HCW</td>
<td>health care worker</td>
</tr>
<tr>
<td>HDV</td>
<td>hepatitis D virus</td>
</tr>
<tr>
<td>IFN γ</td>
<td>interferon gamma</td>
</tr>
<tr>
<td>IG</td>
<td>immunoglobulin</td>
</tr>
<tr>
<td>IgA</td>
<td>immunoglobulin A</td>
</tr>
<tr>
<td>IgG</td>
<td>immunoglobulin G</td>
</tr>
<tr>
<td>IL</td>
<td>interleukins</td>
</tr>
<tr>
<td>IgM</td>
<td>immunoglobulin M</td>
</tr>
<tr>
<td>IM</td>
<td>intramuscular</td>
</tr>
</tbody>
</table>
**PRECAUTIONS BEFORE VACCINATION**

1. **Vaccines should not be administered**
   if there was a severe reaction such as anaphylaxis following administration of that particular vaccine or a component of that vaccine. (Exception- refer Chapter 9 Influenza Vaccine)

2. **Live vaccines should not be administered**
   - to a person having a malignancy of the reticulo-endothelial system*
   - during pregnancy
   - if a live vaccine had been administered within one month
   - if the person has had blood or blood products including immunoglobulin within three months
   - for two weeks after stopping long term oral steroids
     \( \geq 2\text{mg/kg/day prednisolone or equivalent or 20 mg/day for > 2 weeks in children or 40 mg/day > 2 weeks in adults} \)
   - for three months after stopping immunosuppressive therapy

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

3. **Postpone vaccination**
   - if the vaccinee is suffering from an acute infection or fever
     \( \text{temperature} > 38.5^\circ C \)

4. **Be cautious if there is**
   - a bleeding disorder
   - a history of Guillain Barre Syndrome
   - a progressive neurological disorder

---

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ThH</td>
<td>follicular helper T cells</td>
</tr>
<tr>
<td>TIG</td>
<td>tetanus immunoglobulin</td>
</tr>
<tr>
<td>TIV</td>
<td>trivalent inactivated vaccine (influenza)</td>
</tr>
<tr>
<td>TST</td>
<td>tuberculin skin test</td>
</tr>
<tr>
<td>TT</td>
<td>tetanus toxoid</td>
</tr>
<tr>
<td>UNICEF</td>
<td>United Nations Childrens Fund</td>
</tr>
<tr>
<td>VAPP</td>
<td>vaccination associated paralytic poliomyelitis</td>
</tr>
<tr>
<td>VDPV</td>
<td>vaccine derived polio virus</td>
</tr>
<tr>
<td>iVDPV</td>
<td>immunodeficiency associated vaccine derived polio virus</td>
</tr>
<tr>
<td>VZIG</td>
<td>varicella zoster immunoglobulin</td>
</tr>
<tr>
<td>VVM</td>
<td>vaccine vial monitor</td>
</tr>
<tr>
<td>VZV</td>
<td>varicella zoster virus</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>WPV</td>
<td>wild polio virus</td>
</tr>
<tr>
<td>YEL-AND</td>
<td>Yellow fever associated neurotropic disease</td>
</tr>
<tr>
<td>YEL-AVD</td>
<td>Yellow fever associated viscerotropic disease</td>
</tr>
<tr>
<td>YF</td>
<td>Yellow fever vaccine</td>
</tr>
<tr>
<td>YF-JE</td>
<td>Yellow fever – Japanese encephalitis chimeric vaccine</td>
</tr>
</tbody>
</table>
5. **Postpone pregnancy**
   - for three months after varicella vaccination
   - for one month after MMR

6. Vaccination should be given in a hospital if there is history of severe allergy.

7. Vaccination should be given only in clinics where the following minimum facilities are available. - adrenaline, syringes, canula, saline and a bed.
   
   It is preferable to have a complete emergency tray. (refer Chapter 25 Management of Anaphylaxis.)

---

**Dr Maxie Fernandopulle MBBS, MRCP**

*Consultant Paediatrician, Colombo.*

---

**CHAPTER 1**

**IMMUNOLOGICAL BASIS OF VACCINATION**

**Introduction**

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

**Normal immune response**

The immune system provides protection against infectious agents. Classically, the system is divided into the innate immune system and the specific or acquired immune system. The innate immune system consists of cells (monocytes, macrophages, dendritic cells, neutrophils, eosinophils and natural killer cells) and molecules (complement, cytokines, chemokines etc) while the specific immune system is composed of lymphocytes. These include B lymphocytes producing antibody, and subsets of T lymphocytes including CD4+ T lymphocytes and CD8+ cytotoxic T lymphocytes. The CD4+T lymphocytes are further divided into T\textsubscript{H}1 cells producing inflammatory cytokines such as interferon \(\gamma\) (IFN\(\gamma\)) and T\textsubscript{H}2 cells, as well as regulatory T cells and T\textsubscript{H}17 cells\(^1,2\).

The innate immune system recognizes the pathogen and subsequently activates the specific immune system\(^3\). Then these two systems act in concert against the infection. Pathogens that enter the body through skin/mucous membranes are taken up by resident antigen presenting cells in these tissues. The main antigen presenting cell (APC) is the dendritic cell, the macrophage being another APC. The antigen presenting cells and molecules of the innate immune system have receptors (pattern recognition receptors) that can recognize conserved foreign molecules found only on pathogens (pathogen associated molecular patterns). Recognition is followed by activation of these cells and molecules. Dendritic cells along with the macrophage, found in the skin and other
sites are crucial in the subsequent activation of the specific immune system. The dendritic cell senses potential ‘danger’ when recognizing pathogen associated molecular patterns. Recognition is followed by uptake of the pathogen and activation of the dendritic cell and other antigen presenting cells.

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

Blood borne pathogens are directly taken up by dendritic cells in the white pulp of the spleen.

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

T and B cells have receptors that recognize antigen. Most circulating lymphocytes recognize non self-antigen. Lymphocytes circulate in the body between blood and peripheral lymphoid tissue (cell trafficking). Activated dendritic cells present peptides derived from pathogens, in conjunction with MHC Class II molecules to CD4+ T cells in the T cell areas of the lymph nodes and spleen. The CD4+ T cell will be activated only if second signals are provided by co-stimulatory molecules on the surface of dendritic cells. These co-stimulators are up regulated only if pathogen associated molecular patterns are recognized by the dendritic cells. As these patterns are only found on pathogens, the dendritic cell will activate non-self reacting CD4+ T cells. Depending on the pathogen and the cytokine milieu around the reaction, the CD4+ T cells become either armed effector T\(_\mathrm{H}^\dagger\) or T\(_\mathrm{H}^\ddagger\) cells or memory cells.

Dendritic cells which are activated by microorganisms such as \textit{M. tuberculosis} produce cytokines that switch a naïve CD4+ T cell to an activated T\(_\mathrm{H}^\dagger\) cell, while helminths and some bacterial pathogens induce a T\(_\mathrm{H}^\ddagger\) response. T\(_\mathrm{H}^\dagger\) cells produce cytokines (IL2, IFN\(\gamma\)) that activate CD8+cytotoxic T lymphocytes, macrophages and B lymphocytes, while T\(_\mathrm{H}^\ddagger\) cells activate B cells by producing IL4, 6 and 13.

B cells that recognize protein antigens need help from CD4+ T cells (T\(_\mathrm{H}^\dagger\) and T\(_\mathrm{H}^\ddagger\)) to produce antibody. The initial B cell response takes place extra follicularly (outside the germinal centre) and produces low affinity IgM and a small amount of IgG. This occurs within a few days of the infection/immunization and is short lived. This is followed by a response in the germinal centre. B cells move into the germinal centre and encounter their cognate antigen found on the surface of follicular dendritic cells. The B cell proliferates, producing a clone of daughter cells whose antigen binding receptors (immunoglobulin molecules found on the surface of the B cell) have undergone point mutations (somatic hypermutation). These mutations are confined to the antigen binding site of the receptor. B cells with receptors with a greater fit (affinity) would bind to the cognate antigen and survive, while those with a weaker fit would undergo apoptosis. The surviving B cells would differentiate into plasma cells or memory B cells. With time, high affinity (affinity maturation) IgG, IgA and IgE antibodies are produced (isotype switching) by plasma cells, some being long lived. Memory B cells are capable of producing high affinity, class switched antibody with great rapidity, after re-exposure to the same microorganism. Affinity maturation, isotype switching and memory need T cell help and are hallmarks of antibody responses to protein antigens. T cell help is provided in germinal centers by follicular helper T cells (TfH cells). This response takes 10-14 days to appear and terminates in 3-6 weeks. Peak antibody concentrations occur 4-6 weeks after primary immunization.

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

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

Protection against intracellular microorganisms is through cell mediated immunity. Viruses infect cells and produce virus derived proteins in the cytoplasm. Peptides derived from these proteins are presented on MHC Class I molecules by all nucleated cells. These are recognized by previously activated cytotoxic T lymphocytes and the infected cell is destroyed. Microorganisms residing in intracellular vesicles of macrophages such as \(M\) \(tuberculosis\), are dealt with by \(T_H1\) cells activating the macrophage, resulting in intracellular killing of the bacteria.

**Vaccines**

Different types of vaccines have been produced\(^5\).

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

**Immune response to vaccines**

Vaccine induced immunity is mainly due to IgG antibodies. Antibodies are capable of binding toxins and extracellular pathogens. The quality of the antibody (avidity), the persistence of the response and generation of memory cells capable of a rapid response to reinfection are key determinants of vaccine effectiveness. For protection against bacterial diseases that result from the production of toxins (tetanus and diphtheria) the presence of long lasting antitoxin antibody and memory B cells are necessary, ensuring the presence of antitoxin antibody at the time of exposure to the toxin. With viruses such as hepatitis B, undetectable antibody titers are seen in many vaccine recipients but due to the long incubation period of the virus, memory B cells can be reactivated in time to combat the infection.

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

Live, inactivated and subunit vaccines evoke a T dependent response, producing high quality antibody and memory B cells. Polysaccharide vaccines (eg. pneumococcal 23 valent vaccine) evoke a T independent response\(^4\) where the IgG produced is of poor quality (affinity) and memory B cells are not produced. However, conjugation of the polysaccharide with a protein (conjugate vaccines) evokes a T dependent response.

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

Antibody responses are ineffective against intracellular organisms such as \(M.\) \(tuberculosis\). There is evidence that a \(CD4 T_H1\) response, with production of IFN \(\gamma\) leading to activation of infected macrophages is elicited following BCG vaccination\(^6\).
The quality of the immune response depends on the type of vaccine. Live viral vaccines evoke a strong immune response.

This is due to:

- having sufficient pathogen associated molecular patterns to efficiently activate immature dendritic cells, a key requirement for the development of specific immunity.
- the vaccine virus multiplying at the site of inoculation and disseminating widely, and being taken up by dendritic cells at many sites. These dendritic cells are then activated and are carried to many peripheral lymphoid organs, where activation of antigen specific B and T lymphocytes occur. As the immune response occurs at multiple sites, live viral vaccines evoke a strong immune response persisting for decades. Due to the early and efficient dissemination of the virus, the site or route of inoculation does not matter (eg. SC versus IM). BCG vaccine acts similarly, by multiplying at the site of inoculation and at distant sites as well.

Non-live vaccines may have enough pathogen associated molecular patterns to activate dendritic cells but in the absence of microbial replication this activation is limited in time and is restricted to the site of inoculation. As the immune response is restricted to the local lymph nodes, it is weaker than with a live vaccine. Therefore, repeated booster doses are necessary. As only the regional nodes are involved, multiple non live vaccines can be given, provided the inoculations are performed at different sites. Booster doses are ineffective with polysaccharide vaccines as memory B cells are not produced.

In addition, the route of inoculation is important. The dermis has many dendritic cells, and for example, the rabies vaccine given intradermally at 1/10th the IM dose can evoke an equally good response. Where the vaccine is not very immunogenic (eg. hepatitis B vaccine), IM injections are preferred over SC as muscle tissue has many dendritic cells, unlike adipose tissue.

Determinants of primary vaccine response

- Intrinsic immunogenicity of the vaccine.
- Type of the vaccine – Live viral vaccines elicit better responses than non-live vaccines. Non-live vaccines rarely induce high and sustained antibody responses after a single dose. Therefore, primary immunization schedules usually include at least two doses, repeated at a minimum interval of 4 weeks to generate successive waves of B cell responses. Even so, the response usually wanes with time.
- Dose – As a rule, higher doses of non-live antigens, up to a certain threshold, elicit higher primary antibody responses. This may be particularly useful when immunocompetence is limited eg. for hepatitis B immunization of patients with end stage renal failure.
- Nature of the protein carrier.
- Genetic composition of the individual.
- Age – responses at the extremes of age are weaker and less persistent.

Determinants of duration of vaccine response

Plasma cells which produce antibodies are usually short lasting, while a few plasma cells produced in the germinal centre may survive for long periods in the bone marrow. These cells are responsible for the maintenance of protective antibodies for long periods. This occurs most efficiently with live vaccines, less efficiently with non-live vaccines, but not with polysaccharide vaccines. Live viral vaccines are the most efficient at evoking long lasting immune responses that may persist lifelong due to the presence of viral antigens that may regularly activate the immune system.

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

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

For non-live vaccines, adjuvants are incorporated to provide the ‘danger’ signal to the antigen presenting cells. Adjuvants are also needed to prolong the antigen delivery at the site of inoculation, thereby recruiting more dendritic cells. They should also be non-toxic.

The known adjuvants used in human vaccines are

- Alum – an aluminum salt-based adjuvant.
- AS04 – a combination adjuvant composed of monophosphoryl lipid A adsorbed to alum.
- Oil-in-water emulsions – such as MF59 and AS03

Summary

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

Live viral vaccines evoke cytotoxic T lymphocyte responses which act against intracellular pathogens. Similarly, the BCG vaccine activates T_{H1} cells, whose cytokines help macrophages control M. tuberculosis. Live viral vaccines produce long lasting, even lifelong immunity compared to non-live vaccines.

References


Dr Rajiva de Silva  Dip. Med. Micro, MD(Micro.)
Consultant Immunologist, Medical Research Institute, Colombo.
CHAPTER 2

BCG

Introduction

Tuberculosis is a chronic disease caused by *Mycobacterium tuberculosis*. Primary infection often goes unnoticed clinically; tuberculin sensitivity appears within few weeks and lesions commonly become inactive. It may progress to pulmonary tuberculosis and extrapulmonary tuberculosis, miliary tuberculosis or meningitis. The only vaccine available for the prevention of tuberculosis is BCG (Bacillus Calmette-Guerin), which was first developed in 1920s.

The coverage of BCG is 99% in Sri Lanka. The Type of vaccine

Live attenuated vaccine

Efficacy

BCG is a relatively weak protective vaccine because only 50% of randomized control trials shows it to be effective.

However, childhood immunization with BCG has caused a remarkable reduction in the incidence of miliary tuberculosis and tuberculous meningitis in children.

Indications

At birth, (including low birth weight babies and before discharge from hospital)

Children between 6 months and 5 years of age without BCG scar. (A tuberculin test is not required up to the age of 5 years)

Children over 5 years and adults who are tuberculin negative (less than 10 mm)

Certain strains of BCG may be useful in the treatment of early bladder cancer.

Dosage and administration

Freeze dried vaccine (1 ampoule of 20 doses) is dissolved in 1 mL of diluent.

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

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

The vaccine should be injected by a trained person, strictly via the ID route, avoiding the SC route. For each injection, use one syringe for ID use fitted with a fine (gauge 27), short (1 cm) bevelled needle. No spirit or antiseptic should be applied over the site before injection. 0.9% NaCl (normal saline) can be used to clean the area. Hold the arm and stretching the skin, introduce the needle with bevel upwards, tangentially to the skin. As soon as the bevel has penetrated the skin, push the plunger gently to introduce the liquid. The injection, administered in the deltoid region of the left arm, should produce a papule with a diameter of about 3-4 mm in infants and 6-8 mm in adults immediately after inoculation.

Administration of BCG to any other site is not recommended.

Administration of BCG should be postponed if an elder sibling had died in the first year of life, due to unexplained causes or infection. The baby should be referred to a consultant for evaluation of his immune status.

Contraindications

Hypersensitivity to any component of the preparation.
Immunodeficiency affecting cell mediated immunity.

HIV infection
(Infants born to HIV positive mothers should be tested for HIV using HIV RNA test offered by the STD/AIDS control programme and if results are negative BCG should be administered).

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

A local reaction is normal after BCG vaccination. A few days after vaccination, an induration develops at the point of injection, gradually changing to a small vesicle and then an ulcer in 2 to 4 weeks. The local reaction usually regresses in 2 to 5 months, leaving a superficial scar.

Adverse effects
In rare cases, an abscess may appear at the point of injection. Axillary or rarely cervical adenitis may occur leading in exceptional cases to suppuration, requiring treatment with anti-tuberculous therapy.

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

Storage
2°C - 8°C

References

Prof Anura Weerasinghe MBBS, MD, DCH, DTM&H, FRCP, FCCP, PhD
Professor of Medicine and Immunology, Dr Neville Fernando Teaching Hospital of South Asian Institute of Technology and Medicine, Malabe.
Visiting Professor, Rajarata University of Sri Lanka.
CHAPTER 3

CHOLERA VACCINE

Introduction

Cholera is an acute intestinal infection caused by the toxigenic Gram negative bacterium *Vibrio cholerae*. The infection is often asymptomatic or mild and self limited. In severe illness, the patient develops profuse painless diarrhoea with characteristic “rice water stools” associated with vomiting, thirst and muscle cramps. This may lead to rapid volume depletion, sometimes resulting in circulatory collapse. Death may occur in severely dehydrated patients within a few hours after the onset of symptoms. The case fatality rate may exceed 50% among untreated severe cases, but is less than 1% with proper and timely treatment. Infection is acquired primarily by ingesting contaminated water or food. The incubation period varies from few hours to 5 days, usually 2-3 days.

Continued occurrence of cholera outbreaks in the world, emergence of new, more virulent strains of *V. cholerae* O1, emergence and spread of antibiotic-resistant strains have raised serious concerns. Since 2010, Haiti is fighting the largest cholera epidemic in the world in 5 decades.

Types of vaccine

Two types of inactivated oral cholera vaccines (OCV) are currently available.

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

Efficacy

The currently available OCVs are safe and offer protection of >50% for at least 2 years among endemic populations. Since immunization does not provide complete protection against cholera infection, all travellers to a cholera endemic country should be cautioned that the best protection against cholera is to avoid contaminated food and water.

Indications

Oral cholera vaccine is recommended for travellers to endemic or epidemic areas. However, currently there is no mandatory requirement for cholera vaccination as a prerequisite for entry into any country.

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

Dosage and administration

The monovalent vaccine is a 3 mL oral suspension, plus a sachet of effervescent sodium hydrogen carbonate granules (buffer). Vaccine and buffer are mixed in either 150 mL of water (for those aged >5 years) or 75 mL (for children aged 2-5 years).


<table>
<thead>
<tr>
<th>Product</th>
<th>Primary immunization</th>
<th>Booster</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monovalent vaccine</td>
<td>Adults &amp; children ≥ 6 years of age</td>
<td>2 doses, more than 7 days apart (but less than 6 weeks)*</td>
</tr>
<tr>
<td></td>
<td>Children 2-5 years of age</td>
<td>3 doses, more than 7 days apart (but less than 6 weeks)*</td>
</tr>
<tr>
<td>Bivalent vaccine</td>
<td>Adults &amp; children ≥ 1 year of age</td>
<td>2 oral doses 14 days apart</td>
</tr>
</tbody>
</table>

* If the interval between doses is longer than indicated, restart primary immunization.

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

**Contra indications**

General contra indications for vaccines are applicable.

**Adverse effects**

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

**Storage**

2° - 8° C. Do not freeze.

**Use of cholera vaccine in outbreaks**

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

**References**


**Dr Risintha Premaratne** MBBS, MPH, MSc, MD

*Consultant Community Physician, Ministry of Health.*
CHAPTER 4
DIPHTHERIA, TETANUS AND PERTUSSIS VACCINE

Introduction

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

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

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

Types of Diphtheria, Tetanus and Pertussis (DTP) Vaccines

The following preparations of Diphtheria, Tetanus and Pertussis vaccines are available

(i) Diphtheria-Tetanus-whole cell Pertussis vaccine (DTwP)

Diphtheria, tetanus and pertussis adsorbed vaccine is prepared by combining purified diphtheria toxoid, purified tetanus toxoid and suspensions of B. pertussis organisms that have been inactivated, usually by formalin. The antigens are adsorbed onto aluminium phosphate adjuvant.

Each DTaP 0.5 mL dose contains diphtheria toxoid ≥ 30 IU, tetanus toxoid ≥ 40 IU and B. pertussis ≥ 40 PU adsorbed onto aluminium phosphate ≥ 1.5 mg.

(ii) Diphtheria-Tetanus-acellular Pertussis vaccine (DTaP)

The DTaP vaccine contains purified diphtheria toxoid, purified tetanus toxoid and inactivated pertussis toxin either alone or in combination with other B. pertussis components such as filamentous haemagglutinin (FHA), fimbrial antigens and pertactin.

Each DTaP 0.5 mL dose contain diphtheria toxoid ≥ 30 IU, tetanus toxoid ≥ 40 IU and B. pertussis toxoid 25 mcg, FHA 25 mcg and pertactin 8 mcg. The antigens are adsorbed onto aluminium salt adjuvants.

(iii) Diphtheria and Tetanus Vaccine Adsorbed (DT)

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

Each 0.5 mL dose of DT contains diphtheria toxoid ≥ 30 IU and tetanus toxoid ≥ 40 IU and adsorbed onto aluminium phosphate ≥ 1.5 mg.

(iv) Diphtheria and Tetanus Vaccine Adsorbed for Adults and Adolescents (aTd)

Vaccines of lower potency are used for immunization of children aged over 7 years and adults. This reduction of diphtheria toxoid potency minimizes reactogenicity at the injection site but is still sufficient to provoke an antibody response in older children and adults.
Diphtheria and tetanus vaccine adsorbed for adults and adolescents is prepared by combining purified diphtheria toxoid and purified tetanus toxoid. The antigens are adsorbed onto aluminium phosphate adjuvant.

Each 0.5 mL dose of aTd contains diphtheria toxoid $\geq 2$ IU and tetanus toxoid $\geq 40$ IU adsorbed onto aluminium phosphate $\geq 1.5$ mg.

(v) Reduced-antigen Diphtheria Tetanus acellular pertussis vaccine (dTpa)
Each 0.5 mL dose of dTpa contains diphtheria toxoid $\geq 2$ IU, tetanus toxoid $\geq 20$ IU and B. pertussis toxoid 8 mcg, FHA 8 mcg and pertactin 2.5 mcg.

(vi) DTaP-HepB vaccine (Please see Chapter 7 for more details)
(vii) DTwP-Hib vaccine (Please see Chapter 5 for more details)
(viii) DTwP-HepB-Hib (pentavalent vaccine) (Please see Chapters 5 and 7 for more details)
(ix) DTaP-HepB-IPV-Hib (hexavalent vaccine)

Combined triple Diphtheria, Tetanus and Pertussis vaccines (DTwP), has been part of the Immunization Programme of Sri Lanka from 1961 and in 2004 combined pentavalent DTwP-HepB-Hib vaccine was introduced$^1$.

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

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

High-efficacy levels can be obtained with both wP and aP containing vaccines$^2$. However, the best aP vaccines have higher efficacy than low-efficacy wP vaccines, but they may be less efficacious than the highest-efficacy wP vaccines in preventing pertussis$^2$. Available limited data on the interchangeability of pertussis vaccines shows that changing among or within the wP and aP vaccine groups is unlikely to interfere with the safety or immunogenicity of these vaccines$^2$.

Revaccination of adults against diphtheria and tetanus every 10 years may be necessary to sustain immunity in some epidemiological settings$^{3,4}$. In order to prevent allergic reactions to the protein of diphtheria toxoid, the quantity of the toxoid has been markedly reduced in these adult vaccines.

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

(ii) Adsorbed diphtheria and tetanus vaccine (DT)
- It is recommended for children immediately before school entry (on completion of 5 years), preferably after at least 3 years from the last dose of the primary course.
• For primary immunization of children, when immunization against pertussis antigen containing vaccine (DTP) is contraindicated.

(iii) Diphtheria and tetanus vaccine adsorbed for adults and adolescents (aTd)
• For primary vaccination and re-vaccination of adults and adolescents, who are having contraindications for DTP primary vaccination and re-vaccination of children older than seven years. (In Sri Lanka, aTd is given at the age of 10-12 years).

(iv) Reduced antigen diphtheria tetanus acellular pertussis vaccine (dTpa)
• For booster vaccination against diphtheria, tetanus and pertussis of individuals from age six years onwards.

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

Contraindications for DTwP
This vaccine should not be given to persons who showed a severe reaction to previous doses of DTwP vaccine:
• an extensive area of redness and swelling which becomes indurate and involves most of the antero-lateral surface of the thigh or a major part of the circumference of the upper arm
• bronchospasm; laryngeal oedema
• encephalopathy within 7 days of administration of a previous dose of DTwP and not attributable to another identifiable cause
• prolonged inconsolable screaming lasting more than 3 hours
• convulsions occurring within 72 hours
• progressive neurological disorder (e.g. infantile spasms)

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

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

Neither a personal or family history of allergy, nor non progressive neurological conditions such as cerebral palsy or spina-bifida are contraindications to immunization with DTP.

Precautions
There are certain groups of children to whom the administration of pertussis vaccine requires special considerations. For these, the risk from vaccine may be higher, but the adverse effects of pertussis could be more severe. The balance of risk and benefit should be assessed in each case. Where there is doubt, appropriate advice should be obtained from a paediatrician before a decision is made to administer the vaccine.

• Acute illness is not a contraindication. Vaccination should be postponed until child has recovered.
• Temperature of 40.5°C or higher within 48 hours after vaccination with a previous dose of DTwP/DTaP
• Collapse or hypotonic hyporesponsive episode (HHE) within 48 hours after receiving a previous dose of DTwP/DTaP
• Convulsions within 72 hours after receiving a previous dose of DTaP
• Children with a documented history of cerebral damage in the neonatal period
• Children with a history of convulsions
Adverse Effects

While in terms of severe adverse events, DTaP and DTwP vaccines appear to have the same high level of safety, mild adverse reactions are relatively common with DTwP vaccine.

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

DTP Vaccine

- **Local reactions**
  Pain, redness and swelling at the injection site may occur and persist for several days; persistent nodules at the injection site may arise if the injection is not given deep enough.

- **Systemic reactions**
  Headache, lethargy, malaise, myalgia and pyrexia may occur uncommonly; anaphylactic reactions and urticaria may occasionally occur and, rarely peripheral neuropathy.

The common, non specific reactions such as crying, screaming and fever may occur for the pertussis component in DTP vaccine. These reactions may also occur after vaccines which do not contain the pertussis component. Attacks of high pitched screaming, episodes of pallor, cyanosis, limpness, and convulsions as well as local and general reactions have been reported. Neurological events including convulsions and encephalopathy may rarely occur after the pertussis component.

DT Vaccine

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

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

Storage

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

References


Dr Ananda Amarasinghe MD
Consultant Epidemiologist, Ministry of Health.
CHAPTER 5

HAEMOPHILUS INFLUENZAE TYPE B VACCINE

*Haemophilus influenzae* type b (Hib) is a common cause of bacterial meningitis, pneumonia and septicemia in children\(^1\). The incidence of meningitis due to Hib in children in Sri Lanka, prior to introduction of the Hib vaccine was estimated to be one of the highest in Asia\(^2\). With the growing antibiotic resistance, immunization has become an increasingly effective means of preventing Hib disease. By mid 2014, 190 countries had Hib vaccine in their National Immunization Programmes (NIP)\(^3\). Out of these 190 countries, three countries (Belarus, India and Indonesia) have partially introduced this vaccine. Thailand and China are yet to introduce Hib vaccine in to their NIP.

**Types of Vaccine**

All currently licensed Hib vaccines are conjugated vaccines. In conjugated Hib vaccines the Hib capsular polysaccharide, polyribosylribitol (PRP) is conjugated to a protein carrier. The conjugated protein carrier induces a long lasting T cell dependent B cell immune response to the PRP polysaccharide and immunological memory\(^4\). Currently available following three Hib conjugated vaccines differ in terms of the type of proteins conjugated to the Hib capsular -PRP polysaccharide\(^5,6\):

(i) Non toxic mutant diphtheria toxin CRM 197 (PRP-CRM197)

(ii) Tetanus toxoid (PRP-T)

(iii) Meningococcal outer membrane protein (PRP-OMP)

A diphtheria toxoid (PRP-D) conjugated vaccine was withdrawn from the market because it was less immunogenic in children under 18 months of age\(^7\).

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

Available Hib vaccines in combination are as follows\(^5\):

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

**Efficacy**

Hib conjugated vaccines are efficacious from early infancy. Though there is evidence of a decrease in antibody levels (over time), in most instances the immunity following the primary series is protective during the years of the highest susceptibility to invasive Hib disease. Except for PRP-D, all other conjugate Hib vaccines have demonstrated remarkably high, consistent efficacy and effectiveness against Hib invasive disease\(^5\).

All Hib conjugated vaccines induce a strong response when given as a booster dose in the second year of life. There is no difference in the immune response to monovalent or combined Hib vaccines\(^8\). However, Hib conjugate vaccines in combination with acellular pertussis antigen induce a lower antibody response than Hib conjugate vaccines in combination with whole cell pertussis antigen or Hib conjugate vaccines separately administered with the DTP containing acellular pertussis antigen\(^5\).

Use of Hib conjugate vaccine has led to a decline of greater than 90% of Hib invasive disease in countries where the vaccine was introduced. Nasopharyngeal colonization has been drastically reduced in populations with high Hib vaccine coverage. This has resulted in greater reduction in the Hib disease incidence than can be directly attributed to the effects of the vaccine suggesting that herd protection is induced by the widespread use of the Hib vaccine\(^6\).
**Indications**

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

Children under two years of age, who have had invasive Hib disease, need the full course of immunization as natural infection does not reliably produce protective immunity. Re-immunization should be initiated approximately one month after the onset of disease.

**Dosage and administration**

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

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

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

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

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

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

**Contraindications**

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

**Adverse effects**

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

**Local reactions** – redness, pain and swelling at the injection site

**Systemic reactions** – fever, loss of appetite, restlessness, irritability, vomiting, diarrhoea and unusual crying.

**Storage**

2°C-8°C
References


**CHAPTER 6**

**HEPATITIS A VACCINE**

Introduction

Hepatitis A virus (HAV) produces an acute hepatitis after an average incubation period of 28 days (range 15 - 50 days) and it is transmitted by the faeco-oral route. In children <16 years, about 70% of the infections are asymptomatic and they shed the virus for longer periods compared to adults, lasting up to 10 weeks after the onset of illness. Viraemia occurs soon after infection. However, the concentration in blood is much lower than in stools. A person is most infectious from 14-21 days before and through 1 week after the onset of symptoms. Complications of hepatitis A include relapsing hepatitis, cholestatic hepatitis and fulminant hepatitis. Fulminant hepatitis leading to liver failure with mortality occurs in less than 0.5% but this increases up to 2% in adults over 50 years. Acute liver failure is more common in pregnancy and in alcoholics with liver disease. HAV does not cause a chronic infection and there are no carriers of the virus. HAV has been transmitted by transfusion of blood and blood products collected from donors during their viraemic phase of infection. Sexual transmission can occur especially among men who have sex with men (MSM).

Outbreaks of hepatitis due to HAV continue to occur in Sri Lanka and several large outbreaks have been reported. Globally, an estimated 1.5 million clinical cases of hepatitis A occur each year. In a hospital based study conducted in Colombo in 2002, seroprevalence for hepatitis A virus was 10.8% in children aged 1 to 12 years. However, according to studies in the South East Asia there is about 75% seroconversion by adolescence.

Types of vaccines

Two types of vaccines are available worldwide.

- Inactivated vaccines (formaldehyde inactivated)
- Live, attenuated vaccines (available only in China and India)
The preparations of inactivated vaccines available in Sri Lanka include:

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

**Efficacy**

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

**Indications**

**Pre-exposure prophylaxis:** Recommended for

- Individuals over 12 months of age
- Travellers to high endemic areas
- Persons with occupational risk
  - Armed forces, persons working in natural disaster or war affected areas, day care staff, hospital workers, laundry and cleaning staff, sewage workers
- Persons at high risk due to lifestyle
  - Intravenous drug users, MSM
- Persons at high risk due to medical conditions
  - Contacts of patients, patients needing repeated transfusions of blood and blood products, persons with chronic liver disease, persons with developmental disabilities
- Food handlers
- Children, adolescents and high risk persons during hepatitis A outbreaks

**Post-exposure prophylaxis**

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

**Normal human immunoglobulin (NHIG)**

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

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

**Hepatitis A vaccine**

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

**Dosage and Administration**

**Monovalent vaccine**

Two doses given at 6-12 month intervals, IM to the deltoid muscle

- 1-15 years - 0.5 mL
- ≥ 16 years - 0.5 or 1.0 mL (depending on the type of vaccine)

Different vaccine brands can be interchanged.

**Combined vaccine:** A combination vaccine containing inactivated hepatitis A and recombinant hepatitis B vaccine is available for use in persons over one year. The combination vaccine is given as a 3-dose series, at 0,
1 and 6 months.
1-15 years - 0.5 mL
≥ 16 years - 1.0 mL

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

Hepatitis A vaccines can be administered simultaneously with vaccines against diphtheria, tetanus, pertussis (DTP), polio (oral and inactivated), *Haemophilus influenzae* type b (Hib), measles, mumps, rubella, typhoid (oral and intramuscular), hepatitis B, Japanese encephalitis, rabies and yellow fever. This can be safely administered to immunocompromised patients including HIV\(^5,6\). It can also be given to pregnant women at risk of developing hepatitis A\(^6\).

**Contraindications**

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

**Adverse Effects**

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

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

**Storage**

2°C-8°C. Do not freeze.

---

**References**


**Dr Geethani Galagoda** Dip. Med Micro, MD
*Consultant Virologist, Medical Research Institute, Colombo.*
CHAPTER 7

HEPATITIS B VACCINE

Introduction

Hepatitis B, is caused by hepatitis B virus (HBV), which produces an illness that is clinically indistinguishable from other forms of hepatitis. It is a significant cause of acute and chronic hepatitis in the world. Acute infection is frequently symptomatic in adults, though usually asymptomatic in young children, particularly infants. Fulminant hepatitis could occur in 0.1-0.6% of acute cases\(^1\). The sequelae of chronic HBV infection vary from an asymptomatic chronic carrier state, to the development of chronic hepatitis, cirrhosis and hepatocellular carcinoma. The rate of progression from acute to chronic hepatitis B is primarily determined by the age of infection, the rate being approx. 80-90% for those infected during the first year of life, 30-50% for infections between the ages 1-4 years, and 5-10% for adult-acquired infection\(^1\). Immune tolerance to viral antigens acquired at birth is believed to play an important role in neonatal HBV persistence, by preventing HBV infection, hepatitis B vaccine also protects against hepatitis D virus (HDV) infection.

Worldwide an estimated 2 billion people have been infected including 350 million with chronic hepatitis B infection. Carrier prevalence of HBV varies in different parts of the world, and may be quite variable within countries. Sero-epidemiological studies done in Sri Lanka have shown varying hepatitis B virus surface antigen (HBsAg) prevalence rates ranging from 0.1 to 2.5%\(^2\).

HBV, though similar to HIV in its primary routes of transmission, is hundred times more infectious than HIV. It is transmitted parenterally, sexually, vertically and horizontally. However, in a significant proportion of patients the route of transmission cannot be determined. The hepatitis B virus can survive outside the body for at least seven days and can be a source of infection\(^1\).

Types of Vaccine

Recombinant hepatitis B vaccine was introduced in 1986 and has replaced the plasma-derived hepatitis B vaccine. The recombinant vaccine contains HBsAg and alum is used as an adjuvant. In certain preparations thiomersal is present as a preservative. A new recombinant hepatitis B vaccine that is intended for adult patients with renal insufficiency uses alum and lipid A as adjuvants. These potentiate the immune response and thereby elicit a long standing antibody response after vaccination\(^1\). The vaccine is available as monovalent formulations or in combination with other vaccines, including DTwP, DTaP, Hib, hepatitis A and IPV (please refer Chapter 4).

Efficacy

Efficacy is determined by the presence of an anti-HBs antibody titre of >10 mIU/ml, 1-2 months after the administration of the last vaccine dose. Following vaccination, a protective antibody titre is present in >95% for infants, children and young adults. The duration of protection is over 20 years in healthy persons. The antibody response rate reduces primarily with ageing, in chronic disease, HIV infection, smoking and obesity\(^1\).

Post vaccination efficacy should be tested in:
   a) people at risk of occupationally acquired infection, e.g. healthcare workers (HCW)
   b) infants born to HBsAg-positive mothers
   c) chronic renal disease patients
   d) people with HIV and other immunocompromised conditions
   e) patients undergoing multiple transfusions

Indications

- All children, adolescents and adults
- Persons at high risk of contracting HBV infection including
  - persons with high-risk sexual behaviour
- partners and household contacts of HBsAg-positive persons
- injecting drug users
- persons who frequently require blood or blood products
- recipients of solid organ transplantation
- those at occupational risk, eg healthcare and emergency care staff
- international travellers to HBV-endemic countries.

• All previously unvaccinated adults aged 19 through 59 years with diabetes mellitus (type 1 and type 2) as soon as possible after the diagnosis.
• At birth for babies born to mothers who have had hepatitis B infection during pregnancy or are hepatitis B surface antigen positive (refer post exposure prophylaxis (PEP) for additional information).
• Post exposure vaccination following needle stick injuries (refer PEP for additional information).

Vaccination schedules
Infants: In the national immunization programme three doses are given to all infants at 2, 4 and 6 months of age.
Children and adults: 3 doses of vaccine can be given at any age, at 0,1 and 6 month schedule.
Travellers and high risk groups: The accelerated schedule of 0,1,2 months and a booster at 12 months.

Contraindications
Hypersensitivity to any of the vaccine components
Anaphylactic reaction to a previous dose of hepatitis B vaccine
Allergy to common bakers yeast.

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

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

Storage
2°C to 8°C. Do not freeze.

POST-EXPOSURE PROPHYLAXIS (PEP)
Prophylactic treatment to prevent infection after exposure to HBV should be considered in the following situations:
1) Percutaneous or permucosal exposure to HBsAg-positive blood
2) Perinatal exposure of an infant born to a HBsAg-positive mother.
3) Sexual exposure to a HBsAg-positive person
4) Household exposure

Dosage and administration
The recommended dose varies by product and with the age of the recipient. Therefore, manufacturer’s recommendation for dosage should be followed.
In most cases, infants and adolescents receive 50% of the adult dose.

The vaccine is administered by IM route. The anterolateral aspect of the thigh is the preferred site of injection for infants and children aged below 2 years; the deltoid muscle is preferred for older children and adults. Administration in the buttock is not recommended as this is associated with decreased protective antibody levels.

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

53
1) **Perinatal exposure**

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

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

- HBIG + HBV vaccine at 0, 2, 4, 6 months as per the National Immunization Programme or
- HBIG + HBV vaccine at 0, 1, 6 months or
- If HBIG is not available HBV vaccine accelerated schedule at 0, 1, 2, and 12 months.

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

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

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

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

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

4) **Sexual partners and household contacts of chronic carriers**

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

5) **Percutaneous or permucosal exposure to HbsAg positive blood**

Management is as in table below:

<table>
<thead>
<tr>
<th>Exposed person Status</th>
<th>Management when source is found to be</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>HbsAg</em>+</td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>HBIG × 1 and initiate HBV vaccination (preferably within 24hrs)</td>
</tr>
<tr>
<td>Vaccinated responder (a person with Anti HBs of ≥10mIU/mL)</td>
<td>No Immunization</td>
</tr>
<tr>
<td>Vaccinated nonresponder*</td>
<td>HBIG × 2 one month apart or HBIG 1 dose and initiate revaccination</td>
</tr>
</tbody>
</table>

(Continued)
Exposed person
Status

<table>
<thead>
<tr>
<th>Management when source is found to be</th>
<th>$HbsAg^+$</th>
<th>$HbsAg$-ve</th>
<th>$HbsAg$ status unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccinated</td>
<td>Test exposed person for anti-HBs. If inadequate ** HBIG x 1 + hepatitis B vaccine dose If adequate no Immunization</td>
<td>No Immunization</td>
<td>Test exposed person for anti-HBs. If adequate no Immunization. If inadequate ** initiate revaccination</td>
</tr>
<tr>
<td>unknown response or partially vaccinated</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

# Post vaccination testing of HCW for anti HBs titres should be done 1 - 2 months after completion of vaccination. If titres are < 10mIU/mL the response to vaccination is inadequate. In such an instance the person should be evaluated for HBs antigen positivity. If HBs antigen is negative a second three dose vaccine series should be given. A vaccine non responder is a person who does not develop protective HBs antibodies after completing 2 full series of hepatitis B vaccine and for whom an acute or chronic hepatitis B infection has been ruled out.


Prof. Jennifer Perera MBBS, MD (Microbiology), DipMedEd (Dundee).
*Senior Professor of Microbiology, Faculty of Medicine, University of Colombo.*

References


CHAPTER 8
HUMAN PAPILLOMAVIRUS VACCINE

Introduction

Cervical cancer is one of the leading causes of cancer morbidity and mortality in women throughout the world. Persistent infection with oncogenic human papillomavirus (HPV) is associated with the development of cervical cancer. Infection with oncogenic HPV types is also implicated in the development of other malignancies including neoplasms of the vulva, vagina, anus and penis. Of the oncogenic HPV types, 16 and 18 accounts for about 70% of cervical cancers. Non-oncogenic HPV types 6 and 11 cause genital warts. HPV is a common asymptomatic infection with an estimated 40% of sexually active women becoming infected during life. HPV infection can lead to both squamous and adenodysplasias, and cancers.

A vaccine to prevent infection with oncogenic HPV types will reduce the incidence of precursor lesions and cervical cancer. Vaccines prevent the disease by producing high level of neutralizing antibodies which is several folds higher than levels produced by natural infection. HPV vaccine is not therapeutic and is not intended to treat patients with cervical cytological abnormalities or genital warts.

Components of the vaccine

The L1 major capsid protein of HPV is the antigen used for HPV vaccine. Using recombinant DNA technology, the L1 protein is expressed in Saccharomyces cerevisiae (yeast).

Types of vaccines

There are two types of vaccines commercially available.

1. Bivalent HPV vaccine – This is a mixture of two HPV type-specific virus like particles prepared from the L1 proteins of HPV 16, and 18 combined with an adjuvant AS04.

2. Quadrivalent HPV vaccine – This is a mixture of four HPV type-specific virus like particles prepared from the L1 proteins of HPV 6, 11, 16, and 18 combined with an aluminum adjuvant (aluminum hydroxyphosphate sulfate). The quadrivalent HPV vaccine contains no thimerosal or antibiotics.

Efficacy

HPV vaccine has a high efficacy for prevention of HPV subtypes 16 and 18 related persistent infection and vaccine type-related cervical intraepithelial neoplasia (CIN) 1/2/3. In addition quadrivalent HPV vaccine prevents genital warts. Recent studies have shown that the vaccine provides significant cross protection against CIN lesions associated with oncogenic subtypes 31, 33 and 45. Clinical significance of this cross protection is yet to be demonstrated.

Duration of protection

Proof of principle trials have shown the vaccine to be highly immunogenic. Follow up studies after 10 years indicate that the antibody level remains high not requiring booster doses. The need for booster doses can only be determined by further follow up data.

Indications

Ideally the vaccine has to be given before sexual debut. Routine vaccination is recommended for females aged 11 to 18 years. The vaccination series can be started as young as age 9 years. Catch-up vaccination is recommended for females aged 18-26 years who have not been routinely vaccinated.

Both quadrivalent and bivalent vaccines are licensed for use in females aged 9 to 45 years.
Dosage and administration

1. Bivalent vaccine – given intramuscularly to the deltoid region as 3 separate 0.5 mL doses. The second dose should be administered 1 month and the third dose 6 months after the first dose.

2. Quadrivalent vaccine – given intramuscularly to the deltoid region as 3 separate 0.5 mL doses. The second dose should be administered 2 months and the third dose 6 months after the first dose.

The vaccine is available as a sterile suspension for injection in a single dose vial or a prefilled syringe.

Vaccination of sexually active women

Sexually active women can receive the HPV vaccine. Women with a history of previous HPV infection will most likely benefit from protection against diseases caused by the other HPV vaccine genotypes with which they have not been infected. The need to continue cervical cytology screening according to the recommended national policies should be emphasized. These persons should be counseled that the vaccine may be less effective in women who have been exposed to HPV before vaccination, than in women with no prior HPV exposure at the time of vaccination.

Cervical cytology screening

Current cervical cytology screening recommendations remain unchanged and should be followed regardless of the vaccination status.

Simultaneous administration with other vaccines

As HPV vaccine is a recombinant vaccine it can be given simultaneously with other vaccines.

Safety and Adverse Events

Side effects are minimal with the most common side effect seen mainly at the injection site as pain, swelling and erythema. Uncommon side effects are gastrointestinal symptoms, pruritus, urticaria, arthralgia, bronchospasm and dizziness and rarely anaphylaxis.

Pregnancy and lactation

HPV vaccine is not recommended for use during pregnancy. There is no evidence to suggest that administration of the vaccine adversely affects fertility, pregnancy or infant outcomes. Women who become pregnant during the course of vaccination should defer subsequent doses until completion of the pregnancy. Vaccination may be resumed soon after delivery. The remaining one or two doses could be given at appropriate intervals without resuming the full course.

Lactating women can receive HPV vaccine.

Immunocompromised persons

It can be administered to females who are immunosuppressed as a result of disease or medications. The immune response and vaccine efficacy might be less than that in persons who are immunocompetent.

Contraindications

Hypersensitivity to any component of the preparation.

Precautions

1. HPV vaccine can be administered to persons with minor acute illnesses. However for persons with moderate or severe acute illnesses vaccination should be deferred until after the patient improves.

2. Syncope could occur after vaccination, most commonly among adolescents and young adults. Vaccine providers should observe vaccinees for 30 minutes after they receive the vaccine.
Storage
2°C-8°C. Do not freeze.

References


Dr. Kanishka Karunaratne MS, FRCOG, FRCS
Consultant Oncological Gynaecological Surgeon, National Cancer Institute, Maharagama.

Introduction
Influenza occurs globally with an annual attack rate estimated at 5%-10% in adults and 20%-30% in children. In temperate regions, seasonal epidemics are experienced mainly during the winter, while in tropical regions influenza occurs throughout the year, causing irregular outbreaks. Vaccination is currently the only effective means of reducing the burden of influenza in the community.

Influenza vaccine contains three influenza viruses: Two influenza A virus strains, A (H1N1) virus and A (H3N2) and one influenza B virus strain in trivalent vaccine and four influenza viruses: Two influenza A virus strains, A (H1N1) virus and A (H3N2) and two influenza B virus strains from each lineage in quadrivalent vaccine. The virus strains in the vaccine change each year based on global surveillance and scientists’ estimations which types and strains of virus will circulate during the next season.

There are two types of vaccine formulations for northern and southern hemispheres. For countries in equatorial regions, epidemiological considerations influence the choice of the vaccine.

Types of vaccine
1. Trivalent inactivated vaccine TIV includes killed virus. This injectable vaccine is approved for use in persons older than 6 months.

2. Intra nasal live attenuated influenza vaccine LAIV – is not recommended for individuals below the age of 2 years, over 50 years and during pregnancy.

* whole virus/ split virus/ subunit
** cold adapted/ genetically re-assorted
Efficacy

Efficacy varies with the recipient’s age and the antigenic match between the virus strains in the vaccine and those in circulation. The vaccine will prevent illness in 70-90% of healthy adults provided that there is a good antigenic match\(^2\).

Estimates of the efficacy or effectiveness of inactivated vaccine among children vary by age, season and study design (confirmation of influenza, outcome parameters). 40%-58% for those aged 6 to 23 months and 60%-74% for those aged 2 years to 5 years\(^3,4\).

Indications:

1. General population
   a. Any person who wish to be protected from flu
   b. Travellers

2. People at high risk for complications
   a. Residents of institutions for the elderly or disabled
   b. Elderly, non-institutionalized individuals with chronic conditions e.g. chronic cardiovascular, pulmonary, metabolic, renal disease, or who are immuno compromised.
   c. All individuals > 6 months of age with any of the conditions listed above.
   d. All persons over 65 years.
   e. Pregnant women – Influenza vaccine containing the killed virus is safe and is recommended for all pregnant women during an influenza season. Pregnant and postpartum women are at higher risk for severe illness and complications.

3. Special groups
   a. Healthcare workers
   b. Household members who are in close contact with high risk persons
   c. Essential services e.g. servicemen

Dosage and administration:

Inactivated vaccine

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Route/site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previously unvaccinated infants 6 months to 3 years</td>
<td>Half the adult dose Two doses 1 month apart</td>
<td>IM/ Anterolateral aspect of thigh</td>
</tr>
<tr>
<td>Previously unvaccinated child 3-9 yrs</td>
<td>Two doses 1 month apart</td>
<td>IM/Deltoid muscle</td>
</tr>
<tr>
<td>Children &gt; 9 yrs and adults</td>
<td>Single dose</td>
<td>IM/ Deltoid muscle</td>
</tr>
</tbody>
</table>

Contraindications:

- Previous reaction to an influenza vaccine
- Infants under 6 months of age
- Hypersensitivity to any component of influenza vaccine
- Acute febrile illness – vaccination should be postponed
Precaution

Egg allergy\textsuperscript{5,6}

Recent published studies (n=28) involving large number of egg allergy individuals revealed that influenza vaccine can be administered without any serious reactions. The reason that egg-allergic patients tolerate egg-containing vaccine is due to very low amount of egg protein\textsuperscript{7,8}.

Adverse effects:

\begin{itemize}
\item Local reactions at the site of the injection – pain, erythema or induration
\item Systemic effects – low grade fever and body aches last for 1-2 days.
\item Guillain-Barré Syndrome – very rare\textsuperscript{4}
\end{itemize}

Storage:

2\textdegree C to 8\textdegree C. Protect from light. Should not be frozen.

References

1. WHO. Vaccines against influenza. WHO position paper - 2012. Weekly Epidemiological Record; No. 47, 87, 461-76.
5. CDC. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), MMWR September 20, 2013 / 62(RR07); 1-43.

Dr Jude Jayamaha
MBBS, MD
Consultant Virologist, National Influenza Centre, Medical Research Institute, Colombo.
CHAPTER 10
JAPANESE ENCEPHALITIS VACCINE

Introduction

Japanese encephalitis (JE) is a disease of public health importance in many Asian countries. It is caused by a flavivirus transmitted to man through mosquitoes and there are several strains of JE viruses identified. It is an infection of the central nervous system characterized by coma, seizures, paralysis, abnormal movements and death in one third of cases and serious sequelae in 40% of survivors. This disease primarily occurs in children and most infections are asymptomatic. The ratio of infection to symptomatic illness has been estimated to vary between 1:25 and 1:300. The incubation period is 4 to 14 days. There is no specific anti viral treatment for JE.

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

Types of vaccine

• Inactivated vaccine – is of 2 types

1. Vaccine prepared from suspension of mouse brain infected with JE virus (JEV).
   Nakayama strain – Freeze dried or liquid
   Beijin strain – Liquid. This strain of vaccine is not available in Sri Lanka at present.

2. Cell culture derived inactivated JE vaccine based on Beijing P-3 strain.
   Manufactured and available only in China, this vaccine provides broad immunity against heterologous JE viruses and high viral yields when propagated in primary hamster kidney cells.

• Live attenuated vaccine (LJEV)

Freeze dried (SA-14-14-2 strain)
The vaccine is prepared in primary hamster kidney cell culture. This vaccine is based on the genetically stable, neuro-attenuated SA 14-14-2 strain of the JE virus, which elicits broad immunity against heterologous JE viruses.

In the National Immunization Programme, all children are immunized with the live JE vaccine on completion of 9 months.

• Recombinant Yellow fever – Japanese encephalitis chimeric vaccine (YF-JE)

A promising approach for a future JE vaccine has been developed, based on the attenuated 17D YF virus genome, in which the yellow fever virus sequences encoding viral structural proteins prM and E sequences were replaced by the corresponding prM and E sequences from JEV strain SA-14-14-2. The resulting YF-JE chimera virus, was grown in vero cells and was shown to elicit JEV neutralizing antibodies. Vaccine was tested in the US, showing good safety and immunogenicity with 94% of the vaccinees in the phase II trial developing protective neutralizing antibodies after a single dose.

This vaccine is licensed for use in Australia (for adults) and Thailand (for both children and adults).
Efficacy

• **Inactivated vaccine**

  The proportion of vaccinees retaining detectable neutralizing antibodies and their geometric mean titres decline rapidly in the first year after the primary 2 doses.

  78-89% of Nakayama strain vaccine recipients and 88-100% of Beijing – 1 strain vaccine recipients had protective antibody levels before the one year booster\(^1\).

  Given that the most frequent occurrence of JE is in infancy and the likely interference with passively acquired maternal antibodies during the first months of life, vaccination is not recommended for children before the age of 6 months. In people whose immunity is unlikely to be boosted by natural infection, repeated boosters are required for sustained immunity.

• **Live attenuated vaccine**

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

  Case control studies of a large vaccine trial in Nepal showed rapid onset of protection followed by a 5 year efficacy of 96% after a single dose of vaccine\(^1\). Subsequently a study was done in Sri Lanka which gave similar results and based on these data, a single dose has been recommended to be used in Sri Lanka\(^4\).

Indications

Inactivated JE vaccine – Children above 1 year of age and adults.
Live JE vaccine – Children above 9 months of age and adults.

Dosage and administration.

• **Inactivated vaccine – In JE endemic countries**

  Freeze dried or liquid vaccine which contains Nakayama strain, the dose for adults and children above 3 years is 1mL administered subcutaneously (SC). Freeze dried vaccine is reconstituted with the diluent provided.

  For children 1-3 years half the adult dose is recommended. One dose each is administered subcutaneously at an interval of 2 weeks and an additional booster dose given after 1 year.

For travellers visiting JE endemic countries

For travelers aged > 1 year visiting endemic countries for at least 2 weeks, the established current practice is to administer 3 primary doses at days 0, 7 and 28; alternatively 2 primary doses are administered preferably 4 weeks apart. When continued protection is required, a booster dose should be given after 1 year.

• **Live attenuated vaccine**

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

  The primary immunization is recommended for children above 9 months of age given SC. A booster dose after 1 year is recommended by the manufacturer.

Contraindications for inactivated JE vaccine

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

Contraindications for live JE vaccine

• Hypersensitivity to any component of the vaccine
• Pregnancy
• Immunodeficiency states (refer chapter 28)
• Leukemia, lymphoma and other malignancies (refer chapter 28)
• History of convulsions during the past 1 year

Though it is not contraindicated, JE vaccine (live or inactivated) should be temporarily postponed in the following instances:-
• fever more than 38.5°C
• acute infectious disease
• acute stage of any chronic illness

The following conditions are NOT contraindications:-
• minor illnesses such as common cold, diarrhoea with temp. below 38.5°C
• stable neurological conditions eg. cerebral palsy, Down syndrome
• treatment with topical steroids or systemic use of steroids at low dosages, less than 0.5mg/Kg body wt
• family history of convulsions.

Adverse effects
Local – pain, induration and redness at site of inoculation.
Systemic – headache, fever, malaise, myalgia, urticaria, nausea and vomiting.

Most of the adverse reactions occur 12-72 hours after the administration of the vaccine. They are more frequent after the 2nd or 3rd doses of inactivated vaccine. These reactions appear to be more common in those with a previous history of urticaria.

Acute encephalitis, shock and anaphylactoid reactions are rare. Encephalitis /meningitis have not been reported following LJEV.

Storage
The vaccine should be stored at +2°C to 8°C. Avoid exposure to direct sunlight. The liquid vaccine should not be frozen. Instructions on the product leaflet should be followed.

References

Dr Omala Wimalaratne MBBS, Dip Med Micro, MD
Consultant Virologist and Vaccinologist, Colombo.
CHAPTER 11
MEASLES VACCINE

Introduction
Measles is a highly contagious disease and one of the leading causes of
death among children globally. According to the World Health Organization,
there are more than 20 million people affected each year and 122,000
deaths in the world in 2012\(^1\). Measles is common in developing countries
particularly in parts of Africa, the Eastern Mediterranean and Asia.

Measles is an acute viral illness which is caused by a virus of the
paramyxovirus family. It spreads by airborne droplets or direct contact
with throat or nasal secretions of infected persons. Measles affects only
humans.

The illness is characterized by high fever, which begins 10-14 days
after exposure to an infected person, followed by an erythematous
maculopapular rash, coryza, cough, conjunctivitis and Koplik’s spots
(pathognomonic enanthem)\(^2\).

The majority of measles related deaths are due to complications especially
in children under the age of 5 years, the elderly and persons with co-
morbidities. Severe measles is more likely in poorly nourished children
especially among those with vitamin A deficiency and in immuno-
compromised patients. Complications of measles include, pneumonia,
diarrhoea, otitis media, blindness and encephalitis (including subacute
sclerosing panencephalitis). The measles virus also causes a depression
in cellular immunity making secondary infections more likely. Furthermore,
the nutritional status may deteriorate and a dormant tuberculous focus
could be activated. Infection during pregnancy carries a risk of miscarriage
and preterm delivery. The leading cause of death in measles is due to
secondary bacterial pneumonia, tuberculosis, encephalitis and precipitation
of malnutrition.

Vaccination has made a major impact on the morbidity and mortality
caused by measles. The measles vaccine was introduced in Sri Lanka in
1984 for infants at 9 months. It led to a remarkable reduction in measles.
However, an outbreak of measles occurred in 1999/2000 with more than
20,000 cases and this lead to the introduction of a 2nd dose of measles
containing vaccine (MR vaccine) in 2001 at the age of 3 years. Following
this measles remained at a low level, with only 51 clinical cases. However
the country experienced an outbreak of measles in 2013 with 4024 clinical
cases\(^3\).

Type of vaccine
- Live attenuated, freeze dried (lyophilized) vaccine.
- Vaccine strains: Most of the live, attenuated measles vaccines
  used now originate from the Edmonston strain of measles virus
  which has been propagated in human diploid cells.
  Schwartz strain grown in chick embryo fibroblasts.

Efficacy
Two doses are required for 100% efficacy.
Single measles and incorporated measles containing vaccines (with rubella
and / or mumps vaccines) are equally effective in disease prevention.

Indications
- Primary and booster immunization against measles.
- To prevent infection in susceptible contacts during measles
  outbreaks.

In Sri Lanka, the first dose of measles immunization is given as Measles/
Mumps /Rubella (MMR) vaccine at the completion of 1 year according
to the National Immunization Programme. A second dose is given at 3
years of age with MMR.
Antibodies to measles virus develop faster following vaccination than following the natural infection\(^4\). Therefore, measles vaccine can be used effectively to protect susceptible contacts during an outbreak and is protective, if administered within 3 days following an exposure.

**Dosage and administration**

A single dose of 0.5 mL is administered by deep subcutaneous over the deltoid.

The vaccine should be reconstituted only with the supplied diluent.

It can be safely and effectively administered together with other vaccines but at different sites.

**Contraindications**

- Immunocompromised patients
- Hypersensitivity to any component of the vaccine including neomycin
- Pregnancy

**Precautions**

- In acute febrile illness vaccination should be delayed
- Patients with tuberculosis should be under treatment before vaccination with measles, because of the possible exacerbation risk of tuberculosis\(^4\)
- Persons who are tuberculin skin test (Mantoux) positive may become negative following measles vaccination for up to one month after measles vaccination\(^4\)

**Adverse effects**

Reactions are generally mild. A slight increase in temperature (37.6°C) may occur in 5-15% of those vaccinated. A rash which usually lasts less than 48 hours is observed in 1-2% of those vaccinated. Both the fever and the 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 could occur within few days. Thrombocytopenic purpura occurs in approximately 1/30 000 people who are vaccinated and majority recovers within 6 months\(^2,4\). Risk of anaphylactic reactions are very rare.

**Storage**

2°C-8°C

Protect from light.

**References**


Dr Paba Palihawadana MBBS, MSc, MD
Chief Epidemiologist, Epidemiology Unit, Ministry of Health.

Dr Deepa Gamage MBBS, MSc, MD
Consultant Epidemiologist, Epidemiology Unit, Ministry of Health.
CHAPTER 12
MEASLES, MUMPS AND RUBELLA VACCINE (MMR)

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

Measles

Please see chapter 11.

Mumps

Mumps generally occurs during childhood. The clinical case definition of mumps is an acute onset of unilateral or bilateral, tender, self-limiting swelling of the parotid or other salivary glands lasting more than 2 days and without any other apparent cause. Mumps is an acute viral illness caused by an RNA virus in the Paramyxoviridae family transmitted by respiratory droplets. After 3-5 days of viraemia the virus spreads to multiple tissues, such as salivary glands, pancreas, testes, ovaries and the meninges, leading to parotitis, orchitis and aseptic meningitis. Parotitis is the most common manifestation (30-40%). Parotitis may be unilateral or bilateral, and any combination of single or multiple salivary glands may be observed.

The incubation period of mumps is 14-18 days (range: 14-25 days).

Complications

Infections occurring in adults would be more likely to cause complications than in children. Asymptomatic occurrence of aseptic meningitis is common (50-60%). Symptomatic meningitis occurs in up to 10% of patients and resolves without sequelae in 3-10 days. Adults are at a higher risk of developing this complication than children and boys are more commonly affected than girls (3:1). Parotitis may be absent in as many as 50% of patients. Orchitis is a commonly reported complication among post pubertal males, but sterility is rare. Oophoritis occurs in 5% of post pubertal females. However, there is no association with impaired fertility. Nerve deafness caused by mumps virus occurs in approximately 1 per 20,000. Encephalitis is rare (less than 2 per 100,000). Other rare complications include arthritis, thyroiditis, mastitis, glomerulonephritis, myocarditis, pancreatitis, cerebral ataxia and transverse myelitis. Mumps during the first trimester of pregnancy is associated with an increased incidence of spontaneous abortions. Nevertheless, there is no evidence to suggest any link with congenital malformations.

Rubella

Rubella is an acute viral infection which generally results in mild disease in children and adults. It is characterised by low grade fever, a generalised erythematous maculopapular rash and lymphadenopathy, commonly suboccipital, post auricular and cervical. It is caused by a togavirus which is spread by droplets and through direct contact with nasal and throat secretions of infected persons. The incubation period is generally 2-3 weeks. 25-50% of rubella infections are subclinical.

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

The risk of congenital defects in the first trimester is approximately 80%, with the risk falling to 10-20% by the 16th week of pregnancy. Since the introduction of rubella vaccination in the NIP, the incidence of CRS has declined, but sporadic outbreaks continue to occur among young adults.
**Type of vaccine**
Live attenuated combined vaccine of a lyophilised formulation

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

**Mumps strains**
- Jeryl-Lynn; RIT4385 (derived from Jeryl-Lynn) and Urabe
  All grown in chick embryo tissue culture

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

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

The effectiveness of the mumps component of the MMR vaccine is lower than that of the measles or rubella components.

It is strongly suggestive that elimination targets of measles, mumps and rubella can be reached with sufficiently high coverage with the 2 dose MMR vaccination programme. Maintaining high MMR vaccination coverage remains the most effective way to prevent outbreaks and also to limit their extent when they occur.

**Indications**
- Susceptible individuals after 1 year of age, adolescents and adults
- Recommended to use when any of the individual components is indicated

**Dosage and administration**
0.5 mL SC. Can also be given IM

In Sri Lanka, the first dose of the vaccine is recommended routinely to children at 12 months of age with a second dose at the age of 3 years.

Children presenting at preschool age, who have not received the first dose of MMR can also be given a dose of MMR followed three months later by a second dose.

The age 11-12 years also can serve as a catch-up opportunity to verify vaccination status and administer MMR vaccine to those children who have not yet received two doses of MMR. The second dose of MMR may be administered as early as 4 weeks after the first dose. Furthermore, individuals of both sexes at school leaving age who have never received MMR can also be offered the vaccine.

**Post exposure prophylaxis**
MMR vaccine is not routinely recommended for prophylaxis following exposure to mumps, measles or rubella as the antibody response to mumps or rubella components is too slow for effective prophylaxis (for measles please refer chapter 11). However, vaccination after exposure is not harmful and may possibly avert later disease. Recent studies have shown that although two MMR doses are adequate in the prevention of mumps in most settings, administering a third MMR dose may be worthwhile in specific outbreak situations. This may lead to shorter duration of virus shedding, boosting of antibody titres and milder clinical manifestations.

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

Precautions

• Pregnancy should be avoided for one month after vaccination. If pregnancy occurs within three months after MMR vaccination, no teratogenicity has been reported. Therefore, there is no indication to consider termination of pregnancy.

• If there is a beef, pork or mutton allergy, such individuals should be vaccinated in a hospital setting where emergency facilities are available, as there can be cross reactions between gelatin and proteins present in beef, pork or mutton.

• Vaccination should be deferred in persons with acute febrile illness.

• If there is a need for tuberculin skin testing (TST) it is recommended to perform the TST before or on the same day as MMR or 4 weeks following vaccination.

Adverse effects

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

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

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

Storage

At 2 - 8°C

MMRV

Combination vaccine against measles, mumps, rubella and varicella (MMRV) is used in Europe, North America and Australia. Seroconversion rates and antibody titers after the first and second doses were similar to those observed after concomitant administration of the MMR and varicella vaccines. MMRV vaccine is currently not available in Sri Lanka.

References


**Dr Prasanna R. Siriwardena**
MBBS, MD (Fam.Med.), MRCGP (INT.), DFM, DCH
*Consultant Family Physician, Piliyandala.*

---

**CHAPTER 13**

**MENINGOCOCCAL VACCINE**

**Introduction**

*Neisseria meningitidis* meningitis has a case fatality rate of 10-20% in industrialized countries. Invasive meningococcal disease causes substantial morbidity. Approximately 10% to 20% of survivors of meningococcal meningitis are left with permanent sequelae such as mental retardation, deafness and epilepsy. *N. meningitidis* is a Gram-negative diplococcus which causes disease only in humans. It is classified into 12 serogroups (A, B, C, 29E, H, I, K, L, W135, X, Y and Z) based on the structure of the polysaccharide capsule. The majority of invasive meningococcal infections are caused by serogroups A, B, C, X, W135 or Y. African meningitis belt, stretching from Senegal in the west, to Ethiopia in the east has the highest annual incidence of meningococcal disease in the world.

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

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

**Types of vaccine**

The capsular polysaccharide vaccines that are used at present are less immunogenic than the conjugated vaccines. Conjugated vaccines are vaccines containing capsular polysaccharides joined to a protein to enhance immunogenicity. These are currently not available in Sri Lanka.

**Unconjugated vaccines (Polysaccharide vaccines)**

a) Bivalent vaccine – contains polysaccharides to serogroups A+C
b) Trivalent vaccine – contains polysaccharides to serogroups A, C, W-135,
c) Tetravalent vaccine – containing polysaccharides to serogroups A, C, W-135, Y(MPSV4)

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

A vaccine for serogroup B is not yet available widely as native B polysaccharide contains epitopes that potentially cross-react with human antigens leading to poor immunogenicity. Very recently a vaccine against serogroup B has been licensed by the European Medicines Agency of the European Commission. This vaccine has also been approved for use in Australia and Canada. In countries where a vaccine is not available for use in serogroup B outbreaks, chemoprophylaxis is recommended for the close contacts and should be ideally given within 24 hours of diagnosis of the primary case. Rifampicin, ceftriaxone or ciprofloxacin is recommended for adults while rifampicin is recommended for children.

There is no vaccine against serogroup X-disease.

**Conjugated vaccines**

a) Group A conjugate vaccine (conjugated to TT) mainly intended for the African Meningitis belt
b) Group CY vaccine (conjugated either to tetanus or diphtheria toxoid)
c) Tetravalent vaccine, conjugated with diphtheria toxoid (MenACWY)
d) A combination vaccine based on *Haemophilus influenza* type b and *Neisseria meningitides* serogroup C vaccine (HibMenC).

The conjugated vaccines are currently not available in Sri Lanka. The duration of protection of conjugated vaccines is longer compared to unconjugated vaccines.

**Efficacy**

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

**Indications**

Not recommended for routine immunization

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

**Dosage and administration**

**Unconjugated vaccine**

Dose 0.5 mL subcutaneously.

The lyophilised preparation of purified polysaccharides should be reconstituted with the diluent which is sterile saline.

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

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

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

Dose 0.5 mL IM

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

Contraindications

- Acute febrile illness
- Hypersensitivity to any component of the vaccine
- Polysaccharide vaccines are not contraindicated in pregnancy
- A history of Guillain Barre Syndrome (GBS) is a contraindication for receiving MenACWY (A history of GBS continues to be listed as a precaution in the package although in June 2010, after reviewing the two safety studies, ACIP voted to remove the precaution for persons with a history of GBS because the benefits of meningococcal vaccination outweigh the risk for recurrent GBS in these persons, and MPSV4 can be given for short term protection (3-5 years).)

Adverse effects

- Local – erythema, slight induration, tenderness or pain at the injection site
- Systemic – Febrile reactions and chills have rarely been observed within 24 hrs of vaccination
- GBS has been reported after MenACWY
- Adverse effects are commoner with MenACWY than with MPSV4

Storage

2°C-8°C

References


Prof. Jennifer Perera MBBS, MD, Dip Med Edu.
Senior Professor of Microbiology, Faculty of Medicine, University of Colombo.
CHAPTER 14  
PNEUMOCOCCAL VACCINE

Introduction

Over one third of deaths among children under five, are caused by pneumonia and diarrhoea. Pneumonia is the single largest cause of death in children globally killing more than 1.5 million children every year. According to WHO, immunisation against pneumococcus, *Haemophilus influenzae* type b (Hib), measles and pertussis is the most effective way to prevent pneumonia. Vaccines are available against all four infections. Pneumococcal disease (*pneumonia meningitis and septicemia*) is recognized as the world’s leading vaccine preventable child killer, which is estimated to cause up to one million deaths in children under 5 years of age annually. There are about 90 distinct serotypes. Globally about 20 serotypes are associated with > 80% of invasive pneumococcal disease occurring in all age groups.

The introduction of the 7-valent pneumococcal conjugate vaccine (PCV 7) has changed significantly the epidemiology of pneumococcal infections, including invasive pneumococcal disease. PCV 7 was first introduced to children in 2000 in USA and within a decade, pneumococcal infections were almost eliminated in that age group. Furthermore, herd immunity has significantly reduced the incidence of such infections in the over 65 year age group, as well as in older children. Although there has been some increase in the incidence of pneumococcal infections caused by serotypes not covered by PCV 7, especially serotype 19A, the overall incidence of pneumococcal disease has been significantly reduced.

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

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

Types of Vaccine

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

1. **Pneumococcal polysaccharide vaccine**
   It contains purified polysaccharide for 23 capsular types of pneumococci.

Efficacy

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

Indications

- Adults over 65 years
- Persons aged over 2 years who are at increased risk of pneumococcal infection
  - Asplenia or severe dysfunction of the spleen
  - Splenectomy – in elective splenectomy, at least two weeks prior to surgery
  - Patients awaiting cochlear implants, at least two weeks prior to surgery
  - Chronic renal disease or nephrotic syndrome
Immunodeficiency or immunosuppression due to disease or treatment, including HIV infection
– Chronic heart disease
– Chronic lung disease
– Chronic liver disease including cirrhosis
– Diabetes mellitus
– Coeliac disease

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

Contraindications
Severe reaction to a previous dose of vaccine.

Precautions
Acute febrile illness. Postpone vaccination until the child is well.

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

Storage
2°C-8°C (should not be frozen)

2. Pneumococcal conjugate vaccine (PCV)
PCVs are more immunogenic than polysaccharide vaccines, especially in children under 2 years of age. Currently 2 types of vaccine are available

PCV 10 and PCV 13, as PCV 7 has been discontinued. In developed countries PCV 7 is being replaced by PCV 13, due to its formulation. PCV 10 provides protection against some non-typeable Hib (NTHi) infections such as acute otitis media.

Indications
Recommended routinely (if affordable) for children mainly under 2 years of age but could be given up to 5 years.

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

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

Dosage and Administration
0.5 ml IM per dose. In USA a 3 dose primary series at 2, 4, 6 months and a booster dose at 12-15 months.

In Europe a 3 dose schedule at 2, 4 and 12 months.
Children between 1-2 years will need 2 doses, with an interval of 2 months.
Children between 2-5 years will need 1 dose only.
Minimum intervals – 4 weeks between doses given before 12 months
– 8 weeks between doses given at/after 12 months

Transitioning from PCV 7 to PCV 10 or PCV 13
Children aged 2 months to 5 years who have not completed the course, complete the course with PCV 10 or PCV 13.
Children under 5 years of age who have completed a PCV 7 series – one dose of PCV 10 or PCV 13 should be administered.

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

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

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

**Storage**
2°C-8°C (should not be frozen)

**References**


**Professor Sanath P Lamabadusuriya** MBE, MBBS, PhD, DSc, FRCP(Eng), FRCP (Edin), FRCPCH (UK), FCCP, FSLCP, FSLCGP, DCH (Lond) Emeritus Professor of Paediatrics, University of Colombo, Consultant Paediatrician.
CHAPTER 15
POLIOMYELITIS VACCINE

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

There are three antigenic types (type 1, 2, and 3) of wild polio virus (WPV) and paralysis can be caused by all three types. At present, WPV type 1 and type 3 are continuing to circulate the most prevalent strain being the type 1. Infection due to WPV type 2 has not been detected since 1999.

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

Polio Endgame Strategic Plan developed by the World Health Assembly 2012, required the withdrawal of OPV containing OPV type 2 and the introduction of at least one dose of inactivated polio vaccine (IPV) as a risk mitigation measure.

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

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

OPV has been used in Sri Lanka since 1963 to successfully combat polio outbreaks.

Efficacy

Oral Polio Vaccine
OPV is highly effective in producing immunity to all 3 types of polio virus. Three doses of tOPV produces immunity to all 3 types in more than 95% of recipients. As with other live virus vaccines immunity from OPV is probably lifelong. OPV produces good mucosal immunity (mainly in the intestines), which helps prevent infection with the wild virus.

Inactivated Poliovirus Vaccine
IPV is highly effective in producing immunity against polio virus and protection from paralytic poliomyelitis. Ninety percent or more of vaccine recipients develop protective serum antibody to all three poliovirus after 2 doses and at least 99% are immune following 3 doses.

Indications
Infants at 2, 4 and 6 months.
Boosters at 18 months and school entry at the age of 5 years.
Both OPV and IPV could be used. However, only OPV is used at present in the National Immunization Programme (NIP) in Sri Lanka. The Ministry of Health is planning to introduce one dose of IPV, in addition to three doses of OPV as an initial step in shifting over from OPV to IPV. This is in conformity to the OPV withdrawal recommendations of WHO.

At the polio eradication end stage and after eradication of polio, shifting over from OPV to IPV is recommended.

**Dosage and Administration**

OPV is administered as 2 drops orally.

One multi dose vial contains 1 mL and contains 10 doses.

Open vial policy is applicable to OPV (see Chapter 29).

Additional doses are recommended during mass campaigns.

Both OPV and IPV could be administered with other vaccines, including, DTP, Hepatitis B, Measles and Hib.

IPV dosage is 0.5mL and can be inoculated either subcutaneously or intramuscularly. When given in combination with other vaccines such as diphtheria, tetanus and pertussis or hepatitis B the vaccine should be administrated intramuscularly.

**Contraindications**

- Moderate or severe acute febrile illness including severe diarrhoea.
- Severe allergy to vaccine or a component of the vaccine.
- OPV should not be given to immunodeficient individuals or household contacts of individuals who have immune deficiency diseases or immune suppression (due to therapy). IPV must be substituted for OPV in these circumstances.

**Adverse effects**

- Local reactions are uncommon.
- Allergic reactions are very rare.

**Vaccine Associated Paralytic Poliomyelitis (VAPP)**

The vaccine virus carries a small risk (2-4 cases/million birth cohort per year) of causing paralytic poliomyelitis in the vaccine recipient and unimmunized close contacts\(^3\). VAPP risk is increased in persons with immunodeficiency\(^2\).

**Vaccine Derived Polio Virus (VDPV)**

In very rare instances, the vaccine virus can genetically change. These mutated viruses may be excreted and can cause paralysis especially in outbreak situations if a population is under-immunized (cVDPV). cVDPV type 2 is the commonest type identified\(^1\). Patients with immune deficiency may also harbor mutated viruses derived from the oral polio vaccine (iVDPV). These strains may be pathogenic, and may cause paralytic poliomyelitis in the patient. Excretion of iVDPV is very rare, and no cases have been reported to date among contacts\(^3\).

**Storage**

**OPV**

At -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.

**IPV**

2°C to 8°C. Do not freeze.
References

Dr Paba Palihawadana MBBS, MSc, MD
Chief Epidemiologist, Epidemiology Unit, Ministry of Health.

Dr Deepa Gamage MBBS, MSc, MD
Consultant Epidemiologist, Epidemiology Unit, Ministry of Health.

CHAPTER 16
RABIES VACCINE

Introduction
Rabies is an acute encephalomyelitis caused by a rhabdovirus. It is primarily an infection of mammals, spread by bites of infected animals. In many parts of the world especially in South East Asia, dogs are the principal reservoir of rabies. Humans are occasionally infected by wild animals, but domestic dogs and cats are responsible for the majority of cases. In Sri Lanka, rabies has been also detected in mongoose, cattle, goats, pigs, bandicoots, jackals, polecats, civet cats, rock squirrels, monkeys, horses and elephants. House rats have not been implicated in the transmission of rabies in Sri Lanka. Human to human transmission also has not been documented.

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

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

Types of Vaccine
Inactivated anti rabies cell culture vaccine
- Human diploid cell vaccine (HDCV)
• Purified vero cell rabies vaccine (PVRV)*
• Purified chick embryo cell vaccine (PCEC)*

*Vaccines available in Sri Lanka at present.

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

Efficacy
100% seroconversion is achieved with a full course of vaccination$^{3,4}$.

Indications
Pre-exposure immunization
Pre-exposure immunization is recommended for the following risk groups
Veterinary surgeons, support staff and vet students
Laboratory staff handling material contaminated with rabies virus
Abattoir workers, animal handlers and vaccinators
Wild life officers
Employees in animal quarantine facilities and zoological establishments

Dosage and administration
Freeze dried vaccine should be reconstituted with the diluent provided. Administration is by IM or SC route.

Primary immunization
Day 0 1 dose administered IM or SC in the deltoid
Day 7 " " " "
Day 28 " " " "

One booster dose is recommended 1 year later and further boosters every 5 years for maintenance of rabies protective antibody levels.

Management of a person who is on pre-exposure anti rabies vaccine
If an exposure takes place, medical advice should be sought immediately regarding booster doses of vaccine.
Following an exposure, irrespective of the severity, two IM doses are recommended on day 0 and day 3.
Administration of rabies immunoglobulin is contraindicated in persons on pre-exposure therapy.

Post-exposure immunization
It is essential to screen the patient and the animal before a decision is made regarding post-exposure treatment (PET)
Choice of therapy depends on screening of the person exposed and also the animal involved in the incident.
If animal concerned is a dog or a cat, is healthy and alive after 14 days following the bite, the person is not at risk of developing rabies$^{3,4,5}$.

Screening the patient – Categorization of the exposure

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

Minor exposures:
- Single, superficial bite or scratch
- Nibbling of uncovered skin
- Contamination of open wounds with saliva
- Drinking of raw milk of rabid cow or goat
Screening the animal

In case of major exposure to dogs and cats:

- If the animal is healthy, observable and has had a minimum of 2 consecutive rabies vaccinations, 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 suspected to have rabies or is sick, but observable, initiate PET while observing the animal. Discontinue treatment if the animal is healthy after 14 days.
- If the animal is having rabies, confirmed by laboratory diagnosis or unobservable (missing, stray or dead) initiate PET and continue the full course.

In case of minor exposure to dogs and cats:

- If the animal is 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 (missing, stray, killed or dead) 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 becomes sick, develops any abnormal behaviour or dies; the patient should be advised to report to the hospital immediately. In case of death of the animal, patient should be encouraged to send the head of the animal for laboratory confirmation of rabies.

The following are not considered as exposures:

- Contamination of intact skin with saliva of a suspected rabid animal
- Petting, bathing or coming in contact with utensils of a suspected rabid animal

Anti Rabies PET: when indicated:

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

Rabies Immunoglobulin (RIG)

RIG available in Sri Lanka at present:

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

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

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

Method of sensitivity testing (ST) for ERIG

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

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

Patient is kept under observation and the ST should be read after 20 minutes. Examine for itching, induration or urticaria or any systemic effects of anaphylaxis. If the initial diameter of the induration is less than 6 mm and the induration after 20 minutes is over 10 mm or if there is any systemic reaction, ST should be considered as positive. Separate fixed needle-syringes should be used for each patient.

The drug of choice in anaphylaxis is 1:1000 adrenaline 0.5 mL given IM immediately. (Dosage for children – please refer Chapter 26)

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

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

However, in a situation where HRIG is not available:

1. If the animal is healthy and observable, the modified 4 site ID ARV schedule could be considered while observing a healthy animal for 14 days. Report to hospital immediately, if the animal goes missing, falls sick or dies during this period.

2. If the animal is suspected of having rabies or is not observable, WHO recommended method of using ERIG under adrenaline and antihistamine in an emergency care facility (ETU, PCU, A&E or ICU) should be considered. In this situation, modified 4 site ID ARV should not be considered as equivalent for RIG and a course of ARV.

Dosage and Administration of RIG

HRIG 20IU/kg body weight
ERIG 40IU/kg body weight

Part of the dose (as much as possible depending on the site) should be infiltrated in and around all wounds. After infiltration if there is any remaining RIG, it should be given deep SC or IM on the thighs. 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.

Anti rabies vaccines (ARV)

Intramuscular /Subcutaneous schedule

Patients with major exposures should be given rabies cell culture vaccine 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.

Patients with minor exposures should be given a total of 4 doses of rabies cell culture vaccine IM or deep SC on the following days.

Day 0 – 2 doses to be given IM or deep SC, one in each deltoid.
Day 7 – 1 dose IM or deep SC
Day 21 – 1 dose IM or deep SC

Intradermal inoculation of rabies cell culture vaccine

ID vaccination schedule has been recommended by the WHO to be used in developing countries where cost is a major limiting factor. The Recommended ID dose is 0.1mL per site for both PCEC and PVRV.

2 Site ID Schedule

One dose (0.1mL) given ID at each of 2 sites in the deltoids on days 0, 3, 7 and 30.
2 site schedule is routinely used in all patients irrespective of the use of rabies immunoglobulin.

Example: Major exposure – rabies immunoglobulin + 2 site ID schedule of anti rabies vaccine.

Minor exposure – 2 site ID schedule of anti rabies vaccine only.

**Modified 4 Site ID Schedule**
Gives an early antibody response when compared to the 2 site ID schedule.

The modified 4 site schedule is helpful in patients with major exposure, who are sensitive to ERIG and the animal is healthy and observable, patients with a minor exposure who come late for treatment or when rabies immunoglobulin is not available in the country.

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

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

Precautions that should be taken when using ID ARV schedules:

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

**Management of patients who have subsequent exposure to rabies infection**

A. After a full course of ARV

For both major and minor exposures: If the animal is **healthy and observable**, PET could be delayed while observing the animal for 14 days.

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

a. Up to 6 months from the last dose of ARV – PET is not indicated.

b. 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 0.1mL, equally distributed over left and right deltoids or prescapular areas.

c. Up to 5 years from the last dose of ARV, RIG is not indicated.

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

B. After a partial course of ARV

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

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

**Adverse effects**

Local – pain, tenderness, erythema.

Systemic – malaise, headache, nausea, mild fever, urticaria.

**Storage**

2°-8°C
References


Further information: Please contact the Medical Research Institute, Tel: 011 2693532-4, 2698660.

Dr Omala Wimalaratne MBBS, Dip. Med. Micro, MD
Consultant Virologist and Vaccinologist, Colombo.

CHAPTER 17

ROTAVIRUS VACCINE

Introduction

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

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

Rotavirus infection in Sri Lanka is a significant cause of morbidity. Several studies and the ongoing rotavirus surveillance studies show that rotavirus causes about 24% of the watery diarrhoeal infections3. Of this, 80% of the infections occur in the age group < 2 years. However, mortality due to rotavirus infection in Sri Lanka is low.

Virology and transmission

Infection is caused by rotavirus which is a member of the genus reoviridae. It is divided into 7 groups A-G out of which only group A infects humans. The virus has 2 surface glycoproteins G and P. The genotypes of rotavirus are based on these glycoproteins. 27 G types and 35 P types have been identified. Out of this 5 G types are seen commonly G1-4 and G9. The common P types are 8, 6 and 4. The most common genotype seen in the developed world is G1 while the developing countries show a more varying scenario. The Sri Lankan genotypes found commonly are G1-3 and G93,4. Rotavirus is shed in very high numbers during acute infection (1012 viral particles per gram of stools). It is transmitted from person to person by
the faeco-oral route via contaminated fomites. Transmission by contaminated food and water is not common. Transmission via the respiratory route has been suggested. It is infectious in low doses (about 100 viral particles). The virus can survive in the environment for days and in stools for months.

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

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

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

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

Indications
Prevention of childhood gastroenteritis due to rotavirus.

Dosage and administration
- **Human monovalent vaccine (2 doses)**
  Lyophilised vaccine to be reconstituted with a diluent (supplied with the vaccine), 1 mL/dose at 2 and 4 months of age. The minimum age for the first dose is 6 weeks and the minimum interval between the doses is 4 weeks. The second dose should be given before 6 months of age.

- **Bovine-human reassortant pentavalent vaccine (3 doses)**
  Liquid vaccine, 2 mL/dose at 2, 4 and 6 months. The minimum age for the first dose is 6 weeks and should be given between 6-12 weeks of age. The minimum interval between the doses is 4 weeks. All 3 doses should be administered before 8 months of age.

Rotavirus vaccine can be given simultaneously with other childhood vaccines including DTaP, Hib, IPV, Hepatitis B, pneumococcal conjugate vaccine and OPV. There is no restriction on breast feeding or other liquid milk, before or after vaccination.

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

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

Adverse effects

Diarrhoea, vomiting, otitis media and nasopharyngitis.

Storage

2-8°C. Protect from light.

References


Dr Geethani Galagoda MBBS, Dip (Med. Micro), MD
Consultant Virologist, Medical Research Institute, Colombo.
CHAPTER 18
TETANUS VACCINE

Introduction

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

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

The disease is characterised by generalised rigidity and spasms of skeletal muscles. The muscle stiffness initially involves the jaw (lockjaw) and the neck, then becomes generalised. The case-fatality rate ranges from 10-90% and, is highest in infants and the elderly\(^1\).

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

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

Protection against tetanus is antibody-dependent and can be achieved only through active (tetanus vaccine) or passive (tetanus-specific immunoglobulin) immunization\(^2\).

Adequate immunization coverage is the key strategy for prevention of tetanus, as there is no place for herd immunity. Passive immunization using tetanus antitoxin, preferably of human origin, is essential for treatment and occasionally for prophylaxis (e.g. in cases of contaminated wounds in incompletely immunized people). While tetanus antitoxin is useful in the management of tetanus, its use cannot substitute the need to achieve and sustain high tetanus vaccination coverage\(^2\).

Type of vaccine

Inactivated toxoid.

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

It is a cloudy white suspension, supplied either in single or multi dose vials. The vaccine may sediment during storage and should be shaken to get a uniform suspension before administration.

If the vaccine contains clumps of material that cannot be resuspended with vigorous shaking, it should not be used.

Vaccine efficacy

In most clinical trials, efficacy has ranged from 80% to 100% following a full course of vaccination\(^2\).

Indications

To prevent tetanus in all age groups.

To prevent neonatal tetanus by immunizing pregnant women.
Active immunization with tetanus toxoid is indicated for all persons who have not been adequately immunized.

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

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

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

**Dosage and administration – for infants and children – refer Chapter 4**

## Dosage and administration – for adolescents and adults

<table>
<thead>
<tr>
<th>Dosage – 0.5 mL of tetanus toxoid or tetanus containing vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>• A history regarding tetanus immunization should always be taken before tetanus toxoid is given for wound prophylaxis.</td>
</tr>
<tr>
<td>• For persons who have not been vaccinated properly or whose vaccination status is unknown – 3 injections are recommended as follows – 1st stat, 2nd 6 weeks later, 3rd 6 months later.</td>
</tr>
</tbody>
</table>

### Vaccines containing tetanus toxoid with recommended potencies³.

<table>
<thead>
<tr>
<th>Vaccines containing tetanus toxoid</th>
<th>Diphtheria</th>
<th>Tetanus</th>
<th>Pertussis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria, tetanus and pertussis vaccine</td>
<td>≥30 IU/dose</td>
<td>≥40 IU/dose</td>
<td>≥40 IU/dose</td>
</tr>
<tr>
<td>DTwP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphtheria, tetanus and acellular pertussis vaccine</td>
<td>≥30 IU/dose</td>
<td>≥40 IU/dose</td>
<td>≥25µg pertussis toxoid</td>
</tr>
<tr>
<td>DTaP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥25µg filamentous haemagglutinin</td>
<td>≥8µg pertactin per dose</td>
<td></td>
</tr>
<tr>
<td>Diphtheria and tetanus vaccine</td>
<td>≥30 IU/dose</td>
<td>≥40 IU/dose</td>
<td></td>
</tr>
<tr>
<td>DT</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Low antigenic diphtheria, tetanus and acellular pertussis vaccine | ≥2 IU/dose | ≥20 IU/dose | ≥8µg pertussis toxoid |
| dTpa                               |            |         |           |
|                                    | ≥25µg filamentous haemagglutinin | ≥2.5µg pertactin per dose | |
| Diphtheria and tetanus vaccine for adolescents and adults | ≥2 IU/dose | ≥40 IU/dose | |
| aTd                                |            |         |           |
| Tetanus toxoid vaccine | -- | ≥40 IU/dose | -- |
| TT                                |            |         |           |
| Diphtheria, tetanus, pertussis, Hib, hepatitis B vaccine (pentavalent) | ≥30 IU/dose | ≥40 IU/dose | ≥40 IU/dose |
| DTP-HepB-Hib                      |            |         |           |
| Diphtheria, tetanus, acellular pertussis, Hib, hepatitis B, and inactivated polio vaccine (hexavalent) | ≥30 IU/dose | ≥40 IU/dose | ≥25µg pertussis toxoid |
| DTaP-HepB-Hib-IPV                 |            |         |           |
|                                    | ≥25µg filamentous haemagglutinin | ≥8µg pertactin per dose | |
• A single dose of TT given to a person who is not immunized against tetanus, will not produce effective immunity.
• Tetanus toxoid need not be given to children with a history of complete immunization with 5 doses of tetanus containing vaccine.
• Adults with a history of immunization with only 5 doses of tetanus toxoid in childhood, need 1 dose.
• Adults with a history of immunization with 6 doses of tetanus toxoid including the 5 received in childhood do not need tetanus toxoid for wound prophylaxis.
• Persons who have had initial tetanus immunization in adolescence or adulthood with 5 doses of toxoid, do not need any doses for prophylaxis².
• A minimum interval of 4 weeks is required or advised between a given dose of TT or aTd and a dose of dTpa when it is indicated⁴.
• A patient who recovers following tetanus will not have adequate natural immunity, and should be started on a full 3 dose vaccine schedule at the time of discharge from hospital.

Route of administration – Deep intramuscularly into deltoid or anterolateral aspect of thigh.

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


Pregnant women with an inadequate or unknown immunization history should receive 2 doses of tetanus vaccine: the first dose administered after completion of 12 weeks of pregnancy and the second dose, after a minimum of 4 weeks interval. The second dose should be given at least two weeks prior to delivery. Effort should be made to complete the recommended series of 5 immunizations while maintaining the minimum intervals between doses³.

Contraindications
Hypersensitivity to any component of the vaccine

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

Storage
2°C-8°C. Do not freeze.

References

Dr. Kanthi Nanayakkara MBBS, Dip. Med. Micro, MD
Consultant Virologist, Medical Research Institute, Colombo 8.
**CHAPTER 19**  
**TYPHOID VACCINE**

**Introduction**

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

Transmission is by food and water contaminated by faeces. The incubation periods are 7-14 days for typhoid and 1-10 days for paratyphoid.

Typhoid and paratyphoid fever cannot be differentiated clinically. Clinical features include continued fever, headache, abdominal pain, constipation or diarrhoea and splenomegaly. Bacteraemia is present and blood cultures are positive in 50-70% of cases.

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

The currently available typhoid vaccines do not protect against paratyphoid fever.

**Types of vaccine**

Two safe and moderately efficacious vaccines against typhoid fever have been licensed.

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

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

Guidelines for the manufacture and evaluation of Vi conjugate vaccines have been developed but they are not yet available. Ideally, a bivalent vaccine protecting against both typhoid and paratyphoid is required.

**Efficacy**

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

*Oral Ty21a vaccine:*

Efficacy for 3 years is around 48% after 3 doses. Protection commences 7 days after taking the third dose. Those living in endemic areas should be revaccinated every three years and travelers from non-endemic areas need annual revaccination. Herd protection of non-vaccinated population and moderate cross protection against Paratyphi B is also seen.

*Vi polysaccharide vaccine:*

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

**Indications**

- In view of the public health burden of typhoid fever and increasing antibiotic resistance the WHO recommends programmatic use of vaccination in high risk groups and populations to control endemic disease. For each country, data on sub-populations at risk and age-specific rates should be obtained and such groups targeted. Although such data for Sri Lanka is limited, the Epidemiology Unit has identified high risk groups in high risk areas. These groups include food handlers, people who do not
use or do not have proper toilet facilities, close contacts of typhoid patients and communities who do not have access to safe water\textsuperscript{10}.

- Vaccination is also recommended for outbreak control\textsuperscript{5,9}.
- Travellers visiting typhoid endemic areas, especially if staying for more than one month, visiting locations where antibiotic resistant strains are prevalent or travelling to areas where sanitation and food hygiene are likely to be poor\textsuperscript{5}.
- Household contacts of typhoid carriers.
- Laboratory personnel who may handle \textit{S. Typhi} in the course of their work\textsuperscript{11}.

**Dosage and administration**

\textbf{Vi capsular polysaccharide vaccine:}

Single 0.5mL (25µg) dose IM or SC. Booster doses every 3 years\textsuperscript{5}.

**Contraindications**

Previous severe hypersensitivity reaction to any component of the vaccine.

**Adverse effects**

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

**Storage**

2°C-8°C. Do not freeze.

**References**

5. WHO. Typhoid vaccines: WHO position paper. WER 2008; 83: 49-60.

\textbf{Dr Enoka Corea} MBBS, MD

\textit{Senior Lecturer in Microbiology, Faculty of Medicine, University of Colombo}.
CHAPTER 20
VARICELLA VACCINE

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

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

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

Efficacy
Two doses of vaccine are effective in preventing any form of clinical disease in 98% of recipients and 100% effective against severe disease, 10 years after vaccination. With the use of 2 doses, individuals have not shown any waning of immunity even after 14 years since receiving the vaccine. Immune responses are influenced by the number of doses given, immune status and age of receiving the vaccine.

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

Indications
- Susceptible children over 1 year of age, adolescents and adults.
- Those at a higher risk of contracting chickenpox: Health-care workers, family contacts of immunocompromised persons, teachers of young children, day care employees and residents and staff in institutional settings, hostels, school children, university students, inmates and staff of correctional institutions and military personnel, those going for studies in temperate climates.
- Non-pregnant women of childbearing age. They should be advised to avoid pregnancy for 3 months following each dose of vaccine. No adverse effects have been reported in instances where the vaccine has been mistakenly administered in pregnant women.
- Patients with human immunodeficiency virus (HIV) infection, if CD4 > 200 cells/μL, or if CD4 counts >25% of the total lymphocyte count (in children).

Dosage and administration
- 0.5mL given subcutaneously.
Aged 12 months to 12 years

- First dose of varicella vaccine could be given at age 12-15 months. A second dose of varicella vaccine is recommended routinely for all children aged 4-6 years (booster dose).
- The booster dose may be administered at an earlier age provided that the interval between the first and second dose is more than 3 months.
- Those who have received only one dose of the vaccine during childhood based on earlier guidelines are recommended another dose of the vaccine.

Persons Aged ≥13 Years

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

Post exposure prophylaxis

The varicella vaccine is effective in preventing illness or modifying the illness if given to children within 3 days following exposure to a rash. Vaccination within 3 days of exposure to rash was ≥90% effective in preventing varicella whereas vaccination within 5 days of exposure to rash was approximately 70% effective in preventing varicella and 100% effective in modifying severe disease. Therefore, the varicella vaccine is recommended for postexposure administration for unvaccinated persons without other evidence of immunity. (please see Chapter 24 Passive Immunization).

Herpes zoster

The incidence of herpes zoster (HZ) among persons older than 75 years of age is >10/1,000 person-years and the lifetime risk of HZ following chickenpox is estimated to be 10-20%. The incidence is significantly higher in individuals with impaired cell mediated immune responses such as those with malignancy, organ transplant recipients and on immunosuppressant treatment. The most common complication of HZ, particularly in older persons, is postherpetic neuralgia (PHN). PHN is the persisting debilitating pain weeks to months after resolution of HZ. There is currently a safe and effective vaccine for the prevention of herpes zoster, in which the varicella virus concentration is at least 14 times more than that of the VZV vaccine. This vaccine is administered as a single subcutaneous dose and is recommended to be used in individuals over 60 years of age.

As the VZV vaccine is a live attenuated vaccine, the vaccine virus also establishes latency similar to the wild type virus. The prevalence of HZ among young adults who received the VZV vaccine 20 years ago was shown to 0.9/1,000 person-years, which is significantly less than the prevalence of HZ following natural infection.

Absolute contraindications

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

Relative contraindications

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

- Mild pain, redness at site of administration.
- Causes a vesicular rash in 5% of recipients.
- The virus is able to establish latent infection in the vaccinated host and reactivation may occur, although less frequently than in those following natural infection.

Storage

At 2-8°C. Please refer to manufacturers instructions.

References

1. Munasingha HM. Epidemiological profile of varicella, cost of illness and felt need of a vaccine in the Colombo District. MD Community Medicine (Thesis).

Prof Sirimali Fernando MBBS, Dip (Micro), MSc
Chairperson, National Science Foundation and Prof. of Microbiology, University of Sri Jayawardenapura.

Dr Neelika Malavige MBBS (Col), MRCP (UK), DPhil (Oxon)
Senior Lecturer and Immunologist, Faculty Medical Sciences, University of Sri Jayawardenapura.
CHAPTER 21

YELLOW FEVER VACCINE

Yellow fever

Yellow fever is a viral haemorrhagic fever which is endemic in the tropics of Africa and South America. It poses a significant hazard to unvaccinated travelers to these areas. The case fatality rate may reach 20% to 80%\(^1\). Yellow fever is transmitted in a cycle involving monkeys and mosquitoes but human beings can also serve as the viraemic host for mosquito infection. Although the vector mosquito \textit{Aedes aegypti} is found in Sri Lanka, yellow fever has not been reported. The emphasis is on preventive vaccination as there is no specific anti viral therapy.

Type of vaccine

Live attenuated vaccines

- The French neurotropic vaccine from human virus passaged in mouse brain.
- The 17D vaccine from human virus passaged in embryonated chicken eggs.

Only the latter is available in Sri Lanka.

Efficacy

Neutralizing antibodies develop between the 7th and 21st day after immunization. 95% of recipients develop antibodies. Immunity lasts for 10 years\(^2\).

Indications

Those over 6 months of age who are travelling to countries where yellow fever vaccination is required Eg; Africa and South America\(^3\).

Travellers are expected to get immunized two weeks prior to departure. They are advised to keep the immunization records (yellow book) while travelling, as they may have to show such records on arrival to a country with yellow fever.

Because of the risk of serious adverse events that can occur after yellow fever vaccination, clinicians should only vaccinate people who

1) are at risk of exposure to yellow fever virus or
2) require proof of vaccination to enter a country\(^4\).

Dosage

Reconstitution

Once reconstituted with the diluent provided, the vaccine should be used immediately, as at 37°C the vaccine loses all potency within 1 hour. The reconstituted vaccine could be stored for a maximum of 3 hours at 2°C to 8°C.

Administration

0.5 ml subcutaneously

The only authorized place for administration of this vaccine for the travelers to countries with risk, is the office of the Assistant Port Health Officer in the premises of the Medical Research Institute, Colombo 8.

Contraindications

Allergy to one of the vaccine components, notably egg albumin.

Congenital or acquired immunodeficiency (asymptomatic HIV infection is not a contraindication).

Active malignant disorders.

Infants below the age of 6 months.

Pregnancy.
Adverse effects

A) Common adverse reactions
Reactions to yellow fever vaccine are generally mild; reported events typically include low-grade fever, headache, and myalgia that begin within days after vaccination and last 5-10 days.

B) Severe adverse reactions

Hypersensitivity
Immediate hypersensitivity reactions are uncommon. Anaphylaxis after yellow fever vaccine is reported to occur at a rate of 1.8 cases per 100,000 doses administered.

Yellow fever vaccine associated neurotropic disease (YEL-AND)
YEL-AND includes meningoencephalitis, Guillain-Barre syndrome, acute disseminated encephalomyelitis, bulbar palsy, and Bell’s palsy. Four to six cases occur per 1 million doses distributed. The illness occurs 3-28 days after vaccination, and almost all cases were in first-time vaccine recipients. YEL-AND is rarely fatal and is commoner in people aged ≥60 years.

Yellow fever vaccine associated viscerotropic disease (YEL-AVD)
YEL-AVD is a severe illness similar to wild-type disease, with vaccine virus proliferating in multiple organs and often leading to multisystem organ failure and death. YEL-AVD appears to occur after the first dose of yellow fever vaccine, rather than with booster doses. The onset of illness for YEL-AVD cases averaged 3 days (range, 1-8 days) after vaccination. The case fatality ratio for reported YEL-AVD cases is 65%. The rate is higher for people aged ≥60 years. The frequency is 3-5 cases per 1 million doses distributed6.

Precautions
- Infants aged 6-8 months as the incidence of YEL-AND is higher.
- Adults over 60 years of age when receiving the vaccine for the first time as incidence of YEL-AND and YEL-AVD is higher.
- Breast feeding as YEL-AND is reported in breast fed babies less than one month.

Storage
2°C-8°C. Do not freeze.

References
3. CDC Health Information for International Travel 2011.

Prof Anura Weerasinghe MBBS, MD, DCH, DTM&H, FRCP, FCCP, PhD
Professor of Medicine and Immunology, Dr Neville Fernando Teaching Hospital of South Asia Institute of Technology and Medicine, Malabe and Visiting Professor Rajarata University of Sri Lanka.
Immunization is an important measure to protect people living with HIV/AIDS (PLHIV) against certain vaccine preventable diseases. Compared with healthy individuals, PLHIV may have an increased risk of infection or experience more severe disease following exposure to vaccine-preventable diseases. The antibody response is frequently impaired in them, as the virus attacks the CD4 T cell, which is necessary for antibody formation. They might need higher or more frequent vaccine doses and more frequent testing for serological response. Certain vaccines enhance virus replication and transiently increase HIV viral load. Theoretically, vaccination should be given before the immune status of the patient is suppressed. Persons with severe immunodeficiency* may have impaired humoral response, and may not respond to vaccines or they may require supplemental doses to develop serological evidence of protection. If possible, vaccines should be administered before the CD4 count decreases to <200 cells/µL.

All inactivated vaccines can be administered safely to persons with altered immunocompetence whether the vaccine is a killed whole organism or a recombinant, subunit, toxoid, polysaccharide, or polysaccharide protein-conjugate vaccine. The usual doses and schedules are recommended. However, the effectiveness of such vaccinations might be suboptimal.

Persons with severe cell-mediated immune deficiency should not receive live attenuated vaccines. However, live vaccines like measles, mumps, rubella, yellow fever and varicella can be given to persons who are not severely immunosuppressed (i.e., those with age-specific CD4 cell percentages of >15%). Consultation with an immunologist or a vaccinologist is advised.

General principles of immunization in HIV-infected children
- Vaccines may be less effective in HIV infected children. However, these children also have an increased risk of vaccine preventable diseases and may have more severe illness if they are infected. Completing immunization is thus important, but consideration should be given to the most appropriate time for immunization, as vaccination is more likely to be effective after immune reconstitution in the severely immunocompromised.
- DNA PCR test is useful in early diagnosis of children (less than 18 months old) infected with HIV. The HIV antibody test is used to diagnose older children (more than 18 months). HIV antibodies are passively transferred from the infected mother to the baby and these may last up to 18 months in the baby.

General principles of immunization in HIV-infected adults
- Persons with symptomatic HIV infection or CD4 counts <200/µL should not be given live vaccines. Vaccination may be reconsidered when immune restoration occurs with antiretroviral therapy^2.
- Transient increases in plasma HIV RNA load have been reported after administration of several vaccines to HIV-infected persons. Available evidence indicates that these transient increases do not have clinical significance and should not prevent the use of any vaccine^2.

---

* HIV-infected persons >5 years of age with CD4 percentage <15% and CD4 counts <200 cells/µL, history of an AIDS-defining illness or clinical manifestations of symptomatic HIV are considered to have severe immunosuppression. Children ≤5 years of age with CD4 percentage <15% are considered to have severe immunosuppression. Asymptomatic HIV-infected persons with CD4 counts between 200-500 cells/µL are considered to have limited immune deficiency^1.
Schedule for pre-exposure vaccination in HIV-infected adults

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Indication</th>
<th>Primary course</th>
<th>Boosting</th>
<th>CD4 count (cells/µL)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis A</td>
<td>RS</td>
<td>Two or three doses</td>
<td>5 years</td>
<td>*</td>
<td>Three doses if CD4 count &lt;300 cells/µL</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>R</td>
<td>Three or four doses</td>
<td>HBsAb &lt;10 IU/L</td>
<td>*</td>
<td>HBsAb levels yearly</td>
</tr>
<tr>
<td><strong>Haemophilus influenzae type b</strong></td>
<td>RS</td>
<td>Single dose</td>
<td>None</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Human papilloma virus</td>
<td>RS</td>
<td>3 doses</td>
<td>none</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Influenza-parenteral</td>
<td>R</td>
<td>Single dose</td>
<td>Repeat yearly</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Measles, mumps, rubella (MMR)</td>
<td>RS</td>
<td>One or two doses</td>
<td>None</td>
<td>&gt;200</td>
<td>Two doses if measles IgG negative</td>
</tr>
<tr>
<td>Meningococcal (ACWY)</td>
<td>RS</td>
<td>Single dose</td>
<td>5 years</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Pneumococcal (polysaccharide)</td>
<td>R</td>
<td>Single dose</td>
<td>5 years</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Tetanus-diphtheria</td>
<td>R</td>
<td>One to five doses</td>
<td>10 years</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Inactivated poliomyelitis (IPV)</td>
<td>R</td>
<td>One to five doses</td>
<td>10 years</td>
<td>*</td>
<td></td>
</tr>
</tbody>
</table>

Vaccinations can be given irrespective of the CD4 count.
CS – consider in selected persons; HBsAb – Hepatitis B surface antibody; R – recommended; RS – recommended in selected persons.

**Inactivated Polio Vaccine (IPV)**

The IPV is recommended for HIV-infected children. This gives good antibody titres in most patients with CD4 counts of >200 cells/µL. A small number of patients with CD4 counts of <200 cells/µL may fail to respond.

**Oral Polio Vaccine (OPV)**

There has been no data to suggest HIV leads to prolonged poliovirus excretion of virus or increased risk of immunodeficiency-associated vaccine-derived poliovirus (iVDPV). Therefore, the OPV may (can) be used in HIV infected children as in the usual immunization schedule of Sri Lanka.
Measles, mumps and rubella (MMR) vaccine

Two doses of MMR vaccine are recommended for all HIV-infected persons aged ≥1 year and who are not severely immunosuppressed (with severe immunosuppression defined as a CD4 percentage of <15%). The first dose of MMR vaccine should be administered at 1 year of age and the second dose at 3 years of age. Older children and adults without immunity should receive 2 doses of vaccine 28 days apart. Serological response may be poor in HIV infection.

BCG

A delayed approach is recommended, in which vaccination is delayed in infants known to have been exposed to HIV in utero or during birth, until HIV infection is ruled out. The child should be closely followed for ascertainment of HIV status and BCG vaccination given after HIV infection is excluded.

If the mother is HIV positive, the baby should be tested for HIV prior to administration of the vaccine. If infection status can be established with early virological testing, BCG may be administered once HIV infection has been ruled out.

Varicella vaccine

Varicella vaccine is contraindicated in severe immunodeficiency. It is regarded as safe in children aged <8 years with asymptomatic or minimally symptomatic HIV infection and an age-specific CD4 cell count of >15%. HIV-infected persons aged >8 years with a CD4 count >200 cells/µL can be vaccinated safely, but the immunogenicity might be lower than in younger children. 2 doses of vaccine should be given with an interval of 3 months. It is also recommended for susceptible close contacts of HIV-infected persons because of risk of transmission of varicella.

Haemophilus influenzae type b (Hib) vaccine

HIV-infected children aged ≤5 years should receive the Hib conjugate vaccine as per routine vaccination schedule. Unimmunized children aged ≥5 years who have HIV infection should receive 1 dose of Hib vaccine. Because the incidence of Hib infections among HIV-infected adults is low, Hib vaccine is not recommended for them.

Pneumococcal conjugate vaccine

HIV-infected children aged <2 years can be given the pneumococcal conjugate vaccine. Children aged >2 years should receive the 23-valent pneumococcal polysaccharide vaccine with a single booster dose 5 years later.

Meningococcal vaccine

HIV infection is not a contraindication to receiving meningococcal vaccine.

Live attenuated Japanese encephalitis vaccine

Immunosuppression is a contraindication at present.

Inactivated Japanese encephalitis (JE) vaccine

The inactivated JE vaccine can be given safely in HIV infected patients. The WHO recommends that the inactivated JE vaccine should be given for immunocompromised patients until further studies regarding live JE vaccine are available.

Rabies vaccine

Rabies vaccine can be given safely in HIV infected patients who are exposed to the rabies virus. They should be administered both rabies immunoglobulin and vaccine. The vaccine has to be given by the IM route and not the intra-dermal route. The immune response is affected by the CD4 cell count and low or absent antibody responses have been reported in some persons with CD4 counts <200 cells/µL.
**Human Papilloma virus (HPV) vaccine**

Immunogenicity and efficacy of this in HIV infected population has not been established. However, because HPV vaccine is noninfectious, it can be administered to females who are immunosuppressed. Vaccine efficacy might be less than in immunocompetent persons.

**References**


**Dr Geethani Galagoda** MBBS, MD

*Consultant Virologist, Medical Research Institute, Colombo.*

**Dr Lilani Rajapakse** MBBS, MSc, MD

*Consultant Venereologist, National Sexually Transmitted Diseases and AIDS Control Programme, Colombo.*

---

**CHAPTER 23**

**IMMUNIZATION FOR THE ELDERLY**

**Introduction**

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

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

With aging there will be waning immunity for certain infections which they may have had immunity during their younger days, either following natural infection or immunization. Hence, certain vaccines are recommended routinely for the elderly.

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

Pneumococcal disease is a significant cause of morbidity and mortality in the elderly. The case fatality rate of invasive pneumococcal disease increases from 20% for those > 65 years of age to 40% for those > 85 years. The risk of multidrug-resistant pneumococcal infections is increasing in this group due to prolonged hospitalization and long term antibiotic therapy.
The morbidity and mortality following varicella and its complications are also higher with advancing age. The reactivation disease of varicella (herpes zoster (HZ) / shingles) occur in up to 25% of persons following primary infection and the incidence of zoster and postherpetic neuralgia (PHN) is markedly higher in the elderly\(^1\). More than two-thirds of the cases of HZ occur in persons > 50 years of age.

Routinely recommended vaccinations for the elderly include –

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

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

**Influenza vaccine:**
- Only the inactivated influenza vaccine is recommended for the elderly\(^3\).
- Seasonal influenza vaccine with a good match for prevailing viral strains are effective.
- Single dose of vaccine given intramuscularly followed with annual boosters.
- Can be given simultaneously with other vaccines.

**Pneumococcal vaccine:**
- 23 valent purified bacterial capsular polysaccharide vaccine is recommended.
- Single dose of vaccine given intramuscularly.
- Only a single booster dose is recommended after 5 years for adults > 65 years of age, if the first dose has been given before the age of 65 years\(^3\).
- One time re-vaccination after 5 years is recommended for older adults with chronic renal failure, nephrotic syndrome and immunocompromised situations\(^3,4\).
- Can be given simultaneously with other vaccines.

**Diphtheria, tetanus and pertussis booster (dTpa / Tdap):**
- Single intramuscular dose.
- Booster dose is recommended every 10 years as antitoxin titres drop gradually to the minimal protective level by 10 years after the last dose\(^1\).
- Can be given simultaneously with other vaccines.

**Varicella vaccine:**
- Two doses of varicella vaccine are recommended for non immune adults.
- Live attenuated varicella vaccine is given subcutaneously.
- Second dose is recommended with a gap of 4-12 weeks.

**Zoster vaccine:** Not available in Sri Lanka at present.
- A single dose of live attenuated zoster vaccine is given subcutaneously.
Zoster vaccine substantially reduces the risk of HZ by 51% and PHN by 67% by increasing VZV specific cell mediated immunity¹.

The vaccine is not 100% effective in preventing HZ. However, cases of HZ and PHN after vaccination appear to be much milder than in persons who have not had the vaccination.

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

References


3. Centers for Disease Control and Prevention, MMWR General Recommendations on Immunizations, ACIP Recommendations and Reports, January 28, 2011 / 60 (RR02); 1-60.


Dr Kanthi Nanayakkara MBBS, Dip. Med. Micro, MD
Consultant Virologist, Medical Research Institute, Colombo 8.

CHAPTER 24
PASSIVE IMMUNIZATION

Introduction

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

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

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

Administration

*Intramuscular:* Immunoglobulin for passive immunization (to be used for
the prevention of infection) is licensed to be administered intramuscularly. It should be administered in to a large muscle mass such as the gluteal region (upper outer quadrant) in an adult or the lateral thigh region in a child. No more than 5 mL should be administered at one site in adults, and adolescents; a lesser volume per site (1-3 mL) should be given to small children and infants.

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

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

**Indications for use of pooled human immunoglobulins (given IM)**

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

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

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

- Infants who are between the ages of 6 to 11 months can be given the MMR vaccine instead of immunoglobulins. In such cases the MMR should be administered within 72 hours of exposure.
- Pregnant women without evidence of measles immunity.
- Severely immunocompromised persons: these individuals should receive immunoglobulins regardless of previous vaccination status due to the possibility of very severe infection.

Any nonimmune individual exposed to measles who received IG should subsequently receive MMR vaccine (no earlier than six months after IGIM or eight months after IGIV), provided the individual is ≥12 months and the vaccine is not otherwise contraindicated.

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

**Indications for specific (hyperimmune) immunoglobulins (given IM)**

1. **Hepatitis B immunoglobulin (HBIG):** should be administered as soon as possible after an exposure and preferably within 24 hours. The hepatitis B vaccine should be administered at the same time as immunoglobulins (different sites). Indications are as follows:

- Neonate of HBsAg positive mother: HBIG should be given intramuscularly (IM), preferably within 12 hours of birth.
- Percutaneous (bite or needle stick) or mucosal exposure to HBsAg positive blood or body fluids.
- Victim of sexual abuse.
Individuals with a history of completed hepatitis B vaccination schedule should receive a booster dose of the vaccine, if exposed to a known patient who is Hepatitis Bs antigen positive. However, in exposure to a patient with an unknown hepatitis B status, no further action is required in individuals who have completed the vaccination schedule are exposed.2

2. Varicella zoster immunoglobulin (VZV-IG): should be administered within 10 days following exposure although the greatest protection is seen when given within 96 hours of exposure. It is recommended that VZIG should be given to the following group of individuals:3

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

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

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


4. Tetanus immunoglobulin: Human tetanus immunoglobulin should be given as a single dose intramuscularly with part of the dose infiltrated around the wound as soon as possible. If tetanus immunoglobulin is not available intravenous immunoglobulin (IVIG) should be used intravenously as it contains antibodies to the tetanus toxoid. Please refer manufacturers’ instructions for dosing. Part of the recommended dose should be infiltrated locally.

5. Botulism immunoglobulin: Antitoxin does not reverse paralysis but can arrest the progression and decrease the duration and dependence on mechanical ventilation. Antitoxin should be given early in the course of illness, ideally <24 h after onset of symptoms because antitoxin neutralizes only toxin molecules that are yet unbound to nerve endings. Skin testing should ideally be done before administration. Re-administration of the antitoxin is not recommended as it has a half life of 5 to 8 days.

Subsequent administration of other vaccines

When immunoglobulins are given intramuscularly for the prevention of infectious diseases (post exposure prophylaxis), inactivated vaccines can be administered at the same time, but at a different site. Use of immunoglobulins is known to interfere with immune responses to subsequent vaccines if given soon after administration of immunoglobulins. For instance, after the use of immunoglobulins or other blood products, immune responses to live vaccines have been shown to be inhibited even 3-4 months after the use of these products. Therefore, use of live vaccines should be delayed at least for 3 months after the use of immunoglobulin preparations.

Adverse effects

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

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

References
1. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization practices (ACIP), MMWR Recomm Rep. 2007; 56.

Dr Neelika Malavige MBBS, MRCP, DPhil
Senior Lecturer and Immunologist, Faculty of Medical Sciences, University of Sri Jayawardenapura.
Vaccine Reactions

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.

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

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

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

Most of the rare and more serious vaccine reactions [e.g seizures, thrombocytopenia, hypotonic hyporesponsive episodes (HHE), persistent inconsolable screaming] do not lead to long term problems. Anaphylaxis, while potentially fatal, is treatable without having any long term effects. Although encephalopathy is included as a rare reaction to measles or DTP vaccine, it is not certain whether these vaccines in fact cause encephalopathy.

**Surveillance of AEFI**

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

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

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

**Figure. AEFI surveillance system in Sri Lanka**

![AEFI Surveillance System in Sri Lanka](image)

**Responsibilities of medical officers in AEFI surveillance:**

- Should take a comprehensive immunization history of the child.
- Reporting should be done immediately to MOH of the patient's residential area on suspicion of AEFI using the Notification form for AEFI. Deaths should be notified directly to the Epidemiology Unit. (Telephone 0112695112)
- Communication with parents, other members of the community and health staff need to be carried out under all circumstances. They should be kept informed about the investigation, and action being taken or to be taken regarding the AEFI. It is crucial to highlight the benefits of immunization while communicating with the public/medical staff/stake holders.

**References**


**Dr Ananda Amerasinghe** MD
Consultant Epidemiologist, Ministry of Health.
CHAPTER 26
MANAGEMENT OF ANAPHYLAXIS

Introduction
Anaphylaxis following routine vaccination is rare, but can be fatal\(^1\). All immunization service providers must be able to recognize the symptoms and signs of anaphylaxis. A fainting attack (vasovagal episode) maybe mistakenly diagnosed as anaphylaxis. The features useful in differentiating a fainting attack from anaphylaxis are given in Table 1.

Table 1. Differences between a fainting attack and anaphylaxis

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

(Continued)
Anaphylaxis occurs without warning, usually within 15 minutes of giving a vaccine hence the vaccinated person should remain under observation for at least 30 minutes. The more rapidly anaphylaxis occurs after exposure, the more likely the reaction will be severe and potentially life-threatening. Even a few minutes delay in recognizing and treating can lead to hypoxic-ischaemic encephalopathy or death. Therefore, a written protocol for the management of anaphylaxis, adrenaline and 1 mL syringes must always be immediately at hand whenever vaccines are given.  

Diagnosis  
The key to diagnosis involves pattern recognition: sudden onset of characteristic symptoms and signs within minutes to hours after exposure to a vaccine. Typically, symptoms and signs occur in 2 or more body systems: skin and mucous membranes, upper and lower respiratory tract, gastrointestinal tract, cardiovascular system and central nervous system within minutes of exposure. Clinical criteria for the diagnosis of anaphylaxis are detailed in Figure 1 and Table 2. In infancy, anaphylaxis can be difficult to recognise as they cannot describe their symptoms. Some of the signs of anaphylaxis are normal occurrences in babies; for example, flushing and dysphonia after crying, spitting out after feeding and incontinence. Healthy infants have a lower blood pressure and a higher resting heart rate than older children and adults. Therefore, age-appropriate criteria should be used for documenting hypotension and tachycardia.  

Pathophysiology  
Anaphylaxis following vaccination is usually an IgE-mediated immune reaction that results in the sudden systemic release of allergenic mediators (e.g. histamine, leukotrienes, prostaglandins, tryptase) from mast cells and basophils. Within 10 minutes, increased vascular permeability allows transfer of as much as 50% of the intravascular fluid into the extravascular space. As a result, haemodynamic collapse might occur rapidly with little or no cutaneous or respiratory manifestations.

---

**Figure 1.**
<table>
<thead>
<tr>
<th><strong>Table 2. Diagnostic features of anaphylaxis</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skin</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Cardio-vascular</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Central nervous system</strong></td>
</tr>
<tr>
<td><strong>Gastro-intestinal</strong></td>
</tr>
<tr>
<td><strong>Ocular</strong></td>
</tr>
<tr>
<td><strong>Other</strong></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

**Systematic approach to the treatment of anaphylaxis**

A systematic approach to management is critically important for a favourable outcome. If precious minutes are lost early in the treatment of an acute anaphylactic episode, subsequent management becomes difficult. Basic initial protocol even in a low resource environment is outlined in Figure 2 and Table 3. After rapid assessment of the patient’s circulation,
airway, breathing, mental status, skin and estimation of the body weight treatment begins with implementation of the protocol. **Steps 3, 4, 5 and 6 should be performed promptly and simultaneously as soon as anaphylaxis is diagnosed or suspected** (Figure 2).

**Table 3. Adrenaline in the INITIAL management of acute anaphylaxis**

<table>
<thead>
<tr>
<th>Drug, site and route of administration</th>
<th>Frequency of administration</th>
<th>Dose (adult)</th>
<th>Dose (child)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenaline (epinephrine) 1:1000, IM to the midpoint of the anterolateral aspect of the middle third of the thigh immediately</td>
<td>Repeat every 5-15 min as needed until there is resolution of the anaphylaxis or signs of hyperadrenalism (Refer table 5)</td>
<td>0.3 - 0.5 mL (0.3 - 0.5 mg) 0.3 mL (0.3 mg) for smaller adults (30-50 kg) 0.5 mL (0.5 mg) (&gt;50 kg)</td>
<td>0.01 mL/kg (up to maximum of 0.3 mL or 0.3 mg/dose)</td>
</tr>
</tbody>
</table>

**Note:** Persisting or worsening cough associated with pulmonary oedema is an important sign of adrenaline overdose and toxicity.

- Adrenaline (epinephrine) is the most important life-saving therapeutic agents administered in anaphylaxis. Inject adrenaline intramuscularly in the mid-anterolateral thigh as soon as anaphylaxis is diagnosed or strongly suspected, in a dose of 0.01 mL/kg (0.01 mg/kg) of a 1:1000 (1 mg/mL) solution, to a maximum of 0.5 mL (0.5 mg) in adults. The dose of children is 0.01 mL/kg (0.01 mg/kg) of 1:1000 solution to a maximum of 0.3 mL (0.3 mg). Record the time of the dose and repeat every 5-15 minutes if needed. Most patients respond to one or two doses.

- Monitor the patient’s blood pressure, cardiac rate and function, respiratory status and oxygenation at frequent and regular intervals. If and when possible obtain electrocardiograms and start continuous non-invasive monitoring.

When the need is recognized at any point of time,

- give high flow supplemental oxygen at a flow rate of 6-8 L/min by face mask or by oropharyngeal airway.

- insert an intravenous needle or catheters with wide bore cannulae (14 or 18 gauge for adults) and give intravenous fluid resuscitation.

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

As soon as the patient is stabilized the patient should be transported accompanied by a doctor to a hospital with ICU care.

**Positioning the patient**

Patients with anaphylaxis should not suddenly sit, stand, walk or be placed in the upright position. Instead, they should be placed on the back with their feet elevated or if they are experiencing respiratory
distress or vomiting, in a position of comfort with their feet elevated. This
accomplishes 2 therapeutic goals: 1) preservation of fluid in the circulation
(the central vascular compartment), an important step in managing
distributive shock; and 2) prevention of the empty vena cava/empty
ventricle syndrome, which can occur within seconds when patients with
anaphylaxis suddenly assume or are placed in an upright position². Patients
with this syndrome are at high risk for sudden death and are unlikely to
respond to adrenaline regardless of route of administration, because it
does not reach the heart and therefore, cannot be circulated throughout
the body².

Adrenaline (epinephrine)

Adrenaline (epinephrine) and oxygen are the most important lifesaving
therapeutic agents administered in anaphylaxis. The time-dependent and
concentration-dependent pharmacologic effects of adrenaline have been
confirmed both in-vitro studies and in clinical observations². Hence, if there
is any doubt regarding diagnosis, it is advisable to administer adrenaline
intramuscularly (IM) immediately. 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.

The time to highest blood concentration (Cmax), when studied in
asymptomatic subjects is also shorter when adrenaline is given intra-
muscularly in to the vastus lateralis muscle (mid lateral thigh) than when
it is administered intramuscularly in to the deltoid muscle of the arm. It
should not be given subcutaneously. Table 3 provides details of IM
adrenaline dosing according to age and weight. Adrenaline should not be
given via the intravenous (IV) route as initial treatment because of the
risk of potentially lethal arrhythmias. Erroneous intravenous administration
or epinephrine overdose may lead to cardiac arrhythmias, pulmonary
oedema or even death⁴.

The only indication for adrenaline via the IV route as a slow infusion is
dose is titrated according to non-invasive continuous monitoring of cardiac
rate and function, by doctors who are trained or in liaison with an
emergency/critical care specialist (Table 4). An intravenous bolus dose
of adrenaline is indicated only if cardiac arrest is imminent or has already
occurred⁴. It should be given only by experienced specialists (Table 4).

| Table 4. Intravenous infusion of adrenaline for life-threatening
| anaphylaxis-induced hypotension who have failed to respond
| to several IM doses of adrenaline and intravenous volume
| replacement

<table>
<thead>
<tr>
<th>For specialist use only</th>
<th>Ensure patient is monitored</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenaline IV (1:10,000 adrenaline contains 100 micrograms/mL). Do not give the undiluted 1:1000 adrenaline concentration IV. Bolus dose - adult: 50 microgram boluses according to response. If repeated adrenaline doses are needed, start an IV adrenaline infusion.</td>
<td></td>
</tr>
</tbody>
</table>

With an infusion pump:
Mix 1mL of 1:1000 adrenaline in 100mL of 0.9% saline (10 mcg/mL)
Start at 0.5 to 1 mL/kg/hour (= approximately 30 to 100 mL/hour in adults) depending on reaction severity:

**moderate severity:**
- adrenaline 1 mg in 100 mL sodium chloride 0.9%/0.5 mL/kg/hour (0.08 micrograms/kg/minute)

**severe (hypotensive or hypoxic):**
- adrenaline 1 mg in 100 mL sodium chloride 0.9%/1 mL/kg/hour (0.17 micrograms/kg/minute).

Children
Children with life-threatening anaphylaxis usually have predominantly
bronchospastic reactions and absorption of adrenaline from the intramuscular
site will be good. Furthermore, hypotension can be difficult to assess in
small children. Therefore, in small children it is probably safer to use a second
intramuscular dose rather than an infusion, unless the reaction is being
treated in an emergency/critical care area under specialist supervision.
If you do not have an infusion pump, use a standard IV set
1 mg in 100 mL sodium chloride 0.9% IV, at approximately 100 mL/hour, which is one drop every 2 seconds for most standard drip sets

- Titrate up or down according to response, aiming for lowest effective infusion rate.
- Wait for 5 to 10 minutes after a change in the infusion rate to assess the response.
- Reduce the rate immediately if signs of adrenaline toxicity (tachycardia, tremor and pallor in association with a normal or raised blood pressure) develop. Persisting or worsening cough associated with pulmonary oedema is an important sign of adrenaline overdose and toxicity.
- As the reaction resolves, an infusion that was previously therapeutic can quickly start to have toxic effects. Therefore, when features of anaphylaxis improve, begin reducing the infusion aiming for around half the starting rate if possible.
- One hour after the resolution of all symptoms and signs, wean the infusion over another 30 minutes and stop.

### Adverse effects

Transient pharmacologic effects after a recommended dose of adrenaline by any route of administration include pallor, tremor, anxiety, palpitations, dizziness and headache. These symptoms indicate that a therapeutic dose has been given. Serious adverse effects such as ventricular arrhythmias, hypertensive crisis and pulmonary oedema potentially occur after an overdose of adrenaline by any route of administration. The adverse effects of adrenaline are summarized in Table 5. Typically, serious adverse events are reported after

- rapid intravenous infusion
- bolus IV administration
- dosing error because of intravenous infusion or intravenous injection of the 1:1000 (1 mg/mL) solution appropriate for intramuscular injection, instead of the dilute solutions appropriate for intravenous administration (1:10,000 [0.1 mg/mL] or 1:100,000 [0.01 mg/mL]).

<table>
<thead>
<tr>
<th>Table 5. Potential adverse effects of adrenaline (epinephrine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential adverse effects after the usual adrenaline dose of 0.01 mg/kg of a 1:1000 (1 mg/mL) solution intramuscularly (to a maximum of 0.5 mL/0.5 mg [adult] or 0.3 mL/0.3 mg [child])</td>
</tr>
<tr>
<td>Pallor, tremor, anxiety, palpitations, dizziness, headache; these symptoms indicate that a pharmacologic dose has been injected</td>
</tr>
<tr>
<td>Potential adverse effects after adrenaline overdose e.g.</td>
</tr>
<tr>
<td>Overly rapid intravenous infusion</td>
</tr>
<tr>
<td>Intravenous bolus dose</td>
</tr>
<tr>
<td>Dosing error, e.g. intravenous administration of 1:1000 (1 mg/mL) solution appropriate for intramuscular injection, instead of the dilute solutions appropriate for intravenous administration (1:10,000 [0.1 mg/mL] or 1:100,000 [0.01 mg/mL]).</td>
</tr>
<tr>
<td>Ventricular arrhythmias, hypertension, pulmonary oedema; Note that the heart itself is a potential target organ in anaphylaxis; therefore, acute coronary syndromes (angina, myocardial infarction, arrhythmias) can also occur in untreated anaphylaxis in patients with known coronary artery disease, in those in whom subclinical coronary artery disease is unmasked and even in patients (including children) without coronary artery disease in whom the symptoms are due to transient vasospasm.</td>
</tr>
<tr>
<td>Reasons for apparent lack of response to adrenaline</td>
</tr>
<tr>
<td>Error in diagnosis, patient suddenly stands or sits (or is placed in the upright position) after adrenaline injection; rapid progression of anaphylaxis; patient taking a beta-adrenergic blocker, ACE inhibitor or other medication that interferes with actions of adrenaline; adrenaline injected too late; dose too low on mg/kg basis; adrenaline is past expiry date; route not optimal; injection site not optimal</td>
</tr>
</tbody>
</table>

---

169 170
In Sri Lanka, adrenaline is mostly under-used and patients have received hydrocortisone as the initial treatment. In addition, there have been a few instances where it has been inappropriately administered as a bolus dose via the intravenous route which may have contributed to pulmonary oedema and death seen in these patients.

**Management of respiratory distress**

Continuous monitoring of oxygenation by pulse oximetry is desirable. Supplemental oxygen should be administered by face mask or by oropharyngeal airway at a flow rate of 6-8 L/min to

- all patients with respiratory distress
- those receiving repeated doses of adrenaline
- any patient with anaphylaxis who has concomitant asthma, other chronic respiratory or cardiovascular disease

**Management of hypotension and shock**

During anaphylaxis, large volumes of fluids leave the patient’s circulation and enter the interstitial tissue; therefore, rapid intravenous infusion of 0.9% isotonic saline (normal saline) should be commenced as soon as the need for it is recognized. Give 1-2 litres of 0.9% saline rapidly; 5-10mL/kg in the first 5-10 minutes to an adult, or 10mL/kg to a child. The rate of administration should be titrated according to the blood pressure, cardiac rate and function and urine output. All patients receiving such treatment should be monitored for volume overload.

**The role of H<sub>1</sub>/H<sub>2</sub>-antihistamines and corticosteroids in anaphylaxis**

H<sub>1</sub>-antihistamines and corticosteroids are no longer considered drugs of choice in the initial treatment of anaphylaxis because they do not relieve life threatening respiratory symptoms or shock. These are considered to be second line treatment. Table 6 provides guidance on dosing of second line medicines. Some guidelines such as “The Australian Immunisation Handbook” do not recommend antihistamines and/or hydrocortisone in the emergency management of anaphylaxis, citing lack of supporting evidence from randomized controlled trials. However, given their proven benefit with localized allergic reactions such as urticaria, some guidelines recommend H<sub>1</sub>-antihistamines in various intravenous and oral dosing regimens.

### Table 6. Pharmacologic treatment once patient’s condition is stabilized with adrenaline and fluids

<table>
<thead>
<tr>
<th>Drug and route of administration</th>
<th>Route and frequency of administration</th>
<th>Dose (adult)</th>
<th>Dose (child)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetirizine PO</td>
<td>Single daily dose</td>
<td>10 mg OD</td>
<td>6 months to &lt;2 years 2.5 mg OD 2–5 years: 2.5-5 mg OD &gt;5 years: 5-10 mg OD</td>
</tr>
<tr>
<td>Chlorpheniramine IM/ IV slowly</td>
<td></td>
<td>10 mg</td>
<td>&gt;6-12 years: 5 mg &gt;6 months – 6 years: 2.5 mg &lt;6 months: 250 micrograms/kg</td>
</tr>
<tr>
<td>Corticosteroids: when patient’s condition is stabilized with adrenaline and fluids</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
Concerns have been raised about the slow onset of action relative to adrenaline and about potential harmful effects on the central nervous system such as somnolence and impairment of cognitive function with H₁-antihistamines. The evidence to support their use is weak, but as there are logical reasons for them, oral non-sedating H₁-antagonists such as cetirizine may be given to relieve the cutaneous symptoms of anaphylaxis (e.g. urticaria, pruritus and angioedema) after initial management with adrenaline. If oral administration is not possible, inject chlorphenamine slowly intravenously or intramuscularly.

Sedating antihistamines IV or oral are best avoided as side effects (drowsiness or lethargy) may mimic some signs of anaphylaxis. Injectable promethazine should not be used in anaphylaxis as it can worsen hypotension and cause muscle necrosis.

An H₂-antihistamine, administered concurrently with an H₁-antihistamine, potentially contributes to decrease in flushing, headache and other symptoms. However, H₂-antihistamines are recommended in only a few anaphylaxis guidelines as the evidence from randomized placebo-controlled trials is not strong.

Corticosteroids

Although the benefit of corticosteroids in anaphylaxis is unproven, they remain in some guidelines because they potentially prevent biphasic anaphylaxis or a reaction with marked or persistent wheeze. The onset of action takes several hours. It is common practice to prescribe a 2-day course of oral steroids (e.g. oral prednisolone 1 mg/kg, maximum 50 mg daily).

Beta-2 adrenergic agonists

Selective beta-2 adrenergic agonists such as salbutamol or terbutaline are sometimes given in anaphylaxis as additional treatment for wheezing, coughing, and shortness of breath not relieved by adrenaline. But never
substitute these medications for adrenaline because they have minimal alpha-1 adrenergic agonist vasoconstrictor effects and do not prevent or relieve laryngeal oedema and upper airway obstruction, hypotension or shock.

Observation and discharge from hospital

Patients who have had a suspected anaphylactic reaction (i.e. an airway, breathing or circulation (ABC) problem) should be treated and then observed for at least 6-8 hours in a hospital with facilities for treating life-threatening ABC problems. They should be reviewed by a consultant and a decision made about the need for further treatment or a longer period of observation. Patients with a good response to initial treatment should be kept under observation for up to 24 hours if they have

• severe reactions with slow onset
• a history of severe asthma or a severe asthmatic component in the current episode
• there is a possibility of continuing absorption of allergen such as vaccines
• a previous history of biphasic reactions
• the anaphylactic episode in the evening or at night
• difficulty in accessing emergency care in case of deterioration.

Laboratory investigations

Measurements of tryptase and histamine levels are recommended for confirmation. Currently, in Sri Lanka there are no facilities for measurement of histamine levels. Blood samples for measurement of tryptase levels should be collected and sent to the Department of Immunology, Medical Research Institute, Borella (MRI). These samples should be optimally obtained 15 minutes to 3 hours after onset of symptom. See Table 7 for ideal sample times and requirement. However, samples taken up to 6 hours after the event may also be assayed. Although not specific, increased serum tryptase levels support the clinical diagnosis of anaphylaxis. Serial measurement of tryptase levels during an anaphylactic episode and measurement of a baseline level after recovery, are reported to be more useful than measurement at only one point in time. However, normal levels of either tryptase or histamine do not rule out the clinical diagnosis of anaphylaxis.

<table>
<thead>
<tr>
<th>Table 7. Tryptase sample timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>The time of onset of the anaphylactic reaction is the time when symptoms were first noticed. It is important that this time is accurately recorded.</td>
</tr>
<tr>
<td>a) Minimum: one sample at 1-2 hours after the start of symptoms.</td>
</tr>
<tr>
<td>b) Ideally: Three timed samples:</td>
</tr>
<tr>
<td>1) Initial sample as soon as feasible after resuscitation has started – do not delay resuscitation to take sample.</td>
</tr>
<tr>
<td>2) Second sample at 1-2 hours after the start of symptoms.</td>
</tr>
<tr>
<td>3) Third sample either at 24 hours or in convalescence (even at follow up clinic). This provides baseline tryptase levels – some individuals have an elevated baseline level.</td>
</tr>
<tr>
<td>Serial samples have better specificity and sensitivity than a single measurement in the confirmation of anaphylaxis</td>
</tr>
</tbody>
</table>

Sample requirements

1) Serum or clotted blood sample.
2) Record the timing of each sample accurately on the sample bottle and request form. State on the request form the time of onset of the reaction (symptoms). Record on the sample bottle the number of minutes or hours after the onset of symptoms the sample was taken.
3) As little as 0.5 mL of sample is adequate (children), but 5 mL (adults) is better.
4) Optimally, store the serum from spun samples frozen (-20°C) in the hospital laboratory, before dispatch to MRI.
5) Tryptase is very stable (50% of tryptase is still detectable after 4 days at room temperature), so even samples stored at room temperature over a weekend can give useful, though sub-optimal, information.
6) Consult immunologist at MRI if you have any queries.
Reporting

It is essential that all vaccine associated anaphylaxis be reported to the Epidemiological Unit in the format given as an annex in this book.

References


Professor Rohini Fernandopulle MBBS, PhD
*Clinical Pharmacologist, General Sir John Kotelawala Defence University, Ratmalana.*

Dr Shalini Sri Ranganathan MBBS, MD, DCH, MRCP, PhD, Dip.Med.Tox.
*Department of Pharmacology, Faculty of Medicine, Colombo.*

Dr Rajiva de Silva Dip (Med. Mic), MD (Mic).
*Consultant Immunologist, Medical Research Institute, Colombo.*

CHAPTER 27

IMMUNIZATION FOR INTERNATIONAL TRAVEL

Introduction

In considering immunization for travellers the following information is important.

(a) Current information on vaccine preventable diseases at travel destination

(b) Activities planned during travel and at travel destination

(c) Traveller’s previous immunization history

(d) Traveller’s general health such as age, allergies, medication, pregnancy and chronic disease conditions

(e) Time available before departure.

Immunization for travellers fall into 3 categories

(a) Routine immunization

(b) Required immunizations which are required to enter host countries

(c) Recommended immunizations.

(a) **Routine immunization** – should be up-to-date regardless of travel

(b) **Required immunizations**

Most vaccines take time to become effective and ideally should be given 4-6 weeks before travel.

a) **Yellow fever vaccine**

*For persons travelling to endemic countries*

Yellow fever vaccination is required for people travelling to endemic countries as per International Health Regulations. Currently the endemity to yellow fever is confined to certain countries in sub-Saharan
Africa and tropical South America. Due to the risk of post vaccination encephalitis, infants less than 9 months should be vaccinated only if the risk of contracting yellow fever is high. Vaccinating people with diseases of the thymus should be avoided as there is a higher risk of adverse reactions. Alternate means of prevention should be recommended to these travellers.

**For persons arriving from an endemic country**

The International Health Regulations allow countries to require proof of vaccination, International Certificate of Vaccination (ICV), on entry for travellers arriving from endemic countries. Travellers arriving without a completed ICV may be quarantined or refused entry.

**Duration of protection after vaccination**

Although WHO has concluded that a single dose confers adequate lifelong immunity, booster doses are required every 10 years when visiting endemic countries. HIV patients, infants and other immunocompromised groups require a booster dose to ensure continued protection.

**Certification of vaccination**

For purposes of international travel, yellow fever vaccine produced by different manufacturers worldwide must be approved by WHO and administered at an approved yellow fever vaccination centre. The only authorised place in Sri Lanka for administration of this vaccine is the office of the Assistant Port Health Officer, which is housed in the premises of the Medical Research Institute, Colombo 8. Vaccinees should receive a completed ICV, signed and validated with the official stamp. This certificate is valid from 10 days after vaccination and for 10 years.

**Contraindications to vaccination**

Yellow fever vaccine is contraindicated for persons with a thymus disorder that is associated with abnormal immune cell function, such as thymoma or myasthenia gravis, AIDS and other immune deficiency disorders and for those who are on immunosuppressive and immunomodulatory therapies.

If a physician concludes that a particular vaccination should not be administered for medical reasons, the traveller should be given a signed and dated statement of the reasons on the physician’s letterhead. Under these conditions, the traveller should obtain specific advice from the embassy or consulate of the country or countries the person plans to visit.

In addition to vaccination all travellers should take adequate measures against exposure to mosquito bites.

(Please refer Chapter 21)

**b) Meningococcal vaccine**

Vaccination against meningococcal disease is required by the government of Saudi Arabia for travellers performing Hajj or arriving for employment. The vaccine should be administered at least 10 days before arrival in Saudi Arabia. It is effective for 3 years.

Children over the age of 2 years and adults should be immunized with the quadrivalent vaccine (serogroups A, C, Y and W135).

Children between 3 months and 2 years of age should receive two doses of the serogroup A conjugate vaccine with a 3-month interval between the two doses. This vaccine is not available in Sri Lanka.

Meningococcal vaccine is also recommended for students who travel to countries that are endemic for meningococcal disease if they plan to live in dormitories or residence halls.

(Please refer Chapter 13)

**c) Poliomyelitis vaccine**

Some polio-free countries may also require travellers from polio-endemic countries to be immunized against polio in order to obtain an entry visa, e.g. Saudi Arabia (proof of oral poliovirus vaccination is required 6 weeks
before application for an entry visa for visitors arriving from countries reporting poliomyelitis cases). This is not a requirement for travellers from Sri Lanka.

Travellers to polio-infected areas who have not received any polio vaccine previously should complete a primary schedule of polio vaccination\(^3\). (Please refer Chapter 15)

\((d)\) **Recommended immunizations**

These vaccines are administered to protect travellers from illnesses present in other parts of the world and to prevent the importation of infectious diseases across international borders. The vaccinations depend on the travel destination, age, health status, and previous immunization. Most immunization for travel fall into the recommended category.

**Varicella vaccine**

Varicella infections in adults may result in severe disease with complications. Travellers who are likely to bring them into close contact with children in schools and day care centres, healthcare settings and refugee camps should be immunized before travel if no history of varicella is available. Protection occurs 14 days after the first dose. It is not recommended for pregnant women and immunocompromised persons. (Please refer Chapter 20)

**Hepatitis B vaccine**

Hepatitis B is endemic in some countries in South America, Africa, Asia and the South Pacific. Immunization is recommended for people who will experience close contact with residents in countries visited. The accelerated schedule of 0, 1, 2 months and a booster at 12 months or 0, 7, 21 days and a booster at 12 months is recommended for travellers. Hepatitis B vaccination is recommended for persons who travel to endemic countries for medical care as there is a relatively higher risk of acquiring the disease (eg India). (Please refer Chapter 7)

**Pneumococcal vaccine**

Recommended for adults more than 65 years old and adults with chronic cardio-pulmonary conditions and those with chronic disease. Protection occurs 14 days after vaccination. (Please refer Chapter 14)

**Hepatitis A vaccine**

All susceptible persons travelling to or working in countries that have high or intermediate hepatitis A endemicity should be vaccinated and age appropriate dose should be administered. The first dose of hepatitis A vaccine should be administered as soon as travel is considered and second dose should be administered after 6-12 months for long term protection.

One dose of single-antigen hepatitis A vaccine administered at any time before departure can provide adequate protection for most healthy persons. Older adults, immunocompromised persons, and persons with chronic liver disease or other chronic medical conditions planning to depart in <2 weeks should receive the initial dose of vaccine and HNIG (0.02 mL/kg) at the same time at separate anatomical sites.

Travellers aged <12 months, or are allergic to a vaccine component should receive a single dose of HNIG (0.02 mL/kg), which provides effective protection for up to 3 months. (Please refer Chapter 6)

**Typhoid vaccine**

Immunity is obtained 2-3 weeks after parenteral (Vi capsular polysaccharide) vaccination. The typhoid vaccines currently available do not offer protection against *Salmonella*. Paratyphi infections. (Please refer Chapter 19)

**Rabies vaccine**

Recommended for travellers to rabies endemic areas. Three doses at 0, 7 and 21/28 days are recommended for pre-exposure vaccination. A booster should be given after one year.
If all three doses are not completed, the traveller will not be considered previously vaccinated and will require full postexposure prophylaxis, if an exposure occurs.

Rabies immune globulin (RIG) is not recommended following a rabies exposure in persons who are currently protected by pre-exposure vaccination. When exposed to rabies they would require two boosters of a WHO recommended cell culture rabies vaccine on days 0 and 3. (Please refer Chapter 16)

Japanese encephalitis vaccine

The risk of Japanese encephalitis is highest in pig farming areas of China, Korea and South East Asia. Immunization should be completed 10 days before travel. Immunization schedule with the killed vaccine is 0, 7 and 28 days. (Please refer Chapter 10)

Influenza vaccine

The risk for exposure to influenza during international travel depends on the time of year and destination. In the tropics, influenza can occur throughout the year, while in the temperate regions disease activity occurs during the winter. The vaccine that the traveller receives should be active against the strains of influenza virus prevalent in the country the person visits. Every year the WHO recommends which strains to be included. The vaccine should be administered 2 weeks prior to travel. These vaccines are not recommended for children under the age of 6 months. (Please refer Chapter 9)

Long stay travellers

Persons who travel for long term stay such as education and employment should inquire regarding host country vaccine requirements from the respective organisations, eg. educational institutes or employing organisations well before travel. This will enable completion of vaccination prior to travel. For example, it is recommended to vaccinate long stay travellers to India, Bangladesh, Nepal, Pakistan and China against hepatitis A, hepatitis B, typhoid fever, meningococcal disease and Japanese encephalitis. Students who travel to UK and Europe may require meningococcal and MMR vaccination.

Additional information

1) A number of vaccines, both live and inactivated may be required prior to travel. All commonly used vaccines are relatively safe and can be given simultaneously, at different sites, without impairing antibody responses or increasing rates of adverse reactions. Inactivated vaccines generally do not interfere with the immune response to other inactivated or live-virus vaccines. It could be given at any time before or after a different inactivated vaccine or a live-virus vaccine. If two parenteral live-virus vaccines are not administered on the same day, the second vaccine should be administered at least 4 weeks later.

2) In the case of immunocompromised travellers the vaccination must be considered from the following perspectives: 1) safety in the context of the underlying illness and concurrent medication  2) the possibility of decreased effectiveness of the vaccine. The doctor should expain to the traveller the risks and benefits of immunization.

Because the situation is evolving, travellers and clinicians can stay updated of new developments by visiting the official U.S. government website for travel (http://www.cdc.gov/travel) and the WHO website www.who.int.

References


3. International Travel & Health, Poliomyelitis, World Health Organization
   http://www.who.int/ith/vaccines/polio/en/

4. Update: Prevention of Hepatitis A After Exposure to Hepatitis A Virus
   and in International Travellers. Updated Recommendations of the
   Advisory Committee on Immunization Practices (ACIP) MMWR
   October 19, 2007 / Vol. 56 / No. 41 1080-84.

5. Centers for Disease Control and Prevention : Health information for
   international travel. US Department of Health and Human service

Senior Professor of Microbiology, University of Colombo.

CHAPTER 28
IMMUNIZATION IN SPECIAL CLINICAL CIRCUMSTANCES

Preterm and low birth weight infants
Preterm infants and infants of low birth weight (lower than 2500g) should
receive routinely recommended childhood vaccines at the same
chronological age as term infants. Vaccine doses should not be reduced
when given to preterm and low birth weight infants. Babies born
prematurely should receive BCG when they are fit to be discharged from
hospital1. All immunizations required at 2 months of age can be administered
to preterm or low birth weight infants except for rotavirus vaccine which
should be deferred until the infant is discharged from the hospital to prevent
potential spread of this live vaccine virus2.

Before pregnancy
Rubella vaccine should be given 1 month and varicella vaccine 3 months
prior to pregnancy2.

Pregnancy
Immunization during pregnancy poses theoretical risks to the developing
foetus. Pregnant women should receive a vaccine when the vaccine is
unlikely to cause harm, the risk of disease exposure is high and the infection
would pose a significant risk to mother or foetus. When a vaccine is to be
given during pregnancy, it should be postponed if possible to the second
or third trimester of pregnancy to minimize the theoretical concern about
teratogenicity. Routine vaccinations considered safe in pregnancy are
inactivated influenza, diphtheria and tetanus toxoid. Hepatitis A and B
vaccines can be given if indicated. Inactivated polio virus (IPV) vaccine
can be given to pregnant women who have never received polio virus
vaccine or are partially immunized.
Pregnancy is a contraindication to administration of live vaccines. Therefore measles, mumps, rubella, varicella, BCG, live attenuated influenza, oral polio and yellow fever vaccinations should be avoided during pregnancy.

Pregnant women at risk of exposure to pathogens liable to cause certain serious illnesses should be considered for immunization. These include pneumococcal and meningococcal infections, Japanese encephalitis, typhoid and rabies. To prevent such infections the relevant inactivated vaccines are recommended. Human papilloma virus (HPV) vaccine contains no live virus but data on immunization during pregnancy are limited. Therefore initiation of the vaccine series should be delayed until after completion of the pregnancy.

Pregnant women are at increased risk of complications from influenza. Therefore, inactivated influenza vaccine should be administered to pregnant women during an influenza epidemic, regardless of the trimester. Immunization of pregnant women also protects the infant against influenza².

Immunocompromised patients

Safety and effectiveness of vaccines in persons with immune deficiency are determined by the nature and degree of immunosupression. Such people will vary in their susceptibility to infection.

Immune deficiency conditions are grouped into primary and secondary (acquired) immune deficiency disorders.

Primary immune deficiencies

These are usually inherited and involve a part of the immune defenses such as B-lymphocyte (humoral) immunity, T-lymphocyte (cell mediated) immunity, complement or phagocytic function.

Live vaccines are contraindicated for severe B-lymphocyte defects but not for selective IgA deficiency and IgG subclass deficiencies.

Live vaccines are contraindicated for all T-lymphocyte mediated immune disorders. Live bacterial vaccines such as BCG and the oral typhoid vaccine are contraindicated in phagocytic function disorders, such as chronic granulomatous disease.

Live virus vaccines are safe to administer to children with complement deficiencies and disorders of phagocytic function. Patients with complement deficiencies should be given Hib, pneumococcal and meningococcal vaccines.

Secondary (acquired) immune deficiencies

Secondary or acquired immune deficiency disorders occur in people with HIV/AIDS, malignant neoplasms, splenectomy, organ transplantation and in persons on immunosuppressive drugs or radiation therapy. It may also occur in persons with severe malnutrition or protein loss as in nephrotic syndrome.

Live viral vaccines are generally contraindicated because of the increased risk of adverse events. After immunosuppressive therapy for cancer, live virus vaccines are withheld for a minimum of 3 months after discontinuation of therapy and the patient should be in remission. The interval until immune reconstitution varies with the intensity and type of immunosuppressive therapy and the underlying disease. Therefore, often it is not possible to make a definite recommendation when live virus vaccines can be given safely and effectively.

Persons on corticosteroid therapy

Persons on high dose corticosteroid therapy (≥2 mg/kg/day of prednisolone or ≥20 mg/day in children weighing > 10 kg for 2 weeks or 40 mg/day for >2 weeks in adults) can become immunosuppressed. They should receive live vaccines only after 1 month of cessation of therapy². The interval of 1 month after discontinuation of therapy is based on the assumption that the disease is in remission or under control and that the immune response has been restored.
Solid organ transplant recipients

Children, adolescents and adults being considered for solid organ transplants should receive immunizations recommended for their age prior to transplantation. Vaccines will be more immunogenic before transplantation because medications given after, may be immunosuppressive by adversely affecting the number and function of B and T lymphocytes. All patients awaiting transplants should be immunized with hepatitis B and varicella vaccines before transplantation. Live virus vaccines should be given at least 1 month prior to transplantation and should not be given to patients receiving immunosuppressive medications after transplantation.

Information about use of live virus vaccines in patients after solid organ transplantation is limited. After solid organ transplantation, DTaP, Hib, hepatitis B, hepatitis A, inactivated influenza, pneumococcal and meningococcal vaccines can be administered, if indicated. Safety and immunogenicity data for these vaccines in children after transplantation are limited. Most experts recommend waiting for at least 6 months after transplantation, when immunosuppression is less intense, for resumption of immunization schedule.

Haemopoetic stem cell transplant

Many factors can affect immunity to vaccine preventable diseases for a person recovering from a successful haemopoetic stem cell transplantation or bone marrow transplantation. These include:

- Donor’s immunity
- Type of transplant (ie autologous or allogenic, blood or haemopoetic stem cell)
- Time interval since transplantation
- Receipt of immunosuppressive medications
- Presence of graft-versus-host disease

Although many will acquire donor’s immunity, some will lose serological evidence of immunity. Therefore, it is advisable to facilitate retention of donor immunity by antigenic stimulation after transplantation. Inactivated vaccines such as diphtheria, tetanus, pertussis, Hib, hepatitis A and B, IPV and pneumococcal and meningococcal vaccines are recommended 6 months after transplantation.

Persons with asplenia or functional asplenia

These result from the following:

- Surgical removal of the spleen
- Sickle cell disease (functional asplenia)
- Congenital asplenia

All children, adolescents and adults with asplenia, irrespective of the cause, have an increased risk of fulminant bacteremia and need immunization with pneumococcal, Hib and meningococcal vaccines. When surgical splenectomy is planned, immunization status for Hib, pneumococcus and meningococcus should be ascertained and the required vaccines should be administered at least 2 weeks prior to splenectomy. If splenectomy is urgent, vaccines should be administered prior to discharge. For booster doses of the vaccines consultation with a specialist is recommended.

In general, antimicrobial prophylaxis in addition to immunization should be initiated after splenectomy. Some experts continue prophylaxis throughout childhood and into adulthood for high risk patients with asplenia.

Immunization of HIV infected persons

Please refer Chapter 22.

Immunization of renal dialysis patients and patients with chronic renal disease

Children with chronic renal disease should receive all routine immunizations according to the schedule for healthy children.

Patients with renal failure have an increased risk of infection with a variety of pathogens particularly hepatitis B and pneumococcus.
Hepatitis B vaccination is recommended for pre-end-stage renal disease before they become dialysis dependent. Patients with uraemia who were vaccinated before they required dialysis have been shown to have higher seroconversion rates and antibody titres. For patients undergoing haemodialysis, higher vaccine doses or increased number of doses are required. Clinically significant hepatitis B infection has been documented in patients who have not maintained anti-HBs concentrations \( \geq 10 \text{ mIU/mL} \). A booster dose should be administered when the level is less.

(Please refer Chapter 7)

Pneumococcal vaccine – Patients with renal failure have an increased risk for pneumococcal infections. The efficacy of pneumococcal vaccination may be lower for some of these patients. They may require repeat vaccinations or an increased dose of vaccine. Because secondary antibody responses are less affected than primary antibody responses, immunization strategies should be formulated early in the course of progressive renal disease. This approach is particularly important if transplantation and immunosuppressive therapy are being considered.

DTaP, Hib, hepatitis A, Japanese encephalitis, MMR, meningococcal, IPV, rabies, typhoid, varicella, yellow fever and inactivated influenza vaccines may be administered prior to commencement of dialysis, if indicated.

Patients requiring repeated blood transfusions /blood products

A large number of infections can be transmitted by blood transfusions. These include HIV, hepatitis A, B and C, syphilis, malaria, human T cell lymphotropic virus types 1 and 2, cytomegalovirus, Epstein-Barr virus and parvovirus B19. Since immunization is at present available only for hepatitis A and B, donor blood screening is essential before blood transfusion. Nucleic acid amplification testing (NAT) identifies viral genes in the window period before antibodies develop and is available for infections such as HIV and hepatitis C.

All patients requiring repeated transfusions should be immunized with hepatitis A and B vaccines prior to commencement of dialysis.

Patients with chronic diseases

Some chronic diseases make people susceptible to severe manifestations and complications of common infections. In general, immunizations recommended for healthy people should be given to such persons with the exception of persons with immunological disorders.

People with chronic liver disease who are at risk of severe clinical manifestations of acute infection with hepatitis viruses should receive hepatitis A and hepatitis B vaccines if they have not received them already\(^2\).

Children with history of seizures

Infants and children with a history of seizures could be given routine immunizations except Japanese encephalitis vaccine. Japanese encephalitis vaccine can be given 1 year after the last seizure, provided there is no progressive neurological disorder. If a seizure follows the first dose of any vaccine, that vaccine should not be repeated. In the case of pertussis immunization during infancy, administration of DTaP could coincide with a seizure or hasten the recognition of a disorder associated with seizures such as infantile spasms or myoclonic epilepsy of infancy, and cause confusion about the role of pertussis immunization. Hence, pertussis immunization in infants with a history of recent seizures should be deferred until a progressive neurological disorder has been excluded or the cause of the earlier seizure has been determined\(^2\).

Healthcare personnel

Healthcare personnel should protect themselves by receiving all appropriate immunizations. All those without evidence of immunity, should receive the MMR and varicella vaccines before initial contact or during continuing contact with patients. Hepatitis B vaccine should be given to all personnel who are likely to be exposed to blood or blood containing body fluids. A single dose of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) should be given to all those who have not received it earlier\(^2\).
Adolescents and young adults

Adolescents and young adults may not be protected against all vaccine preventable diseases because they have escaped natural infection and they have not received all recommended vaccines. Rarely persons who have received immunizations according to the routine schedules may not be immune. To ensure age appropriate immunization, all children should have a routine appointment at 11 to 12 years of age for administration of appropriate vaccines. During adolescent visits, immunization status should be reviewed and deficiencies corrected. Adolescents and young adults intending to travel abroad should have their immunization status reviewed according to their travel plans at least 2 months prior to departure, to allow time to administer required vaccines.1

References


Dr N. P. S. Gunaratna MBBS, FRCP, FCCP, DCH, FSLCPaed
Consultant Paediatrician

CHAPTER 29

THE STORAGE AND TRANSPORT OF VACCINES

Introduction

Vaccines are sensitive to heat and freezing and therefore, should be stored and transported at the correct temperature from the time they are manufactured until they are used. The system used for keeping and distributing vaccines in the recommended condition is called the cold chain. Non adherence to the recommended cold chain conditions results in reduction of vaccine efficacy leading to vaccine failure. It can also lead to an increased risk of adverse reactions following immunization, particularly after the use of unduly frozen vaccines. Depending on the nature of the product, vaccines can be damaged either by exposure to heat or freezing. In addition, there are certain vaccines which are sensitive to light.

Tables 1 and 2 illustrate the degree of sensitivity of different vaccines to heat and freezing.1

Table 1. Heat sensitivity of different vaccines

<table>
<thead>
<tr>
<th>Range</th>
<th>Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>most sensitive</td>
<td>OPV</td>
</tr>
<tr>
<td></td>
<td>Measles, MR, MMR</td>
</tr>
<tr>
<td></td>
<td>DTP, DTP-Hep B, DTP-Hib,</td>
</tr>
<tr>
<td></td>
<td>DTP-HepB+Hib, YF</td>
</tr>
<tr>
<td></td>
<td>BCG</td>
</tr>
<tr>
<td></td>
<td>Hib, DT</td>
</tr>
<tr>
<td>least sensitive</td>
<td>Td, TT, HepB, JE</td>
</tr>
</tbody>
</table>
Table 2. Freeze sensitivity of different vaccines

<table>
<thead>
<tr>
<th>Range</th>
<th>Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>most sensitive</td>
<td>HepB</td>
</tr>
<tr>
<td></td>
<td>Hib (liquid)</td>
</tr>
<tr>
<td></td>
<td>DTP, DTP-Hep B, DTP-Hib, DTP-HepB+Hib, YF</td>
</tr>
<tr>
<td>least sensitive</td>
<td>TT, Hib lyophilised</td>
</tr>
</tbody>
</table>

Exposure to heat over time can be monitored using vaccine vial monitors (VVM) and the change in colour will guide decisions on the suitability of vaccines for use.

During storage and transportation of freeze-sensitive vaccines (eg. DTP, TT, DT, aTd, hepatitis B and Hib) the risk of freezing is greater than the risk of heat exposure. If exposure to freezing temperature is suspected the shake test should be done as VVM do not indicate exposure to freezing (Figure 4).

This chapter provides general guidelines on storage of vaccines. However, manufacturer’s product information and package inserts should be referred to, for specific and detailed information about storage and handling of specific vaccines.

**Storage temperature for vaccines**

All inactivated vaccines require refrigerator storage temperatures between 2°C and 8°C, with a desired average temperature of 4°C. An open vial of oral polio vaccine can be kept at 8°C for a maximum period of 3 months. Storage of oral polio vaccine for a longer duration should be in the freezer compartment.

**Storage of vaccines in a refrigerator:** (Figure 1)

- Food, drinks and other medications should not be stored in the refrigerator used for storing vaccines.
- The refrigerator door shelves should not be used for storing vaccines and the door should not be opened frequently.
- Combination freezer/refrigerator units with one exterior door are not recommended for storage of vaccines as the risk of freezing of vaccines is high. If this type of refrigerator is used the vaccines that are sensitive to freezing should not be stored on the shelf immediately below the freezing compartment and should be kept away from side and bottom linings of the refrigerator where freezing could occur.
- Multi-socket outlets should not be used for connecting the refrigerator to a power supply.
- Freeze and store ice-packs in the freezer compartment.
- Arrange the boxes of vaccines in such a way that air can circulate.
- The temperature of the main compartment of the refrigerator should range between 2°C to 8°C and the freezer compartment should have a temperature range between -5°C to -15°C.
- Every vaccine containing refrigerator should have a calibrated thermometer.
- In case of a power failure, do not open the refrigerator. Take immediate steps to restore power.
- If the power failure is likely to last for more than 8 hours, vaccines should be moved to another storage site.
- Vaccine storage refrigerators should have generator backup.
- Prior to storing vaccines in a refrigerator, the temperature should be allowed to stabilize. New refrigerators may need 2 or more days of operation to establish a stable operating temperature.
- If at any time it is discovered that stored vaccines have been exposed to temperatures outside the recommended ranges, these vaccines should remain properly stored, but segregated and marked “Do NOT Use” until guidance can be obtained.
Open vial policy

Opened multi-dose vials of liquid vaccines from which one or more doses have been removed, using standard sterile procedures, may be used within **30 days, if all of the following conditions are met:**

a) The expiry date has not passed; and
b) The vaccine has not been contaminated; and
c) The vials have been stored under appropriate cold chain conditions; and
d) The VVM on the vial, if attached, has not reached the discard point.

- Liquid vaccines to which the statement above applies include OPV, DPT, TT, DT, aTd, hepatitis B, and liquid formulations of Hib.
- Freeze-dried vaccines, which include BCG, measles, MMR, yellow fever, and freeze-dried formulations of Hib, must be discarded six hours after reconstitution or at the end of the immunization session, whichever comes sooner, and therefore opened vials of these vaccines cannot be stored for future use.
- Keep opened multi-dose vials of OPV, DPT, TT, DT, aTd, hepatitis B and liquid formulations of Hib that meet the conditions above, in a special box in the main section of the refrigerator, so that you remember to use them first in the next session (Figure 1).
- Discard opened vials of any vaccine (including single dose and multi-dose, liquid and freeze dried) immediately, if any of the following conditions apply:
  - Sterile procedures have not been followed when handling the vaccine vials; or
  - If there is evidence of contamination, such as floating particles in the vaccine; or
  - When you suspect that the vaccine has been contaminated.

Diluent

Diluent vials must **NEVER** be frozen. If the manufacturer supplies a freeze-dried vaccine packed with its diluent, ALWAYS store the product between 2°C and 8°C. The diluents supplied by the manufacturer should always be used for reconstitution of the freeze-dried vaccines.

Temperature monitoring systems

Regular temperature monitoring is vital for proper cold chain management.

A) **Thermometers** (Figure 2)

Temperatures in the refrigerator should be read twice a day, once in the morning and once before leaving at the end of the day. A
temperature log should be posted on the door of the refrigerator where the twice daily temperature readings are recorded. Use only calibrated thermometers with a Certificate of Traceability and Calibration. Calibration of thermometers is carried out at the Sri Lanka Standards Institute (SLSI) and the Industrial Technology Institute (ITI) in Colombo.

However, it is recommended that twice daily manual temperature recording be continued irrespective of the use of data loggers due to reported failures in systems that use electronic monitoring.

Cold chain monitoring systems

A) Vaccine vial monitors (VVM)
VVM will measure exposure to heat, but not exposure to freezing temperatures. VVM label contain heat-sensitive material. It registers cumulative heat exposure over time. The combined effects of time and temperature cause the inner square of the VVM to darken, gradually and irreversibly. A direct relationship exists between the rate of colour change and temperature. The lower the temperature, the slower the colour change and higher the temperature, the faster the colour change.

B) Data loggers
Data loggers (data recorders) are electronic, automatic, continuous, temperature monitoring devices which provide assurance of temperature maintenance during transport and in refrigerators. They are useful even when there is no person to monitor temperature specially when the clinic is closed. One of the primary benefits of using data loggers is the ability to automatically collect data on changes in temperature on a 24-hour basis. They measure the temperature using sensors and are generally small, battery powered and portable. They are equipped with a microprocessor and an internal memory for data storage. Some data loggers utilize software to access and analyse the stored, while others have a local interface device (keypad, LCD) where the data is displayed. In more advanced types, the data can be stored even up to 120 days.
Figure 3b. Interpretation of the vaccine vial monitor².

B) Freeze-tag™ (Figure 4a)
The Freeze-tag™ consists of an electronic temperature measuring circuit with an LCD-display and detects exposure to freezing. If the indicator is exposed to a temperature below 0°C ± 0.3°C for more than 60 minutes ± 3 minutes the display will change from the “OK” status into the “alarm” status as indicated in the picture below.

Figure 4a. Indicators used to detect freezing – B) Freeze-tag.™

C) Freeze Watch™ (Figure 4b)
Freeze Watch™ is an indicator used for detecting freezing and consists of a card embedded with a thin walled glass vial containing a coloured liquid. When exposed to temperatures below 0°C for more than one hour, the vial bursts and releases the coloured liquid, staining the white backing card.

Figure 4b. Indicators used to detect freezing – Freeze Watch,™

Shake Test
When the above freeze indicators show signs of exposure to freezing temperatures or if it is suspected that vaccines have been exposed to freezing, the shake test is carried out. However, the following types of vaccine vials should be discarded immediately without subjecting them to a shake test:

a) When a vaccine vial is found to be frozen
b) When a suspect vial cannot produce a homogenous solution after shaking

The “Shake Test” is carried out on adsorbed vaccines (eg. DTP, DT, aTd, TT) or liquid vaccines (eg. hepatitis B) suspected as having being exposed to freezing temperatures likely to have damaged them.
The Shake Test procedure: (Figure 5)

- Obtain a vial of vaccine of the same batch from the same manufacturer and freeze it at solid state for at least 10 hrs at -10°C and then let it thaw. This is the control vial.
- Choose your test vial from the batch suspected as having been frozen.
- Shake the test and control vials together in one hand for 10-15 seconds.
- Allow to rest on a table.
- Compare the sedimentation rates of deliberately frozen control vial with the suspect vial.
- If the test vial has a sedimentation rate similar to or faster than the control vial the batch of vaccines should not be used.

Light sensitivity

Some vaccines are very sensitive to strong light and exposure to ultraviolet light (sunlight or fluorescent light) causes loss of potency. BCG, measles, MR and MMR vaccines are sensitive to light. Normally, these vaccines are supplied in vials made of dark brown glass, which gives them some protection against damage due to light, but care should be taken to keep them protected from strong light at all times.

Transport of vaccines to outreach health centres

Vaccine carriers (Figures 6 and 7) are used for this purpose. They are insulated containers that, when lined with frozen ice-packs, keep vaccines and diluents cold during transportation. These are also used for temporary storage of vaccines when the refrigerator is being defrosted.

Placing adsorbed vaccine vials such as tetanus, DPT and liquid vaccines such as hepatitis B in direct contact with ice cubes is not recommended as this could damage the potency of vaccines. The floatation of open vials on melting ice may also lead to contamination of contents in vials.
Procedure for packing the vaccine carrier

- Remove the icepacks from the freezer.
- Wait for them to be free of frost (approximately 10 - 15 minutes).
- Place the frost free ice-packs around the inside walls of the carrier.
- Stack live vaccines near the frozen ice packs at the bottom.
- Take precautions to prevent vulnerable vaccines from being frozen (by keeping them in their packaging or wrapping a sheet of paper around or placing them in a plastic container).
- Place a layer of frozen ice-packs on top.
- Secure the lid tightly.

Emergency plans

Each facility should have a detailed written emergency vaccine retrieval and storage plan in the event of refrigerator and/or freezer malfunctions, during power failures, natural disasters or other emergencies which might compromise appropriate vaccine storage conditions.

References

1. Temperature sensitivity of vaccines. WHO/IVB/06.10. /2006
2. Immunisation in Practice: Module 3 – Cold Chain. WHO/EPI/TRAM/98.01-11.
4. Vaccine storage and handling toolkit, November 2012, Centre for Disease Control and Prevention, USA.

Senior Professor of Microbiology, University of Colombo.

CHAPTER 30
GENERAL INFORMATION ON VACCINES

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

Interchangeability of vaccines

Similar vaccines produced by different manufacturers may differ in their components and formulations and may elicit different immune responses. However, such vaccines have been considered interchangeable when administered according to their licensed indications, although data documenting interchangeability are limited.

Lapsed immunizations

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

Unknown or uncertain immunization status

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

Most vaccines can be simultaneously administered safely and effectively. Healthy infants, children and adults have sufficient immunological capacity to respond to multiple vaccines. Simultaneous administration of IPV, MMR, varicella, or DTP vaccines results in rates of seroconversion and adverse effects similar to those observed when the vaccines are administered at separate visits. When vaccines are administered simultaneously, separate syringes and separate sites should be used, and injections into the same extremity should be separated by at least 1 inch so that any local reactions can be differentiated. Individual vaccines should never be mixed in the same syringe unless they are specifically licensed and labeled for administration in one syringe. If live vaccines are not administered concurrently, a minimum gap of 4 weeks should be kept between immunizations. There is no required interval between administration of a live vaccine and an inactivated vaccine or between inactivated vaccines. If an inactivated vaccine and an immunoglobulin product are indicated concurrently (eg, hepatitis B vaccine and HBIG, rabies vaccine and RIG), they should be administered at separate anatomical sites. Live vaccines administered by the oral route (OPV, oral typhoid, rotavirus vaccine) do not interfere with each other if given simultaneously. These vaccines may be given at any time before or after each other. Live vaccines should not be given within three months of receiving immunoglobulin, blood or blood products.

Allergy to egg protein

Presently available influenza and yellow fever vaccines contain egg proteins. Yellow fever vaccine is contraindicated in persons who have a history of allergy to egg protein. Persons who have allergy to eggs (immediate hypersensitivity) should be seen by a physician for appropriate evaluation to determine whether to proceed with influenza vaccination or defer. If decided to proceed with vaccination, it should be given in a hospital setting.

Injection techniques

A vaccine recommended to be administered through intramuscular route, should not be administered subcutaneously. All parenteral live vaccines are administered subcutaneously.

1. Subcutaneous (SC) injections

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

Needle size:

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

Sites recommended for subcutaneous injections:

Upper Arm: Deltoid region.
Abdomen: On either sides of the umbilicus.
Thigh: Antero-lateral region.

Figure. Sites on the body where a subcutaneous injection can be given.
2. Intramuscular (IM) injections

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

All adjuvanted vaccines should be given IM.

**Sites recommended for intramuscular injections:**

- Infants – Ante-rolateral thigh
- Children over 1 year and adults – deltidoid region

**Needle size:**

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

3. Intradermal (ID) injections

For intradermal injection, a needle of 25 or 27G and 3/8 to 3/4 inch (1-2 cm) is inserted into the skin parallel to the skin surface, with the bevel of the needle facing upward (Figure 1). A wheal should appear immediately after injection at the site (Figure 2). The same sites recommended for subcutaneous injections can be used for administering intradermal injections.
CHAPTER 31
FREQUENTLY ASKED QUESTIONS

- In the National Immunization Programme (NIP) of Sri Lanka many vaccines are given routinely and most diseases are well controlled. There are other vaccines available outside the NIP such as rotavirus, chickenpox, hepatitis A, human papillomavirus and pneumococcal. Who should receive such vaccines?

The decision to vaccinate should be taken in consultation with the health care professional based on the individual’s needs.

- Does natural immunity produce better protection than vaccine induced immunity?

Although certain viral diseases such as chickenpox produce natural immunity the disease may be fatal or may cause permanent disability. In addition, many other diseases do not produce the protective level of immunity even after the natural disease, eg. tetanus. Vaccination is safer than contracting the disease and re-vaccination can be carried out, if necessary.

- Is an interval of 4 weeks mandatory between immunizations?

This is true regarding injectable live vaccines, because the desired antibody response may not be achieved if a second live vaccine is given before four weeks.

- Does the interval between vaccinations apply only to live vaccines?

Yes, it is not applicable to killed vaccines.

- If a child has received only one dose of vaccine, is it necessary to restart the schedule?

No. The vaccine schedule can be safely continued as if there has been no delay. The recommended intervals between further doses should be maintained.

References
1. Centers for Disease Control and Prevention, MMWR General Recommendations on Immunizations, ACIP Recommendations and Reports, January 28, 2011 / 60 (RR02); 1-60.

Dr Kanthi Nanayakkara Dip Med Micro, MD
Consultant Virologist, Medical Research Institute, Colombo 8.
• Can children with fever or a cold be immunized?
The vaccination should only be postponed if a child is seriously ill or has a high fever of >38°C at the time of immunization.

• Sometimes we find that certain vaccines have been administered abroad according to different schedules. What schedule should we follow?
Vaccination schedules are based on the disease prevalence in specific countries. It would be appropriate to continue with the schedule of the country where the person is going to live. For example, if a person is on holiday, it is not rational to restart or reschedule his future vaccination. On the other hand, for persons who have returned from abroad and are going to live in this country it would be advisable to have their subsequent vaccinations rescheduled according to the local schedule.

• Students going for overseas studies are recommended a number of vaccines within a short period. Is it safe to give all of them?
It is advisable to plan an overseas stay well in advance enabling adequate time intervals for vaccinations. Please refer to the accelerated schedules under each chapter.
Most vaccines can be given as accelerated schedules with the exception of cholera and yellow fever vaccines. Two live vaccines such as MMR and varicella can be concurrently administered or with an interval of 4 weeks. Delaying the other vaccines depend on the travel plan. Killed and subunit vaccines can be given at intervals of 1-2 weeks.

• Should vaccination be delayed in low birth weight babies?
Low birth weight babies should receive BCG vaccine when they are fit to be discharged from the hospital. They should also receive their routine vaccinations at the recommended age.

• What precautions should be taken when vaccinating preterm babies?
It is important that preterm infants have their immunizations according to the NIP.
Their age should be calculated from the date of birth. In extremely premature babies (≤ 28 weeks of gestation), the need for monitoring for 48-72 hours should be considered particularly for those with a history of respiratory immaturity due to the risk of developing apnoea. In such situations, the 2 month’s vaccination is recommended to be administered in a hospital where a paediatrician can be consulted for further advice.

• What action should be followed if you find any of your liquid vaccines frozen?
The safety and effectiveness of a vaccine is affected by extreme temperature changes and as such should be discarded safely. However, unopened oral polio vaccine can be stored below 0°C.

• What is your advice for a child who has not developed a scar after BCG vaccination?
It depends on the age of the child. If the child is between 6 months to 5 years of age, repeat the BCG. If the child is more than 5 years, do the Mantoux test and if it is negative, administer the BCG.
In general it takes about 10-12 weeks to produce a scar and non-formation of a scar does not mean that BCG has not been taken up. In 10-12% of vaccinees, scar formation may not take place at all.

• When there is a reaction to DTwP vaccine in the routine EPI schedule, is it better for the patient to go for DTaP vaccine for the next dose or use DT?
As the reactogenicity is less with DTaP vaccine, it can be used when there is a reaction to DTwP vaccine. The DT can also be given, as the DTaP is only available in the private sector.

• Can you interchange different sources of vaccines with regard to children who had begun the vaccination with DTwP or DTaP?
There is no clinical data to support switching from one type of DTwP to another type of DTwP vaccine and DTaP vaccine within the primary vaccination programme, but there is no contraindication to do so. However, it is preferable to continue with the same brand unless it is not available.

- If full DTP vaccinations were completed during childhood vaccination, is it still possible for an adult to get whooping cough?

   Yes. The immunity acquired from immunization is not life-long. Epidemiological evidence suggests that routine immunization of adolescents and adults can significantly result in lowering of the incidence and severity of the disease. Pertussis vaccination for adults (dTpa) may be given at intervals of ten years.

- Why is a booster dose of Hib vaccine given during the 2nd year of life?

   More than 90% of vaccinees achieve a titre of >1.0 µg/mL after 3 doses with protection lasting until 15-18 months of age. More than 50% of the time, the titre falls to less than 0.15 µg/mL (the minimum protective level), by 18 months. If a booster dose is given at 15-18 months of age, the titre rises by 30-90 fold and reaches levels as high as 40µg/mL. Hence a booster dose is recommended at 18 months of age.

- When 2 doses of MMR are to be given to adolescents what should the minimum interval be?

   A minimum of 4 weeks.

- Why is it important to give two doses of MMR vaccine?

   Two doses will provide the recipient and the community with better protection. With the first dose of MMR vaccine, 5-10% children will remain vulnerable to these diseases. However, after the 2nd dose, only 1% will remain susceptible.

- What is the recommended dose of MMR for adults at a high risk of exposure?

   Two doses are recommended for adults at a high risk of exposure and transmission (e.g., students attending higher educational institutions, healthcare personnel, international travellers) and 1 dose for other adults aged ≥18 years.

- Should persons who had been previously diagnosed to have measles, rubella and mumps be excluded from MMR vaccination?

   It is not a safe practice to exclude those individuals without reliable confirmatory serological evidence for all 3 diseases.

- If a person has developed mumps after the first dose of MMR, is it necessary to administer the second dose?

   Yes. As MMR is a combined vaccine, even if the person has contracted natural infection in the past or before the second dose, it is important to complete the schedule. There is no evidence to suggest that an additional dose of vaccine causes any harm.

- How long should a female avoid pregnancy, after receiving rubella and chickenpox containing vaccinations?

   The minimum interval should be 3 months for chickenpox vaccine and one month for rubella containing vaccines, because of the theoretical risk to the developing foetus. However, pregnancy within this period is not an indication for termination as no teratogenic effects have been identified.

- Many children in my practice have had only 1 dose of varicella vaccine. Is it necessary to wait until the 11- to 12-year-old visits to give them the second dose?

- Do not delay giving the second dose of varicella vaccine. The second dose can be given at an earlier age provided that interval between the first and second dose is more than 3 months. If the first dose was given at 12-15 months, it is recommended to give the second dose at
age 4 through 6 years. It is intended to provide improved protection in the 15% to 20% of children who do not respond adequately to the first dose.

- When one member of a family has developed chickenpox is it justifiable to vaccinate the rest of the family?
  Yes. The varicella vaccine, if administered within 3 - 5 days of exposure is 80-90% effective in preventing the disease and complications or modifying the severity of illness. In addition, it is important to protect susceptible immunocompromised persons, neonates and pregnant mothers with varicella zoster immunoglobulin (VZIG) as soon as possible, after exposure.

- "Chickenpox in children is usually not serious". Why not allow children to get the disease?
  It is not possible to predict who will have a mild or serious disease. When there is an effective vaccine, it is not worth taking this risk. Even a child with a mild disease could transmit the disease to susceptible persons in the community.

- Is there 100% assurance that a person is protected from chickenpox if 2 doses of vaccine have been administered?
  No vaccine is 100% effective in preventing any disease. For chickenpox vaccine, about 90% of people with two doses are completely protected from chickenpox infection and almost 100% from severe disease. On the other hand, if a vaccinated person does get chickenpox, it is usually a mild form with <50 skin lesions.

- What do you give to a child younger than 1 year of age if they were exposed to the chickenpox or zoster virus?
  The minimum age for varicella vaccine is 12 months. Vaccination is not recommended for infants younger than 12 months of age even as post-exposure prophylaxis. CDC recommends a healthy infant should receive no specific treatment or vaccination after exposure to VZV.

The child can be treated with acyclovir if chickenpox occurs. Immunocompromised children and neonates should receive VZIG.

- If a child gets breakthrough varicella infection, (less than 50 lesions) can the child go to school?
  Breakthrough varicella represents replication of wild varicella virus in a vaccinated person. Although most breakthrough disease is mild, the child is infectious and activities should be restricted to the same extent as an unvaccinated person with varicella.

- When a mother has chickenpox at the time of delivery, can the neonate be given the vaccine?
  No. The vaccine is only recommended after infancy. To reduce the risk of severe disease in infants, it is recommended that neonates born to mothers who developed varicella within 5 days before to 2 days after delivery should receive VZIG, regardless of whether the mother received VZIG.

- If a person is immunocompromised, is it necessary to vaccinate family members against chickenpox?
  Yes. Because, transmission of vaccine virus from a healthy individual is rare.

- What vaccines are recommended for the household of an immunocompromised person?
  MMR, varicella and rotavirus vaccines as they rarely transmit diseases. However, OPV is contraindicated as the vaccine virus can be transmitted and could cause vaccine associated paralytic polio (VAPP) in the immunocompromised.

- Can the HPV vaccine be given to women who are already sexually active?
  Ideally, HPV immunization should be completed before the onset of sexual activity. However, women who have begun sexual activity
will benefit from vaccination if they have not yet become infected with the vaccine preventable HPV serotypes. Vaccination will also prevent re-infection with vaccine specific serotypes.

- Does the HPV vaccine protect against all types of cervical cancers? No. There are two types of vaccines commercially available – quadrivalent (oncogenic serotypes 16 & 18 and non-oncogenic 6 & 11) and bivalent (oncogenic serotypes 16 & 18). Serotypes 16 and 18 account for nearly 70% of cervical cancers. In addition, there is evidence to suggest that the vaccines provide some cross protection against certain other oncogenic serotypes.

- How long does the HPV vaccine protection last? Current studies have shown that the HPV vaccine results in a high antibody level not requiring booster doses for up to 10 years. Studies will continue and more data regarding the effectiveness of the vaccine will be available in the future.

- Does the HPV vaccine interfere with the efficacy of the contraceptive pill? There is no evidence to suggest that the vaccine affects the efficacy of the contraceptive pill.

- What is the duration of protection of the Hepatitis A vaccine? One dose of Hepatitis A vaccine will protect the recipient for at least 1 year. A second dose given after 6 to 12 months will usually confer lifelong protection.

- Is a history of febrile seizure contraindicated for JE vaccination? Yes. Within one year of any convulsions.

Further reading:

Dr Prasanna Siriwardena MBBS, DCH, MD, DFM, MCGP, MRCGP(INT.) Consultant Family Physician, Piliyandala.
## NATIONAL IMMUNIZATION PROGRAMME OF SRI LANKA 2014

### Annex. I

<table>
<thead>
<tr>
<th>VACCINE</th>
<th>AGE</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG</td>
<td>Birth</td>
<td>Before leaving hospital within 24 hours of birth. To be given to children between 6 months and 5 years of age, with no evident BCG scar.</td>
</tr>
<tr>
<td>Polio</td>
<td>Month 2</td>
<td></td>
</tr>
<tr>
<td>DTP-Hep B-Hib</td>
<td>Month 2</td>
<td></td>
</tr>
<tr>
<td>DTP</td>
<td>Month 2</td>
<td></td>
</tr>
<tr>
<td>JE live vaccine</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>MMR</td>
<td>Month 2, Month 6</td>
<td></td>
</tr>
<tr>
<td>DT</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>aTd (adult tetanus &amp; diptheria)</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Tetanus</td>
<td>*</td>
<td>First Pregnancy – 1st dose after the 12th week of pregnancy. 2nd dose: 6 - 8 weeks after the first dose. One dose of tetanus toxoid should be administered during every subsequent pregnancy, up to a maximum of five doses.</td>
</tr>
</tbody>
</table>

### VACCINES OUTSIDE THE NATIONAL IMMUNIZATION PROGRAMME OF SRI LANKA 2014

### Annex. II

<table>
<thead>
<tr>
<th>VACCINE</th>
<th>AGE</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTaP-Hep B-IPV-Hib</td>
<td>Birth, Month 4, Month 6</td>
<td>DTP-Hep B and Hib when provided by the same manufacturer can be mixed together and administered as one dose.</td>
</tr>
<tr>
<td>DTP-Hib</td>
<td>Month 6, Month 12</td>
<td></td>
</tr>
<tr>
<td>Hib</td>
<td>Month 6</td>
<td></td>
</tr>
<tr>
<td>Pneumococcal conjugate</td>
<td>Month 6</td>
<td></td>
</tr>
<tr>
<td>Rotavirus</td>
<td>Month 6</td>
<td></td>
</tr>
<tr>
<td>JE killed vaccine</td>
<td>Month 6</td>
<td></td>
</tr>
<tr>
<td>Varicella</td>
<td>Month 6</td>
<td></td>
</tr>
<tr>
<td>dTpa (reduced antigen DTP)</td>
<td>Month 6</td>
<td>Adolescents and adults</td>
</tr>
<tr>
<td>Human papillomavirus</td>
<td>Month 6</td>
<td></td>
</tr>
</tbody>
</table>

### INDIVIDUAL

- **Hepatitis A**: For those who have not previously received Hep A vaccination – 2 doses at 0 & 6 to 12 months later (over 2 years)
- **Hepatitis B**: For those who have not previously received Hep B vaccination – 3 doses at 0, 1 & 6 months
- **Hepatitis A + B**: For those who have not previously received Hep A & B vaccination – 3 doses at 0, 1 & 6 months later (over 2 years)
- **Typhoid**: Injectable: 1 dose every 3 years

### SPECIAL CIRCUMSTANCES

- **Meningococcal**
- **Pneumococcal**
- **Cholera**
- **Rabies**
- **Yellow fever**
## RECOMMENDATIONS FOR ROUTE AND SITE OF IMMUNIZATION

<table>
<thead>
<tr>
<th>VACCINE</th>
<th>TYPE</th>
<th>ROUTE</th>
<th>SITE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Tetanus &amp; Diphtheria (aTd) toxoid</td>
<td>Toxoids</td>
<td>IM</td>
<td>Deltoid</td>
</tr>
<tr>
<td>BCG</td>
<td>Live attenuated bacteria</td>
<td>ID</td>
<td>Deltoid of left arm</td>
</tr>
<tr>
<td>Cholera</td>
<td>Live attenuated bacteria</td>
<td>Oral</td>
<td>-</td>
</tr>
<tr>
<td>Diphtheria – Tetanus Toxoid &amp; Pertussis (DTP)</td>
<td>Toxoid &amp; inactivated bacteria</td>
<td>IM</td>
<td>Anterolateral aspect of the thigh</td>
</tr>
<tr>
<td>Diphtheria – Tetanus Toxoid – Pertussis - Hepatitis B &amp; H.influenzae type b (DTP-HepB-Hib)(Pentavalent)</td>
<td>Toxoid &amp; inactivated bacteria, recombinant viral antigen and polysaccharide protein conjugate</td>
<td>IM</td>
<td>Anterolateral aspect of the thigh</td>
</tr>
<tr>
<td>Diphtheria reduced antigen – Tetanus Toxoid – Pertussis reduced antigen (dTpa)</td>
<td>Toxoid &amp; inactivated bacterial antigen</td>
<td>IM</td>
<td>Deltoid</td>
</tr>
<tr>
<td>Diphtheria &amp; Tetanus toxoid (DT)</td>
<td>Toxoids</td>
<td>IM</td>
<td>Deltoid</td>
</tr>
<tr>
<td>H. influenzae type b (Hib)*</td>
<td>Polysaccharide protein conjugate</td>
<td>IM</td>
<td>&lt; 2 years – anterolateral aspect of thigh &gt; 2 years – deltoid</td>
</tr>
<tr>
<td>Hepatitis A + Hepatitis B (combined vaccine)</td>
<td>Inactivated virus and recombinant viral antigen</td>
<td>IM</td>
<td>Deltoid</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Inactivated virus</td>
<td>IM</td>
<td>Deltoid</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Recombinant viral antigen</td>
<td>IM</td>
<td>&lt; 2 years – anterolateral aspect of thigh &gt; 2 years – deltoid</td>
</tr>
<tr>
<td>Influenza A &amp; B</td>
<td>Inactivated viruses</td>
<td>IM</td>
<td>Deltoid</td>
</tr>
<tr>
<td>Human papillomavirus</td>
<td>Recombinant viral antigen</td>
<td>IM</td>
<td>Deltoid</td>
</tr>
<tr>
<td>Japanese encephalitis live</td>
<td>Live attenuated virus</td>
<td>SC</td>
<td>Deltoid</td>
</tr>
<tr>
<td>Japanese encephalitis inactivated</td>
<td>Inactivated virus</td>
<td>SC</td>
<td>Deltoid</td>
</tr>
<tr>
<td>Measles</td>
<td>Live attenuated virus</td>
<td>SC</td>
<td>Deltoid</td>
</tr>
<tr>
<td>Measles, Mumps &amp; Rubella (MMR)</td>
<td>Live attenuated viruses</td>
<td>SC</td>
<td>Deltoid</td>
</tr>
<tr>
<td>Meningococcal</td>
<td>Polysaccharide</td>
<td>SC</td>
<td>Deltoid</td>
</tr>
<tr>
<td>Pneumococcal conjugate</td>
<td>Polysaccharide conjugate</td>
<td>IM or SC</td>
<td>&lt; 2 years – anterolateral aspect of the thigh. &gt;2 years – deltoid</td>
</tr>
<tr>
<td>Pneumococcal polysaccharide</td>
<td>Polysaccharide</td>
<td>IM or SC</td>
<td>&gt;2 years – deltoid</td>
</tr>
<tr>
<td>Oral Polio Vaccine (OPV)</td>
<td>Live attenuated virus</td>
<td>Oral</td>
<td>&lt; 2 years – anterolateral aspect of the thigh. &gt;2 years – deltoid</td>
</tr>
<tr>
<td>Inactivated Polio Vaccinate (IPV)</td>
<td>Inactivated virus</td>
<td>IM</td>
<td>&lt; 2 years – anterolateral aspect of the thigh. &gt;2 years – deltoid</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>Live virus</td>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td>Rabies</td>
<td>Inactivated virus</td>
<td>IM/SC/ID</td>
<td>Deltoid</td>
</tr>
<tr>
<td>Tetanus</td>
<td>Toxoid</td>
<td>IM</td>
<td>Deltoid</td>
</tr>
<tr>
<td>Typhoid</td>
<td>Capsular polysaccharide</td>
<td>IM</td>
<td>Deltoid</td>
</tr>
<tr>
<td>Varicella</td>
<td>Live virus</td>
<td>SC</td>
<td>Deltoid</td>
</tr>
<tr>
<td>Yellow Fever</td>
<td>Live virus</td>
<td>SC</td>
<td>Deltoid</td>
</tr>
</tbody>
</table>

ID - Intradermal
IM - Intramuscular
SC - Subcutaneous
# Annex IV

**Notification Form for Adverse Events Following Immunization (AEFI)**

## Patient Information
- **Name:**
- **MOH Division:**
- **Age:**
- **Sex:** Male □ Female □
- **Telephone:**

**Name & address of the Parent/Guardian:**

## Information on the vaccine (primary suspected and other)

<table>
<thead>
<tr>
<th>Vaccine (Generic Name)</th>
<th>Vaccine (Trade name)*</th>
<th>Route (1×2m, 3×4m)</th>
<th>Batch/Lot Number</th>
<th>Expiry date</th>
<th>VVM Status (I, II, III, IV)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Diluent used:** Yes □ No □ If "yes", Diluent batch/lot number, Expiry date of Diluent

*Trade name is necessary only in private sector immunization

**Place vaccine administered:**

**Date:**

**Person vaccine administered:** Doctor □ PHNS/Nurse □ PHM □ PHI □

**Time:** am/pm

## Adverse Events

### Local Adverse Events
- **Requiring investigation:** Injection site abscess □ BCG Lymphadenitis □ Severe local reaction □

### CNS Adverse Events
- **Requiring investigation:** Vaccine associated paralytic poliomyelitis □ GBS □
- Encephalopathy □ Encephalitis □ Meningitis □
- Seizures Febrile □ Seizures Afebrile □

### Other Adverse Events
- **Requiring investigation:** Anaphylaxis □ Persistent screaming □ Osteitis / Osteomyelitis □
- Hypotonic Hyporesponsive Episode □ Toxic Shock Syndrome □

### Adverse Events Not Requiring Investigation
- **Adverse events:** Allergic reaction □ Arthralgia □
- **High fever:** (>39°C / 102°F) □ Nodule at the injection site □

## Instruction:
Before reporting an AEFI, please refer to the definition for the relevant AEFI given in overleaf and make sure that reporting event agrees with the criteria stipulated in the definition.

**Date & Time onset of adverse event:**

**Date & Time referring to medical care:**

### Medical History/Other

**Hospitalized, Yes No**

**If "Yes": Hospital:**

**BHT:**

**Outcome:** Recovered completely □ Partially recovered □ Death □

### Reporting source

**Date of the notification:**

**Institution & Designation:**

**Telephone:**

**Name & Signature of the notifying officer/General Practitioner:**

---

(Medical Officers who attend any patient suffering from Adverse Effects Following Immunization shall notify in this form to the Medical Officer of Health the area of the patients residence)
Anaphylaxis Event Record
(To be completed by a Medical Officer)

### Patient details

<table>
<thead>
<tr>
<th>Name</th>
<th>MOH Area</th>
<th>RDHS Area</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>Date of birth</th>
<th>Sex</th>
<th>Ethnicity</th>
<th>Hospital</th>
<th>BHT number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Past allergic history:** Has patient had previous allergic reactions? □ Yes □ No
If ‘Yes’, Allergen (Drug/Vaccine/Food/Other) - specify?

### Part 1: Clinical features

**Date & time of clinical examination:** Date(dd/mm/yy) [Time: am/pm]

<table>
<thead>
<tr>
<th>Skin &amp; Mucosa</th>
<th>□ Urticaria □ Erythema □ Pruritus □ Prickle sensation</th>
<th>Specify the site of reaction:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>□ Red bilateral □ Red unilateral □ Itchy</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Respiratory system</th>
<th>□ Sneezing □ Rhinorrhea □ Sore throat □ Hoarse voice □ Stridor □ Severe throat closure □ Cough</th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Circulatory system</th>
<th>□ BP (mmHg) □ Measured hypotension □ Decreased central venous pulse</th>
<th>□ Capillary refill time = 3 secs □ Tachycardia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>□ Heart rate (m) □ Other</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CNS</th>
<th>□ Loss of consciousness □ Distress □ Other(specify):</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>GIT</th>
<th>□ Diarrhoea □ Nausea □ Abdominal pain/ cramp □ Vomiting</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Diagnostic Criteria</th>
<th>□ Rapid onset of occurrence of above sign &amp; symptoms □ Two or more systems are affected</th>
</tr>
</thead>
</table>

### Part 2: Suspected Product and exposure Information

**Date & Time of drug/vaccine administration:** Date(dd/mm/yy) [Time: am/pm]

<table>
<thead>
<tr>
<th>Drug</th>
<th>□ Oral □ Parenteral □ Vaccine □ Serum □ Other (specify):</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Generic name:**

**Trade name:**

<table>
<thead>
<tr>
<th>Batch number</th>
<th>Expiry date</th>
<th>For vaccine: VVM status □ I □ II □ III □ IV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>□ 1st dose □ 2nd dose □ 3rd dose □ 4th dose</td>
</tr>
</tbody>
</table>

If diluent used, specify batch number & expiry date.

If parenteral medicine/vaccine: □ Single dose □ Multi dose □ Liquid □ Lyophilised

**Route of administration:** □ Oral □ IV □ IM □ SC □ ID □ Other (specify):

**Site of Administration:** □ Deltoid □ Thigh □ Buttock □ Other (specify):

**Person who administered:** □ Doctor □ Nurse □ PHI □ PHM □ Other (specify):

**Place of administration/reaction:** □ Hospital □ MOH □ Clinic □ Private Hospital □ GP □ Other (specify):
### Part 3: Management

<table>
<thead>
<tr>
<th>Was Adrenaline administered?</th>
<th>□ Yes</th>
<th>□ No</th>
</tr>
</thead>
<tbody>
<tr>
<td>If ‘Yes’, Route: ☐ IM ☐ SC ☐ IV ☐ Other (specify)</td>
<td></td>
<td>Dose:..............ml</td>
</tr>
<tr>
<td>Place: ☐ Clinic ☐ MOH ☐ Hospital ☐ Other (specify)</td>
<td></td>
<td>Time (of 1st dose):......am/pm</td>
</tr>
<tr>
<td>Person who administered adrenaline: ☐ Doctor ☐ Sister/Nurse ☐ PHI/PHM ☐ Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Yes □ No</td>
<td>If ‘Yes’, describe <em>(including the time)</em></td>
<td></td>
</tr>
<tr>
<td>What other medicines were administered?</td>
<td>If ‘Yes’, describe <em>(including the time)</em></td>
<td></td>
</tr>
<tr>
<td>□ Yes □ No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Any other details concerning medicines/management *(including CPR)*?**

---

### Investigation

<table>
<thead>
<tr>
<th>Blood taken for mast cell Tryptase:</th>
<th>□ Yes</th>
<th>□ No</th>
<th>If ‘Yes’, specify the time interval after event:</th>
</tr>
</thead>
</table>

*(Note: Serum Tryptase levels peak 60-90 min after the onset of anaphylaxis and persist to 6 h. Therefore It is recommended that blood should be taken between 1 and 2 h after the initiation of symptoms.)*

---

### Part 4: Outcome

<table>
<thead>
<tr>
<th>Onset of first symptom:</th>
<th>Date (dd/mm/yy)</th>
<th>Time: ............ am/pm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome: ☐ Full recovery ☐ Not fully recovered ☐ Recovered with sequelae ☐ Death</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Specify details:**

<table>
<thead>
<tr>
<th>Time at outcome (recovery/death): Date (dd/mm/yy)</th>
<th>Time: am/pm ☐ Unknown</th>
</tr>
</thead>
</table>

---

### Highest Impact of Adverse drug event/Adverse Event Following Immunization:

- ☐ Did not interfere with daily activities
- ☐ Interfered, but did not prevent daily activities
- ☐ Prevented daily activities

---

### Part 4: Any other comment

---

### Details of Reporting Source

<table>
<thead>
<tr>
<th>Name:</th>
<th>Designation:</th>
<th>Institute:</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Signature</th>
<th>Date:</th>
<th>Telephone:</th>
</tr>
</thead>
</table>

**Definition:** Anaphylaxis is defined as a severe, life-threatening, generalized or systemic hypersensitivity reaction, characterised by rapidly developing life-threatening airway and/or breathing and/or circulation and/or gastrointestinal problems usually (not always) associated with skin and mucosal changes.