



IAP Guide Book on Immunization

IAP Committee on Immunization 2009-2011

**Editors :
Dr. Vijay Yewale
Dr. Panna Choudhury
Dr. Naveen Thacker**





© 2011: IAP Committee on Immunization

Address for correspondence:

Indian Academy of Pediatrics, Kailas Darshan, Kennedy Bridge, Near Nana Chowk,
Mumbai, India 400 007.

Tel: +91-22-23889565, E-mail: centraloffice@iapindia.org

Website: www.iapcoi.com

Acknowledgement :

The editors gratefully acknowledge the contributions of all committee members and expert reviewers.

Academic grant from :

Bharat Biotech, Chiron Panacea Vaccines, GSK Biologicals, MSD, Novartis,
Pfizer-Wyeth, Sanofi Pasteur

Disclaimer :

While every effort has been made to ensure accuracy of the contents, the editors, publisher and printer will not be held responsible for any inadvertent error(s).

All rights reserved. No part of this publication should be reproduced, stored in a retrieval system, or transmitted in any form or by any means: electronic, mechanical, photocopying, recording or otherwise, without the prior written permission of the Indian Academy of Pediatrics.

Edition : 2011

Typeset & Printed : Print Throb Creation

Publishers : Indian Academy of Pediatrics



INDIAN ACADEMY OF PEDIATRICS

IAP Guide Book on Immunization

IAP Committee on Immunization 2009-2011

**Editors :
Dr. Vijay Yewale
Dr. Panna Choudhury
Dr. Naveen Thacker**





Disease Surveillance by the IAP Committee on Immunization

www.idsurv.org (Case reporting made SARAL)

IAP Committee on Immunization (IAPCOI) in collaboration with the IAP Kutch branch and Child Health Foundation (CHF) has started "Infectious Disease Surveillance (IDSurv) Project" for Childhood vaccine preventable diseases.

Objectives

- To develop an early warning system for pediatric vaccine preventable diseases in India
- To generate data on burden of vaccine preventable diseases in India

Who can participate?

At present pediatricians are encouraged to become part of this network. They can register through the website www.IDSurv.org. A confirmatory email and sms with username and password will be sent once request is scrutinized.

What diseases are covered under IDSurv Project?

At present following diseases are being reported under IDSurv Project?

- | | | |
|------------------------------|-----------------|--------------|
| ▪ Acute Bacterial Meningitis | ▪ Chicken Pox | ▪ Diphtheria |
| ▪ Dengue | ▪ Enteric Fever | ▪ Measles |
| ▪ Mumps | ▪ Pertussis | ▪ Pneumonia |

Registration

If you are a new user you will need to register with idsurv.org. After you complete the registration form, your application would be reviewed and your password would be sent to you via email and sms.

Reporting a case

You can report a case in the following ways

1. Through website idsurv.org after logging into your account.
2. Through sms from your registered mobile number.
3. Through mobile website m.idsurv.org
4. Through IVR (Integrated Voice Recognition System)

Reporting a case through website

Log in to your account. Click on Report a case. Fill up the form and click on submit.

Reporting a case through sms: SMS appropriate codes to 09223050808 For help on sms codes please check the resources area/ SMS icon on the website idsurv.org.

Reporting case through mobile website: Log in to your account on m.idsurv.org. Click on report a case and fill up the form and click on submit.

Reporting case through IVR: check on IVR icon on www.idsurv.org

Viewing/ updating cases reported by you:

After logging in your account you can click on View/Update cases reported by me. You can view all the cases reported by you. Click on a case to change/update information submitted by you. Note that this will contain the cases reported by you through all the mediums *i.e.* website, sms, IVR and mobile website.

Feedback to the reporting pediatrician

The reporting pediatrician will be sent a report on the cases reported by him/her on a weekly basis

For further details please visit www.idsurv.org



FOREWORD



Dear Fellow Academicians,

It is my pleasure and privilege to write a foreword for this prestigious book IAP GUIDE BOOK ON IMMUNISATION published by IAPCOI. Let me at the outset congratulate the Chairperson Dr. Panna Choudhury, Convenor Dr. Vijay Yewale and all the members of IAPCOI for publishing this wonderful book. IAPCOI has almost revised and updated the earlier recommendations on the use of various vaccines available in Indian market. This book will be considered as a reference book by all pediatricians and practitioners throughout the country. Many organizations from public and private sector may use this book for making policy decisions. I have gone through the entire book and it is reader friendly also.

The immunization coverage for UIP vaccines in India is below 50% with some increments in states like Kerala and Tamilnadu *etc.* To improve the immunization coverage we should motivate the public, parents, pediatricians and practitioners. I think this book will definitely motivate fellow pediatricians in rational immunization practices. IAP is planning to distribute this book to 19500 members of IAP throughout the country.

I once again congratulate the members of IAPCOI for releasing this book and wish all the best for this new venture.

Yours in IAP

Dr. T.U. Sukumaran
National President, IAP-2011



Message from IAP President 2010

It is very well known to all of us that Immunization is the most successful, single child survival strategy to date. Immunization has helped in reducing child morbidity and mortality to a great extent. The Under 5 Mortality in India is still very high and Immunization can play an important role to bring it down.

Immunization is one of the main activities of Pediatricians and General Practitioners. Yet, the information at their disposal gathered from various sources is not complete and sometimes confusing. Upgrading Routine Immunization is the need of the hour to help bringing down Under 5 Mortality. But, at the same time knowledge about newer vaccines is important for all of us.

The ongoing research and developments in molecular biology and genetic engineering has given us many new vaccines in recent years and many more to be added to the Vaccine Bag soon. Being, a pediatrician it is necessary for us to gather updated information about these newly launched vaccines and help parents taking an informed decision about giving these vaccines to their children.

Indian Academy of Pediatrics has always taken a lead to educate members on various child health issues. IAP Guide Book on Immunization is one of the examples. This guide book was launched in 1997 and is very popular amongst IAP members and non-member Pediatricians. I am sure this upgraded guide book will serve as a ready reckoner on issues related to vaccines and immunization for all of us.

Dr. Deepak Ugra
President, IAP-2010



Message from IAP President 2009

“Vaccination has greatly reduced the burden of infectious diseases. Only clean water, also considered to be a basic human right, performs better.” - *Plotkin*

Dear Fellow Academicians,

India launched expanded program on immunization in 1978 with six childhood vaccines (Bacillus Calmette-Guerin, TT, DPT, DT, Polio, and Typhoid) followed by Universal Immunization program in 1985 when measles vaccine was introduced. Since then, introduction of newer vaccines in national immunization schedule has been painfully slow. Act of vociferous anti vaccine lobby that thrives today, is also not supporting the cause of immunization.

In recent years, many new vaccines have been licensed in India with proven benefit in other countries. Pediatricians are in the forefront of childhood vaccination and need to familiarize themselves with newer vaccines. It is also pediatricians' duty to see that fruits of science in the form of vaccine reach children to reduce their sufferings. As such Indian Academy of Pediatrics (IAP) has great responsibility to guide its members to promote routine immunization and use newer vaccines in office practice rationally. The Committee of Immunization (COI) of the Indian Academy of Pediatrics has this onerous task for developing and revising immunization guidelines. It is expected that members adhere to immunization practices within the frame work of these guidelines for uniformity. IAPCOI is bringing out guidelines at about 2 year's interval and it is hoped that not only pediatricians but all practitioners of immunization would benefit from this endeavor immensely.

Dr. Panna Choudhury
President, IAP-2009





PREFACE

Immunization is one of the most cost-effective health interventions known to mankind. With immunization, small pox has been eradicated and polio eradication is also in sight.

The Indian Academy of Pediatrics (IAP) publishes a Guide Book on Immunization, for the guidance of its members. It is meant to guide vaccination efforts in India, taking into account the disease prevalence, health priorities, and resource allocation possible. This guidebook presents the key recommendations of the IAP Committee on Immunization (IAPCOI) 2009-10. IAPCOI is committed to provide unbiased, rational, ethical, practical yet balanced guidelines to its members on the various issues related to vaccines and vaccination practices in India.

The recommendations here are the 'best individual practice schedule' for a given child and would necessarily be at some variance from the National Immunization Schedule of the Government of India, which is meant for the public at large. The IAPCOI recommendations thus go beyond the national immunization program and cater primarily to the pediatricians in office practice. The recommendations are formulated after review of available literature and detailed discussion amongst IAPCOI members. Though an attempt has been made to include the Indian data that is available, such India specific epidemiological data is often not available. In the absence of such data, the disease burden and the results of vaccine studies from countries with similar socio-economic-cultural background is taken into account while making recommendations. Review articles published in indexed medical journals, World Health Organization (WHO) position papers and recommendations from the Advisory committee on Immunization Practices of USA (ACIP) are the main resource documents for this edition. Lack of local information or evidence should not be taken as evidence of absence of the disease and should not be a deterrent against formulating policies. The IAPCOI stresses the need to collect local epidemiological data for vaccine preventable diseases so that future recommendations are more robust.

IAPCOI has tried to bring out recommendations in an earnest and unbiased way to promote what is best for the population that is catered to. It is also important to understand that immunization is a dynamic subject and recommendations may need to be revised periodically based on available information. From time to time, updates to the recommendations of the latest Guidebook will be published by the Immunization Committee of the Indian Academy of Pediatrics and updated on the website www.iapcoi.com. We hope that this updated guidebook will continue to serve as a ready-reckoner on issues concerning vaccines and immunization in our country.

Dr. Panna Choudhury
Chairperson

Dr. Naveen Thacker
Co-Chairperson

Dr. Vijay Yewale
Convener

IAP Committee on Immunization, 2009-10



IAPCOI has formulated consensus guidelines on appropriate use of licensed vaccines in office practice. However, members may use their own discretion while using them in a given situation within the framework suggested.



CONTENTS

1. Introduction	10
2. Basic Immunology and Elementary Epidemiology	15
3. Practical Aspects of Immunization	27
4. Cold Chain	32
5. Adverse Events following Immunization	43
6. Immunization Schedule	47
7. Individual Vaccines	51
8. Adolescent Immunization	145
9. Immunization in Special Situations	147
10. Licensing procedure and inclusion of a vaccine in the NIP in India	155
11. Internet Resources for Immunization Information	161
12. Ready Reckoner for Vaccines currently available in India	162
13. Annexures	
i. IAP Immunization Time Table 2011	168
ii. IAP Immunization Schedule 2011	169
iii. List of vaccine brands available in India	171



INTRODUCTION

Immunization in India - Past, Present and Future

Immunization is a proven tool for controlling and even eradicating disease. An immunization campaign carried out by the World Health Organization (WHO) from 1967 to 1977 eradicated smallpox. Eradication of poliomyelitis is within reach. Since Global Polio Eradication Initiative in 1988, infections have fallen by 99%, and some five million people have escaped paralysis. Although international agencies such as the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) and now Global Alliance for Vaccines and Immunization (GAVI) provide extensive support for immunization activities, the success of an immunization programme in any country depends more upon local realities and national policies. A successful immunization program is of particular relevance to India, as the country contributes to one-fourth of global under five mortality with a significant number of deaths attributable to vaccine preventable diseases. There is no doubt that substantial progress has been achieved in India with wider use of vaccines, resulting in prevention of several diseases. However lot remains to be done and in some situations, progress has not been sustained (Table I).

Table I: *Vaccine preventable diseases: India reported cases (Year wise).*

Vaccine preventable diseases	1980	1985	1990	1995	2000	2005	2008
Diphtheria	39,231	15,685	8,425	2,123	5,125	10,231	6,081
Measles	114,036	161,216	89,612	37,494	38,835	52,454	48,181
Pertussis	320,109	184,368	112,416	4,073	31,431	13,955	44,180
Polio	18,975	22,570	10,408	3,263	265	66	559
Tetanus (Neonatal)	-	-	9,313	1,783	3,287	891	811
Tetanus (Total)	45,948	37,647	23,356	-	8,997	3,543	3,714

Source: WHO vaccine-preventable diseases: monitoring system 2010 global summary

Successful immunization strategy for the country goes beyond vaccine coverage in that self reliance in vaccine production, creating epidemiological database for infectious diseases and developing surveillance system are also integral parts of the system. It is apparent that the present strategy focusses on mere vaccine coverage.

The history of vaccine research and production in India is almost as old as the history of vaccines themselves. During the latter half of the 19th century, when institutions for vaccine development and production were taking root in the Western world, the



British rulers in India promoted research and established about fifteen vaccine institutes beginning in the 1890s. Prior to the establishment of these institutions, there were no dedicated organizations for medical research in India. Haffkine's development of the world's first plague vaccine in 1897 (which he developed at the Plague Laboratory, Mumbai, India, later named the Haffkine Institute) and Manson's development of an indigenous Cholera vaccine at Kolkata during the same period bear testimony to the benefits of the early institutionalisation of vaccine research and development in India. Soon, Indian vaccine institutes were also producing Tetanus toxoid (TT), Diphtheria toxoid (DT), and Diphtheria, Pertussis, and Tetanus toxoid (DPT). By the time Indians inherited the leadership of the above institutions in the early 20th century, research and technological innovation were sidelined as demands for routine vaccine production took priority. However, after independence, it took three decades for India to articulate its first official policy for childhood vaccination, a policy that was in alignment with the WHO's policy of "Health for All by 2000" (famously announced in 1978 at Alma Atta, Kazakhstan). The WHO's policy recommended universal immunization of all children to reduce child mortality under its Expanded Programme of Immunization (EPI). In line with Health for All by 2000, in 1978 India introduced six childhood vaccines (Bacillus Calmette-Guerin, TT, DPT, DT, Polio, and Typhoid) in its EPI. Measles vaccine was added much later, in 1985, when the Indian government launched the Universal Immunization Programme (UIP) and a mission to achieve immunization coverage of all children and pregnant women by the 1990s. Even though successive governments have adopted self-reliance in vaccine technology and self-sufficiency in vaccine production as policy objectives in theory, the growing gap between demand and supply meant that in practice, India had increasingly resort to imports. In fact, government of India had withdrawn indigenous production facilities for oral polio vaccine that existed earlier in Conoor, Tamilnadu and at Haffkine's institute in Mumbai for trivial reasons. At Conoor after making several batches of good quality OPV, one batch of OPV has failed to pass the neurovirulence test. This happens with all manufacturers, and if a facility has to be closed down for such reason there would have been no OPV in the world today. Thus, oral polio vaccine has been imported in India for last several years. Similarly decision of production of inactivated polio vaccine in the country was revoked more than two decades ago for no known reasons. Many vaccine manufacturing units have suspended production or closing down in recent years for minor reasons. One wonders who is benefitting by the closure of facilities for manufacturing vaccines in public sector.

The vaccination coverage at present with EPI vaccines is far from complete despite the long-standing commitment to universal coverage. While gains in coverage proved to be rapid throughout the 1980s, taking off from a below 20% coverage to about 60% coverage for some VPDs, subsequent gains have been limited. Estimates from



the 2005-2006 Indian National Family Health Survey (NFHS-3) indicate that only 43.5% of children aged 12-23 months were fully vaccinated (received BCG, measles, and 3 doses of DPT and polio vaccines), and 5% had received no vaccinations at all. Given an annual birth cohort of 24 million surviving infants and an under 5 year mortality rate of 74/1000, this results in over 12.5 million under-immunized children each year.

There is also a tremendous, heterogeneity in state and district level immunization coverage in India. In the recent District Level Health Survey-3 (2007-'08) full immunization coverage of children varies from 30% in Uttar Pradesh, 41% in Bihar, 62% in Orissa to 90% in Goa. Tamil Nadu, Kerala and Pondicherry have above 80 percent coverage (Table II).

TABLE II: Percent of Children age 12-23 months (born during 3 years prior to the survey) who received full vaccination, BCG, three doses of DPT, three doses of polio and measles in DLHS-3 survey (2007-08).

State/UT	Full vaccination	BCG	Three doses of DPT vaccine	Three doses of Polio Vaccine	Measles Vaccine
Andhra Pradesh	67.1	97.5	79	82.1	88.6
Bihar	41.4	81.5	54.4	53.1	54.2
Chhattisgarh	59.3	94.8	71.4	69.7	79.9
Goa	89.8	98.4	91.5	94.1	94.1
Jharkhand	54.1	85	62.6	64.4	70.5
Karnataka	76.7	96.9	84.8	90.3	85.2
Kerala	79.5	99.1	87.1	86.6	87.9
Madhya Pradesh	36.2	84.2	47.4	55.1	57.7
Orissa	62.4	94.2	74.3	78.8	81.1
Pondicherry	80.4	96.6	88.3	88.3	91.1
Rajasthan	48.8	82.8	55.6	63.9	67.5
Sikkim	77.8	98.4	88.7	86.5	92.5
Tamil Nadu	82.6	99.6	90.5	91.1	95.5
Uttar Pradesh	30.3	73.4	38.9	40.4	47
West Bengal	75.8	96.2	83.6	83.8	82.8

Sources:

1. Sharma S. Immunization coverage in India. Working Paper Series No. E/283/2007. www.iegindia.org/workpap/wp283.pdf accessed on 12th June, 2010
2. Nath B, Singh JV, Awasthi S, Bhushan V, Kumar V, Singh SK. A study on determinants of immunization coverage among 12-23 months old children in urban slums of Lucknow District, India. *Indian J Med Sci* 2007; 61: 598-606.
3. Universal Immunization Program Review. www.whoindia.org/LinkFiles/Routine_Immunization_UP.pdf accessed on June 12, 2010.)



The reasons for poor immunization coverage in poor performing states have been found to be-

- Inadequacy in delivery of health services in terms of personnel and facilities.
- Lack of support to ANMs from other health personnel.
- Lack of awareness about importance of immunization.
- Misconceptions on immunization including adverse affects.
- Lack of information on time and location of immunization sessions.
- Lack of supervision, monitoring and microplanning at peripheral level.
- Overemphasis on pulse polio immunization, thus neglecting routine immunization.
- Weak surveillance for vaccine preventable diseases except polio.

An urgent need at present is to strengthen routine immunization coverage in the country with EPI vaccines. India is self sufficient in production of vaccines used in UIP. As such the availability of the vaccine is not an issue. For improving coverage, immunization needs to be brought closer to the communities. There is need to improve immunization practices at fixed sites along with better monitoring and supervision. Effective behavior change and communication would increase the demand for vaccination. There is certainly a need for introducing innovative methods and practices. In Bihar, 'Muskan ek Abhiyan' an innovative initiative started in 2007 is a good example, where a partnership of Government organization, agencies and highly motivated social workers has paid rich dividends. Full vaccination coverage, a mere 11%, in 1992 increased to only 33% in 2005-06 but zoomed to 55% in 2008.

Globally, new vaccines have been introduced with significant results, including the first vaccine to help prevent liver cancer, hepatitis B vaccine, which is now routinely given to infants in many countries. Rapid progress in the development of new vaccines means protection being available against a wider range of serious infectious diseases.

There is a pressing need to introduce more vaccines in EPI. The last couple of decades have seen the advent of many new vaccines in the private Indian market. In fact, most vaccines available in the developed world are available in India. However, most of these vaccines are at present accessible only to those who can afford to pay for them. Paradoxically, these vaccines are most often required by those that cannot afford them. The Government has introduced some of the newer vaccines such as MMR and Hepatitis B in some states and planning to introduce Hib into the EPI soon. Expanding coverage with these vaccines and introducing new vaccines which are cost effective in the Indian scenario are required. Introduction of monovalent and bivalent OPV into the polio eradication strategy have shown dramatic results with



least number of polio cases being reported in 2010. However, there is a need for introduction of inactivated polio vaccine in the routine immunization schedule of states free of polio for more than 5 years.

Several areas in the national immunization program need a revamp. Vaccine production by indigenous manufacturers needs to be encouraged to bring down the costs, reduce dependence on imports and ensure availability of vaccines specifically needed by India (e.g. Typhoid) and custom made to Indian requirements (Rotavirus and Pneumococcal vaccines). The recent vaccination related deaths signal a need for improving immunization safety and accountability and setting up of an adverse event monitoring system. Finally setting up a system for monitoring the incidence of vaccine preventable diseases and conducting an appropriate epidemiological studies is necessary to make evidence based decisions on incorporation of vaccines in the national schedule and study impact of vaccines on disease incidence, serotype replacement, epidemiologic shift and so on.

Immunization is considered most cost-effective health investments. It is estimated in a study that a one-week “supplemental immunization activity” against measles carried out in Kenya in 2002, in which 12.8 million children were vaccinated, would result in a net saving in health costs of US\$ 12 million over the following ten years; during that time it would prevent 3,850,000 cases of measles and 125,000 deaths. In the United States, cost-benefit analysis indicates that every dollar invested in a vaccine dose saves US\$ 2 to US\$ 27 in health expenses.

If India has to achieve Millennium Development Goal 4 of reducing underfive mortality rates by 2/3rd from the levels of year 1990, immunization of children will have to play a very crucial role.



BASIC IMMUNOLOGY AND ELEMENTARY EPIDEMIOLOGY

We herein discuss briefly those principles of immunology, epidemiology and clinical research that are relevant to vaccinology.

Section 1: Basic Immunology of Vaccination

Immunology of Vaccination

Innate and adaptive immune responses:

Immunity may be broadly classified as innate and adaptive immunity. Innate immunity comprises of the skin and mucosal barriers, phagocytes (neutrophils, monocytes and macrophages) and the natural killer (NK) cells. It comes into play immediately on entry of the pathogen and is non specific. Adaptive immunity is provided by the B lymphocytes (humoral/antibody mediated immunity) and T lymphocytes (cellular/cell mediated immunity). The innate immune system triggers the development of adaptive immunity by presenting antigens to the B lymphocytes and T lymphocytes. Adaptive immunity takes time to evolve and is pathogen specific (Table 1).

Table 1: *Differentiating features between innate and adaptive immunity.*

Innate Immunity	Adaptive Immunity
Its response is antigen-independent.	Its response is antigen-dependent.
There is immediate response.	There is a lag time between exposure and maximal response.
It is not antigen-specific.	It is antigen-specific.
Exposure does not result in induction of memory cells.	Exposure results in induction of memory cells.
Some of its cellular components or their products may aid specific immunity	Some of its products may aid non-specific immunity.

Humoral Vs Cell mediated immunity:

Humoral immunity is the principal defence mechanism against extracellular microbes and their toxins. B lymphocytes secrete antibodies that act by neutralization, complement activation or by promoting opsonophagocytosis which results in early reduction of pathogen load and clearance of extracellular pathogens. Antibodies are of several different types (IgG, IgM, IgA, IgD and IgE) and they differ in their structure, half life, site of action and mechanism of action.



Cell mediated immunity (CMI) is the principal defence mechanism against intracellular microbes. The effectors of CMI, the T cells, are of two types. The helper T cells secrete proteins called cytokines that stimulate the proliferation and differentiation of T cells as well as other cells including B lymphocytes, macrophages and NK cells. The cytotoxic T cells act by lysing infected cells. Cellular immunity is essential for clearance of intracellular pathogens. BCG is the only currently used human vaccine for which there is conclusive evidence that T cells are the main effectors.

Active Vs Passive immunity

Active immunity is acquired through natural infection/ immunization and is long lasting. Passive immunity is conferred by maternal antibodies or immunoglobulin preparations and is short lasting.

Type of Vaccines

Vaccines may be broadly classified as live attenuated vaccines and killed/inactivated vaccines. Commonly used live attenuated vaccines include BCG, oral polio, measles, MMR and Chicken Pox vaccines. Killed vaccines may be inactivated toxins/ toxoids (Diphtheria/ Tetanus Toxoids), killed organisms (Whole Cell Pertussis vaccines) or most commonly subunit vaccines (Hib, Hepatitis B, Hepatitis A, Typhoid, Meningococcal, Influenza). Subunit vaccines comprising only of the polysaccharide antigens are called unconjugated vaccines. Conjugation of the polysaccharide with a protein carrier significantly improves the immune response as discussed later.

How do vaccines work?

Early protective efficacy of currently available vaccines is primarily conferred by the induction of antigen-specific antibodies that are capable of binding specifically to a toxin or a pathogen.

The role of cell mediated immunity in currently used vaccines (that have T cell dependent antigens) is mainly by supporting antibody production. Other less common mechanisms by which cell mediated immunity works is by cytotoxic CD8+ T lymphocytes (CTL) that may limit the spread of infectious agents by recognizing and killing infected cells or secreting specific antiviral cytokines. T cell independent antigens (e.g. Polysaccharides) do not stimulate cell mediated immunity and therefore do not produce long lasting immunity. T cell independent antigens can be converted to T cell dependent antigens by conjugating them with proteins.



First steps after immunization

Following injection, the vaccine antigens attract local and systemic dendritic cells, monocytes and neutrophils. These activated cells change their surface receptors and migrate along lymphatic vessels, to the draining lymph nodes where the activation of T and B lymphocytes takes place.

In case of killed vaccines, there is only local and unilateral lymph node activation. Conversely for live vaccines, there is multifocal lymph node activation due to microbial replication and dissemination. Consequently the immunogenicity of killed vaccines is lower than the live vaccines; killed vaccines require adjuvants which improve the immune response by producing local inflammation and recruiting higher number of dendritic cells/ monocytes to the injection site. Secondly, the site of administration of killed vaccines is of importance; the intramuscular route which is well vascularised and has a large number of patrolling dendritic cells is preferred over the subcutaneous route. The site of administration is usually of little significance for live vaccines. Finally due to focal lymph node activation, multiple killed vaccines may be administered at different sites with little immunologic interference. Immunologic interference may occur with multiple live vaccines unless they are given on the same day/ at least 4 weeks apart or by different routes.

Immune responses to vaccines

I. Immune response to polysaccharide antigens

Bacterial (*S. pneumoniae*, *N. meningitidis*, *H. influenzae*, *S. typhi*) polysaccharide (PS) antigens are T cell independent antigens. On being released from the injection site they reach the marginal zone of the spleen / nodes and bind to the specific Ig surface receptors of B cells. In the absence of antigen-specific T cell help, B cells activate, proliferate and differentiate in plasma cells without undergoing affinity maturation in germinal centers. The antibody response sets in 2-4 weeks following immunization, is predominantly IgM with low titers of low affinity IgG. The half life of the plasma cells is short and antibody titers decline rapidly. Additionally the PS antigens are unable to evoke an immune response in those aged less than 2 years due to immaturity of the marginal zones. As PS antigens do not induce germinal centres, bonafide memory B cells are not elicited. Consequently, subsequent re-exposure to the same PS results in a repeat primary response that follows the same kinetics in previously vaccinated as in naïve individuals.

Revaccination with certain bacterial PS, of which Group C Meningococcus is a prototype, may even induce lower antibody responses than the first immunization, a phenomenon referred to as hyporesponsiveness. Due to this phenomena, only a



single booster of either Pneumococcal or Meningococcal polysaccharide vaccine is recommended even in patients who require lifelong protection.

II. Immune response to protein antigens or T cell dependent antigens

Protein antigens which include pure proteins (Hep B, Hep A, HPV, Toxoids) or conjugation of PS antigens with a protein carrier (Hib, Meningo, Pneumo) are T cell dependent antigens. The initial response to these antigens is similar to PS antigens. However the antigen-specific helper T cells that have been activated by antigen-bearing dendritic cells trigger some antigen-specific B cells to migrate towards follicular dendritic cells (FDC's), initiating the Germinal Center (GC) reaction. In GC's, B cells receive additional signals from follicular dendritic cells (FDC) and follicular T cells and undergo massive clonal proliferation, switch from IgM towards IgG/ IgA, undergo affinity maturation and differentiate into plasma cells secreting large amounts of antigen-specific antibodies. Most of the plasma cells die at the end of germinal centre reaction and thus decline in antibody levels is noted 4-8 weeks after vaccination. However a few plasma cells exit nodes/spleen and migrate to survival niches mostly located in the bone marrow, where they survive through signals provided by supporting stromal cells and this results in prolonged persistence of antibodies in the serum. Memory B cells are generated in response to T-dependent antigens, during the GC reaction, in parallel to plasma cells. They persist there as resting cells until re exposed to their specific antigens when they readily proliferate and differentiate into plasma cells, secreting large amounts of high-affinity antibodies that may be detected in the serum within a few days after boosting.

III. Immune response to live vaccines

The live vaccines induce an immune response similar to that seen with protein vaccines. However, the take of live vaccines is not 100% with the first dose. Hence more than 1 dose is recommended with most live vaccines. Once the vaccine has been taken up, immunity is robust and lifelong or at least for several decades. This is because of continuous replication of the organism that is a constant source of the antigen. The second dose of the vaccine is therefore mostly for primary vaccine failures (no uptake of vaccine) and not for secondary vaccine failures (decline in antibodies over time).

Primary Vs Secondary Immune responses

In primary immune response, the antigen exposure elicits an extrafollicular response that results in the rapid appearance of low IgG antibody titers. As B cells proliferate in GCs and differentiate into plasma cells, IgG antibody titers increase up to a peak



value usually reached 4 weeks after immunization. The short life span of these plasma cells results in a rapid decline of antibody titers, which eventually return to baseline levels.

In secondary immune responses, booster exposure to antigen reactivates immune memory and results in a rapid (<7 days) increase of IgG antibody titer. Short-lived plasma cells maintain peak Ab levels during a few weeks—after which serum antibody titers decline initially with the same rapid kinetics as following primary immunization. Long-lived plasma cells that have reached survival niches in the bone marrow continue to produce antigen-specific antibodies, which then decline with slower kinetics. This generic pattern may not apply to live vaccines triggering long-term IgG antibodies for extended periods of time.

Determinants of intensity & duration of immune responses

I. Primary response:

Primary immune responses after vaccination depend on various factors such as vaccine type, nature of antigen, vaccination schedule, genetic and environmental factors and age at immunization.

A. Vaccine type:

Live vs inactivated: Higher intensity of innate responses, higher antigen content following replication and more prolonged antigen persistence generally result into higher antibodies (Ab) responses to live than inactivated vaccines.

Protein vs polysaccharide: Recruitment of T cell help and induction of germinal centers (GCs) results into higher antibody responses to protein or glycoconjugate than to polysaccharide vaccines. Hence, broadly speaking live vaccines are superior (exception BCG, OPV) to protein antigens which in turn are superior to polysaccharide vaccines.

Adjuvants: Adjuvants improve immune responses to inactivated vaccines by either modulation of antigen delivery and persistence (depot or slow-release formulations) or enhancement of Th responses (immunomodulator) which may support or limit antibody responses.

B. Antigen nature:

Polysaccharide antigens: Failure to induce GCs limit immunogenicity.

Protein antigens: Inclusion of epitopes readily recognized by B cells (B cell repertoire), inclusion of epitopes readily recognized by follicular helper T cells, elicitation of efficient



follicular T cell help and the capacity of antigen to associate/persist in association to follicular dendritic cells (FDCs) result into higher antibody responses.

Antigen dose: As a rule, higher antigen doses increase the availability of antigen for B/T cell binding and activation, as well as for association with FDCs.

C. Vaccination schedule:

Interval between doses: The immune response improves with proper spacing of vaccine doses.

Traditionally, '0-1-6' month schedule is considered as a most immunogenic schedule than 6-10-14 week or 2,3,5 month schedules for non-live T-cell dependent vaccines like Hepatitis-B, vaccine. This is mainly due to adequate time interval between first few doses which act by inducing immune responses and last dose that works as boosters. Since, affinity maturation of B-cells in GCs and formation of memory-B cells take at least 4-6 months, this schedule quite well fulfills these requirements. More than one dose is needed for better induction and recruitment of more number of GCs in young age considering young age limitations of immune system. A four week minimal interval between primary doses avoids competition between successive waves of primary responses.

D. Other factors:

Genetic factors: The capacity of antigen epitopes to associate to a large panel of MHC molecules increases the likelihood of responses in the population. MHC restriction may limit T cell responses. Gene polymorphisms in molecules critical for B and T cell activation/differentiation are likely to affect Ab responses.

Environmental factors: Mostly yet to be identified.

Age at immunization: Early life immune immaturity or age-associated immune senescence impairs immune responses to an administered vaccine.

II. Secondary immune responses:

Many factors that determine primary immune responses after immunization also affects secondary immune responses.

Live vs inactivated: Live vaccines generally induce more sustained antibody responses, presumably through prolonged antigen persistence within the host.

Polysaccharide antigens: Failure to generate GCs limits the induction of memory responses and of high-affinity long-lived plasma cells.



Interval between primary doses: A minimal interval of 4 weeks between primary doses allows development of successive waves of antigen-specific primary responses without interference.

Interval before boosting: A minimal interval of 4 months between priming and boosting allows affinity maturation of memory B cells, and thus higher secondary responses.

Age at immunization: Early life immune immaturity and age-associated immunosenescence limit the induction/persistence of long-live plasma cells.

Immune Memory and need for boosters

Immune memory is seen with live vaccines/ protein antigens due to generation of memory B cells which are activated on repeat vaccination/natural exposure. Immune memory allows one to complete an interrupted vaccine schedule without restarting the schedule. Activation of immune memory and generation of protective antibodies usually takes 4-7 days. Diseases which have incubation periods shorter than this period such as Hib, Tetanus, Diphtheria and Pertussis require regular boosters to maintain protective antibody levels. However diseases such as Hepatitis A, Hepatitis B do not need regular boosters as the long incubation period of the disease allows for activation of immune memory cells.

Immune responses during early life immunization

Limitations of young age immunization

The two important factors negatively affect immune responses during young age: maternal antibodies, and immaturity of immune system.

Young age limits antibody responses to most vaccine antigens since maternal antibodies inhibit antibodies responses but not T-Cell response, and due to limitation of B cell responses.

IgG antibodies are actively transferred through the placenta, via the FcRn receptor, from the maternal to the fetal circulation. Upon immunization, maternal antibodies bind to their specific epitopes at the antigen surface, competing with infant B cells and thus limiting B cell activation, proliferation and differentiation. The inhibitory influence of maternal antibodies on infant B cell responses affects all vaccine types, although its influence is more marked for live attenuated viral vaccines that may be neutralized by even minute amounts of passive antibodies. Hence, antibody responses elicited in early life are short lasting. However, even during early life, induction of B memory cells is not limited. The extent and duration of the inhibitory influence of maternal antibodies increase with gestational age, e.g. with the amount



of transferred immunoglobulins, and declines with post-natal age as maternal antibodies wane.

Early life immune responses are characterized by age-dependent limitations of the magnitude of responses to all vaccines. Antibody responses to most PS antigens are not elicited during the first two years of life, which is likely to reflect numerous factors including: the slow maturation of the spleen marginal zone; limited expression of CD21 on B cells; and limited availability of the complement factors. Although this may be circumvented in part by the use of glycoconjugate vaccines, even the most potent glycoconjugate vaccines elicit markedly lower primary IgG responses in young infants.

Although maternal antibodies interfere with the induction of infant antibody responses, they may allow a certain degree of priming, *i.e.* of induction of memory B cells. This likely reflects the fact that limited amounts of unmasked vaccine antigens may be sufficient for priming of memory B cells but not for full-blown GC activation, although direct evidence is lacking. Importantly, however, antibodies of maternal origin do not exert their inhibitory influence on infant T cell responses, which remain largely unaffected or even enhanced.

Limitations of young age immunization can be countered to a certain extent by increasing the number of a vaccine doses for better induction, use of adjuvants to improve immunogenicity of vaccines, and by use of boosters at later age when immune system has shown more maturity than at the time of induction. Increasing the dose of vaccine antigen may also be sufficient to circumvent the inhibitory influence of maternal antibodies, as illustrated for hepatitis A or Measles vaccines.

Impact of young age limitations on immunization schedules

Disease epidemiology of vaccine-preventable diseases (VPDs) in a country often determines a particular vaccination schedule. Since, majority of childhood infectious diseases cause morbidity and mortality at an early age in developing countries, there is need to protect the children at the earliest opportunity through immunizations. This is the reason why early, accelerated schedules are practiced in developing countries despite the known limitations of young age immunization.

Immunization schedules commencing at 2 months and having 2 months spacing between the doses are considered technically appropriate. However for operational reasons and for early completion of immunization the 6, 10, 14 week's schedule is chosen in developing countries. Such a schedule has shown to give adequate protection in recipients.



For killed vaccines such as DPT, Hib, Pneumococcal and Hep B which are administered as early as birth / 6 weeks, the first dose acts only as a priming dose while subsequent doses provide an immune response even in presence of maternal antibodies. However a booster at 15-18 months is required for durable immunity. As the age of commencement of vaccination advances the number of doses reduce (2 doses at 6-12 months followed by a booster dose and 1-2 doses between 12-23 months for Hib and Pneumococcal vaccines).

Live vaccines are even more susceptible to maternal antibodies as compared to killed vaccines. However, BCG may be given as the maternal antibodies actually enhance T cell responses. OPV may be given as there are no maternal IgA in the gut to neutralize the virus. Furthermore, Measles vaccine if given at the age of 6 months (in an outbreak situation) may work by inducing T cell immunity.

Section 2: Elementary Epidemiology of Vaccination

Basics of epidemiology

Epidemiology is the study of the distribution and determinants of disease frequency in man. It is the foundation science of public health. It provides insights for applying intervention. It informs if intervention is succeeding. It is the systematic study of the pathogen amplification and transmission systems. Epidemiology can often pin-point the weak links in the chains of the source and transmission pathways of the pathogen so that interventions can be directed at those points. Vaccination is one such intervention.

Impact of vaccinology on disease epidemiology

Vaccinology often perturbs the epidemiology of infectious diseases. From vaccinology perspective, there are three reasons to learn epidemiology. They are; for the rational choice of vaccines for vaccination programs; to design appropriate intervention program including vaccinations; and to monitor and measure the progress and impact of any vaccination program.

Knowledge of epidemiology helps in choosing the appropriate vaccines for inclusion in public health programs after carefully assessing disease burden and economic factors. It also helps in designing disease-specific control/elimination/eradication strategies after acquiring exact epidemiological data on prevalence, incidence, and transmission characteristics of target pathogens, and their transmission pathways. In the last, it also helps in monitoring intervention success/failure in order to improve performance/efficiency of the vaccination programs.



Incidence and Prevalence of diseases

Basic measures of disease frequency are done by incidence and prevalence. Incidence relates to the number of new cases of the disease which occur during a particular period of time (e.g. new TB cases).

Prevalence relates to total number of cases of a disease in a specified period of time (Includes both old and new cases) usually during a survey. Often it is expressed as a rate which is a misnomer and it is actually a proportion. In the long run, incidence should be more than the deaths and recoveries, for prevalence to accumulate. Prevalence of various diseases is a good indicator of the load on health services.

Force of transmission and Basic Reproductive Number (R_0)

The key determinant of incidence and prevalence of infection is depends on force of transmission which is determined by 'Reproductive Rate'. Reproductive rate is a simple concept in disease epidemiology. Incidence and prevalence of infection depends on reproductive rate.

'Basic reproductive number' (R_0) measures the average number of secondary cases generated by one primary case in a susceptible population. Suppose all others were susceptible – then how many will be infected? That is R_0 . Since population is a mix of susceptible and immune persons, one case must attempt to infect more than one person.

In the long term, pathogen can survive only if one "case" reproduces another "case" (effective reproductive rate, $R_0=1$). If $R_0<1$, the disease is declining (eg. herd effect). If $R_0>1$, an outbreak is occurring. For endemic diseases with periodic fluctuations, R_0 may swing from <1 to >1 but in the long term the average may remain 1. Pathogen can survive if it reproduces. For all endemic infectious diseases (IDs), $R_0=1$ for steady state or for long term endemicity. The community benefit of a vaccination program is to reduce R_0 to <1 and sustain it for long periods. Such beneficial effect, measured as the degree of disease reduction due to a vaccination programme is sometimes called vaccine effectiveness to distinguish it from vaccine efficacy, which refers to only the direct benefit of immunity in vaccinated individuals. R_0 is not a static entity and changes according to different time periods even at a same geographic region.

The magnitude of R_0 varies according to location and population. It is strongly influenced by birth rate, population density and behavioral factors. The magnitude of R_0 can be ascertained by cross sectional surveys. Eradication is difficult when R_0 is large and population density plus net birth rate are high.



'Endemic', 'epidemic' and 'pandemic' patterns of diseases

'Endemic' refers to normal occurrence of disease in defined population *e.g.* cholera, malaria, TB, *etc.* Outbreaks/Epidemics are the occurrence of more cases of disease than expected in a given area or among a specific group of people over a particular period of time *e.g.* Measles, Influenza, Meningococcal disease. During epidemics, the disease spreads rapidly and extensively by infection and affects many individuals in an area at the same time. The difference between epidemic and outbreak is arbitrary. The terms epidemic and outbreaks are often used similarly; however, former usually indicates higher intensity, for example, outbreak of Salmonella in a neonatal unit. A community-based outbreak Meningococcal disease is defined as the occurrence of >3 cases in <3 months in the same area who are not close contacts of each other with a primary disease attack rate of >10 primary cases/100,000 persons. In terms of the Flu, the difference between an outbreak and an epidemic is the percentage of overall deaths caused by the disease.

'Pandemic' is a global epidemic. Disease originates in one country and then spreads to a number of countries *e.g.* AIDS, H1N1, *etc.*

Vaccine characteristics and development

Vaccine immunogenicity

This is the ability of a vaccine to induce antibodies. The protective threshold for most vaccines is defined. However, there is often controversy about the cutoffs (Pneumococcus/ Hib). Levels below the limits may be protective due to other reasons such as immune memory/ T cell immunity. Bridging studies are those that look at vaccine immunogenicity but not efficacy.

Vaccine efficacy

This is the ability of the vaccine to protect an individual. It can be assessed through clinical trials, cohort studies or case control studies. It is calculated as

$$VE = \frac{ARU - ARV}{ARU} \times 100$$

(VE= Vaccine efficacy, ARU = Attack Rate in Unvaccinated population, ARV = Attack Rate in Vaccinated Population)

Vaccine effectiveness

This is the ability of the vaccine to protect the community and is a sum of the vaccine efficacy and herd effect. It is revealed after a vaccine is introduced in a program.



Cost effectiveness

This is a method of economic evaluation which is carried out by mathematical modeling usually prior to introduction of a vaccine in a national program. It is expressed as cost per infections / deaths / hospitalizations prevented/ life years gained.

Phases in vaccine development

Phase 1 trials are conducted on small number of healthy human volunteers for assessing vaccine immunogenicity and safety.

Phase 2 trials are conducted with a similar objective in larger number of subjects.

Phase 3 trials are randomized controlled trials in large number of subjects for assessing vaccine efficacy and safety.

Cost effectiveness analysis is conducted prior to introduction of vaccines in a national program. Data on vaccine effectiveness and more data on safety emerge following use of vaccines on a widespread basis in programs.

Herd immunity and Herd effect

Herd immunity is the proportion immune in a herd. This can be deduced from the vaccination coverage. Herd effect is the protection offered to unvaccinated members when good proportion (usually more than 85%) of the herd is vaccinated. Herd effect is due to reduced carriage of the causative microorganism by the vaccinated cohort and thus is seen only with vaccines against those diseases where humans are the only source. An effective vaccine is a prerequisite for good herd effect; Tetanus and BCG vaccines have no herd effect. Conjugated Pneumococcal vaccine has good herd effect.

Epidemiologic shift

This refers to an upward shift in age of infection/disease in communities with partial immunization coverage. Owing to vaccination, the natural circulation of the pathogen decreases and the age of acquisition of infection advances. This is especially important for diseases like rubella, varicella and hepatitis A, wherein severity of disease worsens with advancing age.

Bibliography:

- 1 Siegrist CA. Vaccine Immunology. In Vaccines Ed. Plotkin SA, Orenstein W, Offit P. Saunders Elsevier, 5th Edition, 2008, pp 17-36.
- 2 Manual of Advancing Science of Vaccinology (ASOV) program of Indian Academy of Pediatrics, 2009-10.



PRACTICAL ASPECTS OF IMMUNIZATION

Communicating with parents/care givers

With several newer vaccines available in open market, it is an arduous task for pediatricians to offer ideal advice to parents regarding pros and cons of each vaccine. Most of these vaccines are included in the IAPCOI recommendations necessitating one to one discussion. Thus, pediatricians are required to communicate properly with clarity and appropriate information that should help parents to make their own decision in favor or against each of these vaccines. Ideally we need to offer a balanced scientific view without appearing to suggest one way or another. Unfortunately, most of the educated parents would leave the choice to their pediatricians and it is quite unfair to take responsibility of making a choice for parents.

Prerequisite of one to one discussion is commitment on the part of pediatrician to inform relevant facts about disease and vaccine. It takes very little time if one uses structured format covering important aspects in simple language. Following points need to be discussed regarding each vaccine.

1. Risk of developing disease – it is not possible to evaluate risk of disease in an individual child, but figures from literature may be quoted *e.g.* the risk of Invasive Pneumococcal Disease (IPD) in a healthy child aged less than 1 year is roughly 200 per 100,000 (as per Western data). Some general statements are also helpful. Water or foodborne infections are preventable to some extent but not airborne droplet infections. Risk of complications of disease is higher in infants and younger children and in undernourished population. Age prevalence of disease decides appropriate age of vaccination as per the standard recommendations.
2. Efficacy of vaccine – no vaccine provides 100% protection though most of the vaccines do offer high degree of protection. Vaccines significantly decrease chance of disease and even partial protection is useful to prevent complications. Occasional failure of vaccine protection is no reason to consider against its use.
3. Safety of vaccine - vaccines are very safe and serious adverse reactions are extremely rare. Media outbursts of fatal reactions to vaccines are mostly due to human error of administration and not due to vaccine itself. Thus benefits of vaccines outweigh the risk of side effects caused by vaccines.
4. Cost of vaccine - decision of affordability should be left to parents. It is important to reiterate facts that all vaccines are equally efficacious even though they may differ in their cost. For example, DTwP and DTaP are equally efficacious though



differ in reactogenicity. Similarly, vaccines from different manufacturers are equally effective and indigenously manufactured vaccines are usually as good as imported ones.

5. Finally it is important to emphasise that above discussion is based on the current understanding of vaccine and its present place in prevention of disease. With increasing experience over time, there can be a change in the recommendations of individual vaccine and it is necessary to adapt to such changes. For example, second dose of MMR is now recommended.

Many new vaccines are likely to be introduced over the next few years. It would be a challenge for pediatricians to develop communication skills to discuss pros and cons of all these vaccines. But far more relevant is the need to keep updated on issues related to vaccines and disease prevention. It is only then that "one to one discussion" will become more meaningful.

Injection procedure

Sterile technique and Injection safety

Hands should be washed with soap and water for 2 minutes using WHO's 6 steps technique; Alternately, alcohol-based waterless antiseptic hand rub can be used. Gloves need not be worn when administering vaccinations, unless the person administering the vaccine has open lesions on hands or is likely to come in contact with potentially infectious body fluids. Needles used for injections must be sterile and preferably disposable. Auto disable (AD) syringes are single use, self locking syringes designed in such a way that these are rendered unusable after single use. Thus they prevent immediate/ downstream reuse and their use is being promoted in the national immunization program. A separate needle and syringe should be used for each injection. Changing needles between drawing vaccine from a vial and injecting it into a recipient is not necessary. If multi dose vials are used, the septum should be swabbed with alcohol prior to each withdrawal and the needle should not be left in the stopper in between uses. Different vaccines should never be mixed in the same syringe unless specifically licensed for such use, and no attempt should be made to transfer between syringes. Pre filling of syringes should not be done because of the potential for administration errors as the majority of vaccines have a similar appearance after being drawn into a syringe. Thus vaccine doses should not be drawn into a syringe until immediately before administration. To prevent inadvertent needle-stick injury or reuse, needles and syringes should be discarded immediately after use in labelled, puncture-proof containers located in the same room where the vaccine is administered. Needles should not be recapped before being discarded.



Injection route, site, method and needle length

With the exception of BCG and sometimes rabies, all parenteral vaccines are given by the intramuscular (IM)/ subcutaneous (SC) route. The SC route is recommended for Measles, MMR, varicella, Meningococcal polysaccharide, JE, Yellow fever vaccines; either SC or IM route may be used for Pneumococcal polysaccharide vaccines, IPV; the rest of the vaccines should be given intramuscularly. Generally speaking, there is no harm done if SC vaccines are given IM. However vaccines designated to be given IM should not be given SC due to risk of side effects (as seen with aluminium adjuvanted vaccines) or reduced efficacy (due to reduced blood supply in SC tissue and hence reduced immunogenicity). The gluteal region should never be used for administration of IM injections due to risk of sciatic nerve injury and reduced efficacy (Rabies and Hepatitis B vaccines). When used at the recommended sites where no large blood vessels exist, pulling back of the syringe to check for blood is not recommended. The needle should be withdrawn a few seconds after finishing administration of the vaccine (to prevent backflow of vaccine into the needle track) following which the injection site should be pressed firmly for a few seconds with cotton. The injection site should not be rubbed following injection.

Table 1: *Injection site, type of needle and technique*

	Site	Type of needle	Comments
Intra muscular injections (needle should enter at a 90° angle)			
Preterms and neonates	Anterolateral thigh (junction of middle and lower third)	22-25 gauge, 5/8 inch	Skin should be stretched between thumb and forefinger
Infants (1 to <12 months)	Anterolateral thigh	22-25 gauge, 1 inch	Bunch the skin, subcutaneous tissue and muscle to prevent striking the bone
Toddlers and older children (12 months- 10 years)	Deltoid or	22-25 G, 5/8 inch	Skin should be stretched between thumb and forefinger
	Anterolateral thigh	22-25 gauge, 1 inch	Bunch the skin, subcutaneous tissue and muscle
Adolescents and adults (11 yrs onwards)	Deltoid or anterolateral thigh	< 60 kg 1 inch	
		>60 kg 1.5 inch	



	Site	Type of needle	Comments
Subcutaneous injections (needle should enter at 45° to the skin)			
Infants	Thigh	22-25 G, 5/8 inch	
>12 months	Outer triceps	22-25 G, 5/8 inch	
Intradermal injections			
All ages	Left deltoid	26/27 G, 0.5 inch	A 5 mm wheal should be raised

If multiple vaccines are administered at a single visit, administration of each preparation at a different anatomic site is desirable. For infants and younger children, if more than two vaccines must be injected in a single limb, the thigh is the preferred site because of the greater muscle mass; the injections should be sufficiently separated (*i.e.*, 1 inch or more if possible) so that any local reactions can be differentiated. For older children and adults, the deltoid muscle can be used for more than one intramuscular injection. If a vaccine and an immune globulin preparation are administered simultaneously (*e.g.*, Td/Tdap and tetanus immune globulin [TIG], HepB and Hepatitis B immunoglobulin [HBIG]), separate anatomic sites should be used for each injection. The location of each injection should be documented in the patients' medical record

Alleviation of pain associated with injections

Comfort measures, such as distraction (*e.g.*, playing music or pretending to blow away the pain), ingestion of sweet liquids, breastfeeding, cooling of the injection site, and topical or oral analgesia, can help infants or children cope with the discomfort associated with vaccination. Pretreatment (30–60 minutes before injection) with 5% topical lidocaine-prilocaine emulsion can decrease the pain of vaccination by causing superficial anesthesia. Topical lidocaine-prilocaine emulsion should not be used on infants aged <12 months who are receiving treatment with methemoglobin-inducing agents because of the possible development of methemoglobinemia. Use of a topical refrigerant (vapocoolant) spray immediately before vaccination can reduce the short-term pain associated with injections and can be as effective as lidocaine-prilocaine cream. Acetaminophen may be used immediately following DTP vaccination @ 15 mg/kg/dose to reduce the discomfort and fever.

Record keeping

The vaccine administrator must record the type of vaccine, brand name and date of



administration of the vaccine in the patient's file/ immunization record. In addition, recording of the batch number of the vaccine is also recommended.

Medicolegal aspects

The vaccine administrator must explain in detail the characteristics and anticipated side effects of the vaccine in reasonable detail to the caregivers prior to immunization. A verbal consent is usually adequate. In any case, the recipient must be observed for any allergic effects for at least 15 minutes after vaccination and all resuscitative equipment must be kept standby for possible anaphylaxis. The care givers should also be counselled about possible side effects, their management and danger signs before the vaccinee is sent home.

Table 2: *Minimum resuscitative equipment*

Airway, ambu bag, mask, IV access (scalp vein, venflon), oxygen cylinder
Injection adrenaline (1: 1000 solution)
IV hydrocortisone
Normal saline



COLD CHAIN

Introduction

The system of transporting, storing and distributing vaccines in a potent state at the recommended temperature from the point of manufacture to the point of use is the Cold Chain. Vaccine potency once lost cannot be restored. The cold chain remains a highly vulnerable point for both National Immunization Programs and office practice in developing countries with tropical climates. Hence presently there is no substitute to rigorous maintenance of cold chain.

The essential components of a cold chain include

1. Personnel responsible for vaccine distribution
2. Appropriate equipment to store and transport vaccines
3. Appropriate transport facilities
4. Maintenance of equipment
5. Monitoring

Temperature and light sensitivity of vaccines

The correct temperature is the most important factor in maintaining the potency of vaccines. Unlike popular belief, vaccines are damaged by excessive cold in addition to heat.

Sensitivity of vaccines to heat

Each exposure to ambient temperature causes some degradation of the vaccine and subsequent exposures lead to a cumulative impact. Vaccine potency cannot be restored after placing back at recommended temperatures. All vaccines are sensitive to heat but to different degrees. Live vaccines are more susceptible and in decreasing order of sensitivity include two brands of varicella and MMRV (currently not available in India), Live Attenuated Influenza Vaccine, OPV, Measles, MMR, BCG, yellow fever, rotavirus and other brands of varicella/ MMRV vaccines.

Sensitivity of vaccines to freezing

Cold injury is more common than assumed. Vaccines susceptible to damage by freezing include mainly all aluminum adjuvanted vaccines (DTwP, DTaP, TT, DT, Td, TT, Hepatitis B, combination vaccines, Hepatitis A, HPV, PCV 7) but also other



vaccines including IPV, PPV 23, Inactivated Influenza vaccines, Meningococcal vaccines, Rotavirus vaccines, Typhoid vaccines, Hib and brands of varicella vaccines. Vaccines that can be frozen without harm include OPV (vial must not be frozen and thawed repeatedly), and lyophilized Measles, MMR, BCG vaccines, LAIV, certain brands of Varicella and MMRV.

Sensitivity of vaccines to light

Lyophilized and reconstituted BCG, Measles, MMR, Varicella, Rotavirus, Human Papilloma Virus, most DTaP containing vaccines are particularly susceptible to light and need protection from strong light, sun light, ultraviolet and fluorescent neon lights.

To ensure that we maintain a desired optimum temperature, we need to use vaccine monitoring tools.

Vaccine Monitoring Tools

Indicators

- Freeze-Tag and Vaccine Vial Monitors

Thermometers

- Dial, Stem, Max/Min, Electronic

Vaccine Vial Monitors

The Vaccine Vial Monitor (VVM) is a time and temperature sensitive colored label that provides an indication of the cumulative heat to which the vial has been exposed. VVMs were first introduced on OPV vials supplied to UNICEF and WHO in 1996. The VVM warns the end user when exposure to heat is likely to have degraded the vaccine beyond an acceptable level. It is used especially for temperature monitoring of OPV, which is the most thermo labile of all vaccines. The VVM is applied to the outside of a vaccine vial, and it applies only to that vial. It cannot be taken as a surrogate marker for the potency of the vaccine in other vials of the same lot or in the same storage facility.

VVMs consist of a temperature sensitive material, which changes color gradually on being exposed to heat. This change of color is irreversible, and thus corresponds to the heat induced damage to the vaccine inside the vial. VVM's do not give any information on cold injury to vaccines. There are different types of VVMs available, to be used according to the heat stability characteristics of different vaccines.



Interpretation of the colour change of VVM is as follows:

1. Inner square is white, or lighter than outer circle: If the expiry date has not passed, vaccine can be used.
2. Inner square matches colour of outer circle or is darker than outer circle: vaccine should be discarded, regardless of the expiry date.


The vaccines can be used as long as the VVM has not changed color to the “discard” level. This is of tremendous help in outreach programs, where vaccine has to be carried to faraway places, or given door to door. Now VVMs are available for all vaccines and should be demanded from all manufacturers. VVMs are thus a low cost tool for assessing the adequacy and finding the weak links in the cold chain. They save children from receiving ineffective with lost potency vaccines and avoid vaccine wastage.




Freeze watch indicators

A freeze watch indicator consists of a small vial of red liquid attached to a white card and covered in plastic. The vial breaks if the temperature where the indicator is located drops below 0°C for more than one hour.

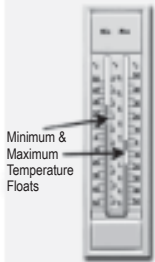
Thermometers



Fluid-filled




Dial Thermometer




Minimum & Maximum Temperature Floats

Max.-Min. Therm



Digital Thermometer with alarm



Electronic thermometer

Place it in the midst of vaccines not in the door or near freezer



CDC recommends using a Continuous, Certified and Calibrated thermometer.

- Continuous means having no gaps, holes or breaks. Temperatures only twice a day gives you just a snap shot of what happened, creating uncertainty about the temperatures the rest of the time.
- Calibration is the process of making a device accurate. If someone tells you the time of the day, how do you know they're correct – is their watch set correctly, too fast, too slow? This same theory applies to a temperature device. 'Calibrated' lets you know this instrument has been compared to a higher standard that is deemed the most accurate instrument to which all other units are compared.
- 'Certified' gives you the assurance of the calibration. It is a document that officially confirms the accuracy of the instrument. The CDC recommends that thermometers be certified by an appropriate agency.

CDC recommends using a Continuous, calibrated and certified chart recording thermometer.

- | | |
|------------------|-------------------------------|
| Continuous..... | Records without break |
| Calibration..... | Accurate reading |
| Certified..... | Assured of proper calibration |



VFC70

Typical Causes of freezing

- Storage of T series vaccines in Ice Lined Refrigerators
- Transport with frozen ice packs
- Belief that colder is better
- Low awareness and understanding
- Incorrect thermostat adjustments

Cold chain equipment

The cold chain involves two complementary aspects: 1) the set chain represented by the walk-in cold rooms, deep freezers and refrigerators and 2) the mobile chain represented by isothermic boxes and vaccine carriers.

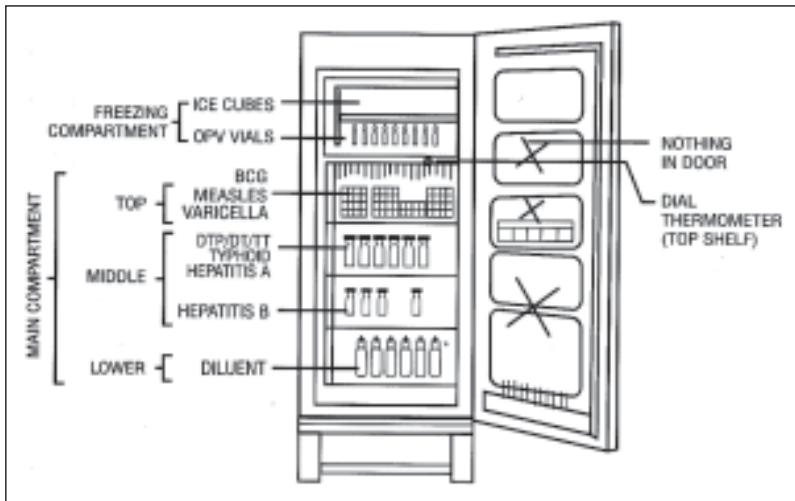
Walk in cold rooms (WIC) and Walk- in freezers (WIF) are used for bulk storage of vaccines at the manufacturer site, or at major distribution points. They have two



cooling units and standby generator sets, and are fitted with temperature recorders and alarm systems. Deep freezers are used for long term storage of OPV/ Measles / MMR vaccines. They are also used for making ice-packs for use in outreach programs. Ice lined refrigerators (ILR) are used where the power supply is intermittent. Most of the space is taken up by water which is frozen when electricity is available. Appropriate temperatures can be maintained for several hours.

Cold chain equipment commonly used in office practice including domestic refrigerators, cold boxes and vaccine carriers are discussed further in detail.

Domestic refrigerator



The main compartment should have a temperature of 2 to 8°C, and the freezer compartment should maintain a temperature of -5 to -15°C. It should be large enough to store the largest inventory of a month and ideally CFC free. Ideally a double door refrigerator should be used. It is impossible to maintain optimum temperatures unless the refrigerator has two separate external doors for the two compartments. Without separate doors, either the freezer will be too warm, or the vaccines in the main compartment will suffer freezing damage. The doors should close snugly, be free of leakages of water and coolant, quiet and have features such as auto defrost and auto door closure. Bar and dormitory fridges should not be used. A voltage stabilizer is mandatory when voltage fluctuations are many and power cuts are frequent. A good well calibrated thermometer is a must; options include a stem thermometer, dial thermometer, digital thermometer, max/min thermometer or a data logger. The thermometer should be placed in both the freezer and the main compartment in the



center and away from the walls, door, air vent or frozen packs and never in the door.

The vaccines can be placed as follows:

- Freezer compartment: BCG, OPV, Measles, and MMR.
- Top shelf: OPV, Measles, MMR and Varicella.
- Middle shelf: DTwP, DTaP, DT, TT, Tdap, Combination vaccines, IPV, HPV, Typhoid, Hepatitis A, Hib, PCV, Influenza, Rotavirus vaccines.
- Middle shelf: Hepatitis B
- Lower shelf: Diluents
- Baffle tray: should be kept empty. No vaccines should be stored in the door.

The following measures are recommended to maintain appropriate temperatures and ensure vaccine potency in domestic refrigerators

- Temperatures should be recorded at least twice a day and a temperature log maintained regardless of temperature alarm, a chart recorder thermometer, or a digital data logger. Fast action should be taken in case of out of range temperatures. The log helps to identify recurring problems and loss of function in ageing units. Temperatures should be monitored twice a day for a week prior to using a new/ repaired refrigerator for vaccine storage.
- The vaccine refrigerator should not be used for any other purpose including storage of food, beverages, pathology specimens and other medications. This will minimize the opening of the door. It is recognized that opening of the door can increase temperatures by as much as 2 to 5°C for as long as 2 to 8 minutes.
- The door should have a warning sticker in order to discourage unnecessary door opening.
- Access to the vaccine refrigerator should be restricted to anyone else than trained staff. A map of inside content of the refrigerator pasted on the outside of the door can minimize opened-door time while searching vaccine inside
- Ice packs and jars should be kept in the freezer and the lowest part (baffle tray) respectively. This increases the cool mass of the refrigerator and helps maintain temperature during power failures and cuts for at least 3 to 4 hours, and minimizes temperature fluctuations during door opening. The thermostat should be reset according to the ambient temperatures; e.g. to coolest during summers.
- The refrigerator should be kept at least 10 cm away from the floor and the walls so as to allow good air circulation.



- The vaccines should be kept in transparent labeled boxes that will help in minimizing time required for retrieving the vaccines. Each vaccine pack/ vial must be labeled with the expiry date and the principle of FEFO (first expired first out) and FIFO (First in first out) followed.
- The refrigerator should not be overloaded and overstocked so as to allow good air circulation around the vaccines.
- The refrigerator should be checked daily for door closure, monthly for coils, door seals, hinges & leveling and undergo maintenance on a periodic basis.
- In non frost free refrigerators, regular cleaning and defrosting should be done weekly or whenever ice layer of more than 4 mm forms in the freezer. Thicker ice layer will hamper proper functioning of the unit. Vaccines should be transferred to a safe place during defrosting and cleaning.
- The power supply should be secured. The plug should have a sticker saying “Do Not Unplug”. Staff must be trained never to turn off the refrigerator that holds vaccines.
- If power cuts are frequent, an alternative power source should be available capable for running for at least 72 hours.
- Rapid action should be taken in case of power failure or refrigerator malfunction. A plan must be in place for dealing with power failure. For short intervals, such as 2-3 hours, it is appropriate to just keep the refrigerator door closed, to maintain the temperature inside. For longer power cuts, it is necessary to move the vaccines, in a vaccine carrier, to a place where a working refrigerator is available. Refrigerator malfunctions need to be dealt with similarly. If the temperature inside is not within the acceptable range, the vaccines must be moved to another refrigerator, in a vaccine carrier. Regular training of staff and audit of practices should be done. Assign duties to specific trained staff to be held responsible for the vaccine storage and identify back up staff. But all the staff should be versed with the plan to handle power failures and out of range temperatures.
- IAPCOI strongly recommends use of purpose built refrigerator because of the several advantages

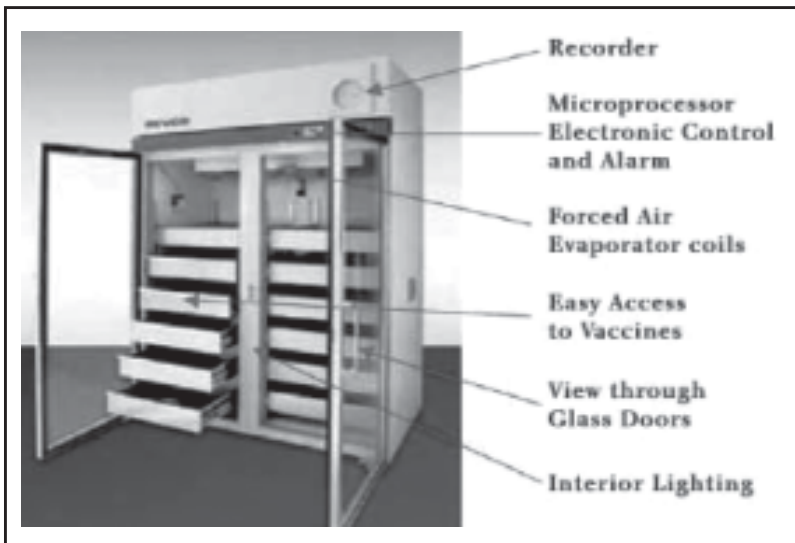
Purpose Built Vaccine Refrigerator Advantages

- Management is simpler.
- Temperatures are maintained in the 2°C to 8°C range.
- Minimises the risk of vaccines being stored outside the recommended temperature.



- Good temperature recovery after a door has been opened.
- There is more usable space for storing vaccines.
- External temperature display with minimum & maximum temperatures.
- Alarm when minimum or maximum temperatures are breached.
- Will automatically defrost, whilst maintaining a 2°C to 8°C range.
- Has a lockable door and is of glass.
- Will meet medical accreditation requirements

Purpose Built Vaccine Refrigerator



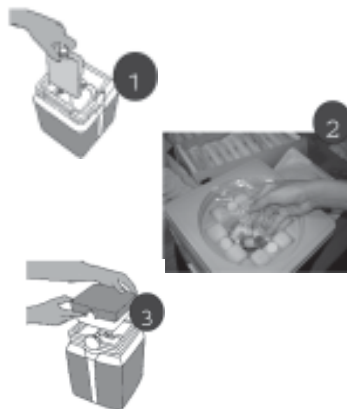
Cold box / Vaccine carriers

These are used for transport of vaccines. They should have frozen ice packs lining the sides. To prevent cold injury conditioned icepacks should be used rather than frozen packs. The vaccine pack should not be placed in direct contact with the icepacks but should have an intervening layer of plastic/ bubble wrap/styrofoam peanuts. A thermometer should be placed in the cold box/ vaccine carrier for recording temperatures. For keeping vaccines for longer durations the walls of the thermocol box should be 2 inches thick and have a snugly fitting lid.



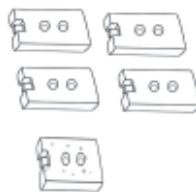
Loading a Vaccine Carrier

- Put conditioned ice-packs against each of the 4 sides of the vaccine carrier
- Take required vaccines and place them inside a plastic bag and place bag inside a vaccine carrier
- In vaccine carriers, place a foam pad on top of the conditioned ice-packs.
- Close the cold box or carrier lid tightly.
- Keep thermometer inside
- Wall should be min 2"



Preparing icepacks for use: Conditioning

- Take the frozen ice-packs you need from the freezer and place on a table
- Allow ice-packs to sweat at room temperature for 15 minutes
- Shake the ice pack, listen to sound of water.



Conditioning an ice-pack

Storage of Vaccines

Vaccines should be kept in original packaging till use to protect from light exposure. All vaccines currently available in India are safe at temperatures between 2 to 8°C. At a temperature of 2 to 8°C, most of these vaccines have a shelf life of 24 months. The manufacturer's instructions regarding shelf life of a given vaccine must be rigorously followed. BCG, OPV, Measles & MMR vaccines should be preferably kept frozen for long term storage (shelf life of 2 years). Even these vaccines, however, can be kept at 2 to 8°C for shorter periods e.g. 6 to 12 months for OPV and 18 to 24 months for measles. Though vaccines may retain potency for variable amounts of time at ambient temperatures, there is no simple and cheap method that can be used in the field to assess whether a vaccine exposed to ambient temperature has retained at least the minimum required potency. Hence such vaccines are best discarded.

Aluminium adjuvanted vaccines (DTwP, DTaP, TT, DT, Td, TT, Hepatitis B, combination



vaccines, Hepatitis A, HPV, PCV) and other vaccines including IPV, PPV 23, Hib, Inactivated Influenza vaccines, Meningococcal vaccines, Rotavirus vaccines, Typhoid vaccines and other brands of varicella vaccines should be stored at 2 to 8°C, must never be frozen and if accidentally frozen, should be discarded. The “Shake Test” can be used to determine if a vaccine vial has been suspected to be frozen at any time. The vial should be shaken so that the sediments, if any, are completely mixed. A frozen control vial should be used to compare with the test vial. During the 15 minutes test time a non-viable test vial will show sediments settling as fast as the control frozen vial. Vaccine vial found in frozen state should be directly discarded and need not undergo shake test. Diluents should never be frozen. They can be stored at 2 to 25°C and can be kept in the door compartments.

Reconstituted lyophilized vaccines (BCG, Measles, MMR, Hib, Rabies, Rotavirus) whether single dose/ multi dose must be stored at 2 to 8°C, protected from light and used within 4 to 6 hours. Multi dose vials of inactivated liquid vaccines once opened may be used till the expiry date on the container. OPV can be subjected to 10 cycles of freeze-thaw provided that the thawed material is kept refrigerated and the total cumulative duration of the thaw is not more than 24 hours. OPV would lose viability if kept at 22 to 25°C for more than a day. Opened vials of OPV, however, may be used in subsequent sessions at a given health facility if it has been preserved at 2 to 8°C. OPV vials used in the field setting or an outreach facility or during a pulse immunization session must be discarded at the end of the day. Vaccine vials should not be taken out to the field more than 3 times, after that these are best discarded irrespective of whether these have been opened or not.

Vaccines should be transported only in cold boxes or vaccine carriers - vacuum flasks should never be used for this purpose. During shipment and transportation, temperature and time sensitive monitor marks are used to check the cold chain. Transport is the most vulnerable time for the cold injury to vaccines.

WHO Multi-dose opened vial policy

Opened vials of DPT, TT, DT, Hepatitis B and OPV vaccines

May be used in subsequent immunization sessions for a maximum of one month, provided that each of the following conditions has been met:

- expiry date has not passed
- vaccines are stored under appropriate cold chain conditions
- The vaccine vial septum has not been submerged in water
- Aseptic technique used to withdraw all doses



Multi-dose opened vial policy

Opened vials of Measles, BCG & Yellow fever vaccines

- Reconstituted vials of Measles, BCG and Yellow fever vaccines must be discarded at the end of each immunization session or at the end of six hours, whichever comes first

Time limits for using vaccines after reconstitution

- Varicella = 30 min (and protect from light)
- MMRV = 30 min (and protect from light)
- Yellow fever = 1 hour
- Measles/MMR = 4 to 6 hours
- Meningococcal Polysaccharide Vaccine single dose vial = 30 min
- DTaP/Hib Combination = 30 min

What is new in cold chain?

WHO is actively considering certain heat stable vaccines to be removed from the cold chain because of following reasons.

- To reach more children beyond the existing cold chain in hard-to-reach rural populations.
- To enable on-time birth doses where home births are common and Hep B is endemic.
- To reduce/eliminate the risk of freezing.
- To limit the need to increase cold storage capacity and transport volumes.
- To limit the growth in energy needs.

WHO is conducting studies with various agencies to remove these vaccines from cold chain, of course it will come with the rider that it will have short expiry date

Conclusions: The cold chain is the Achilles heel in immunization and should be given appropriate attention



ADVERSE EVENTS FOLLOWING IMMUNIZATION

Introduction

An adverse event following immunization (AEFI) or vaccine associated adverse event (VAE) is defined as an untoward (temporally associated) event following immunization that might or might not be caused by the vaccine or the immunization process. These events may be recognized during clinical trials or during post marketing surveillance (e.g. intussusception following human rhesus rotavirus vaccine, febrile seizures following MMRV vaccine and GBS following meningococcal conjugate vaccines). Tolerance to vaccine associated adverse events is generally lower as these are administered to healthy children unlike other pharmaceutical products used in morbid populations. Vaccine associated adverse events are more likely to be noticed and communicated and can often significantly impact immunization programs as noticed with Measles, MMR and Pertussis vaccines.

Classification

AEFI may be a mere coincidence (e.g. sudden infant death syndrome following whole cell Pertussis vaccines) or a true adverse immunization reaction. Adverse immunization reactions may be further classified as

- Adverse vaccine reaction (vaccine induced): Here the vaccine is causally related to the reaction; e.g. VAPP due to Oral Polio Vaccine, anaphylaxis.
- Trigger reaction (vaccine potentiated): Here the reaction is triggered by the vaccine e.g. febrile seizure following vaccination in a predisposed child.
- Programmatic errors: These are most common cause for serious adverse events and death following vaccination. Deaths following Measles vaccination due to toxic shock syndrome resulting from improper reconstitution and storage of Measles vaccine is the most recent example of this phenomenon
- Injection reaction: Examples include syncope due to pain of vaccination, injection site abscesses, sciatic nerve damage due to gluteal injection and transmission of blood borne pathogens such as HIV/HBV/HCV.

It is extremely important to distinguish vaccine reactions that are causally related to the vaccine (adverse vaccine reactions) from other adverse events so that compliance to vaccines does not drop.

AEFI may also be classified as serious or non serious. A serious adverse event (SAE) is defined as that which is either i) fatal or life threatening or ii) results in



persistent or significant disability, incapacity or iii) results in or prolongs hospitalisation or iv) leads to congenital anomalies/birth defects. Important adverse reactions that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the patient should also be considered as serious.

Based on causal association, AEFI may also be classified as i) definitely ii) probably iii) possibly iv) unlikely to be related to the vaccine.

Adverse vaccine reactions

Adverse vaccine reactions are those that are causally related to vaccines and may be classified as local, systemic or allergic. Adverse vaccine reactions have been discussed in detail in the chapter on individual vaccines. Some common and/or serious reactions are discussed further.

Local reactions

Most parenteral vaccines induce some degree of local reactions including pain, erythema and induration. Local reactions are more with whole cell pertussis vaccines and aluminium adjuvanted (DTwP, DTaP, DT, Td, Tdap, TT, Hep B, Hep A, inactivated combination vaccines, HPV and PCV) vaccines. Most studies show the frequency of local reactions to increase with subsequent doses and frequently administered doses (TT). Local reactions may be partly ameliorated by ice application and paracetamol.

Systemic reactions

Fever is the most common systemic reactions and like local reactions, fever is more common with whole cell pertussis vaccines and aluminium adjuvanted vaccines. However, unlike local reactions, the incidence of fever and other systemic reactions usually declines with increasing age and increasing number of doses. Administration of paracetamol at the time of vaccination and later on a regular basis is helpful and indicated especially in children predisposed to febrile seizures. Fever due to vaccination does not usually last for more than 48 hours and any fever persisting beyond this time should be evaluated for other causes.

Severe allergy

Severe allergy or anaphylaxis or anaphylaxis like reactions including generalized urticaria or hives, wheezing, swelling of the mouth and throat, difficulty breathing, hypotension, and shock occur rarely at a frequency of 1 per 10,00,000 vaccinees. These reactions are rarely due to the vaccine antigen; they are usually due to other vaccine constituents including residual animal protein (e.g. egg), stabilizers (e.g. gelatin), antimicrobials (e.g. neomycin) or preservatives (e.g. thiomersol). As a



precautionary measure, the vaccinee should be questioned for any immediate type of hypersensitivity to any of the vaccine constituents listed on the package insert prior to vaccination. Patients with history of serious allergy to any of the vaccine constituents should not receive the vaccine (exception children with egg allergy can safely receive Measles & MMR vaccines). Since occurrence of anaphylaxis cannot be predicted in most vaccinees, all vaccinees should be observed for 15 minutes after vaccination and resuscitative equipment including ambu bag & mask, laryngoscopes, endotracheal tubes, IV access devices, epinephrine, hydrocortisone, antihistaminics, and inotropes should be kept standby. Management of anaphylaxis is detailed in Table 1

Table 1: *Emergency management of anaphylaxis*

1	Administer epinephrine (1:1000 solution) 0.01 ml/kg/dose (max 0.5 ml) intramuscular in anterolateral thigh
2	Set up IV access
3	Lay patient flat and elevate legs if tolerated. Give high flow oxygen and airway/ventilation if needed
4	If hypotensive also, set up additional wide bore access and give IV normal saline 20 ml/kg under pressure over 1-2 minutes
5	IM adrenaline may be repeated after 3-5 minutes if required
6	Oral antihistaminics may be given to ameliorate skin symptoms but IV antihistaminics are not recommended. Oral or injectable corticosteroids equivalent to prednisone 1-2 mg/kg may be given but benefit is yet unproven

Controversies in vaccine safety

Vaccines and Autism

Over the past decade there has been tremendous controversy on the relationship between vaccines particularly MMR and Autism/ Autistic spectrum disorder. Review of all currently available evidence does not support any causal relationship between MMR vaccine and Autism.

Safety of thiomersol

Thiomersol (50% ethyl mercury) a preservative in inactivated vaccines particularly in multi dose vials has been linked in the past to Autistic spectrum disorders and neurodevelopment disorders. Consequently most of the vaccine preparations available in the developed nations are thiomersol free. Systematic review of evidence however has not supported any causal association between thiomersol and neurotoxic



effects. Therefore in developing nations, where multi dose vials significantly bring down vaccine costs and cold chain space requirement, the benefits of thiomersol far outweigh any possible risks.

Vaccine associated adverse event reporting system (VAERS)

A system for reporting VAE is crucial in any immunization program so as to pick up previously unrecognized adverse effects and generate further data on vaccine safety. A robust system for reporting VAE exists in most developed countries including the US. However such a system is currently not available in India. Pediatricians are encouraged to report VAE to the IAP immunization website www.iapcoi.com. Events that should be reported include all SAE, irrespective of causal association, non serious adverse events that are unexpected in nature, severity, frequency or outcome, vaccine failures, and all usage in pregnancy

Conclusions

Vaccines are largely safe. Serious outcomes are usually programmatic/ human errors. It is therefore extremely important to use vaccines strictly as per recommendation and be prepared to handle any eventuality.



IMMUNIZATION SCHEDULE

Expanded Program of Immunization (EPI) and Universal Immunization Program (UIP)

Following the WHO recommendation, India introduced six vaccines under the Expanded Program of Immunization (EPI) in 1978 to reduce child mortality. (Bacillus Calmette-Guerin (BCG), TT, DPT, DT, polio, and typhoid).

Subsequently, in 1985 the Indian government included Measles vaccination and launched the Universal Immunization Programme (UIP) and a mission to achieve immunization coverage of all infants and pregnant women by the 1990's.

National Immunization Schedule

The national immunization schedule comprises of those vaccines that are given free of cost to all children of the country under EPI.

Table 1: *National Immunization Schedule*

Age	Vaccines
Birth	BCG, OPV ⁰ (for institutional deliveries)
6 weeks	DTwP1, OPV1, HepB1, Hib1 ^{\$\$} (BCG if not given at birth)
10 weeks	DTwP2, OPV2, HepB2, Hib2
14 weeks	DTwP3, OPV3, HepB3, Hib3
9-12 months	Measles
16-24 months	DTwP B1, OPV4, MMR ^{\$}
5-6 years	DTwP*
10 years	TT**
16 years	TT**
Pregnant women	TT1 (early in pregnancy) TT2 (1 month later) TT booster (if vaccinated in past 3 years)
Vitamin A	9, 18, 24, 30 and 36 months

\$ MMR is available in some states only

\$\$ Hib is being introduced in two states to begin with.

* A second dose of DTwP vaccine should be given at an interval of one month if there is no clear history or documented evidence of previous immunization with DTwP

** A second dose of TT vaccine should be given at an interval of one month if there is no clear history or documented evidence of previous immunization with DTwP, DT or TT vaccines



IAP Immunization Schedule

The IAP Committee on Immunization submits its position on vaccines not included in the national schedule on a periodic basis as and when they are licensed and made available in the country. The process of issuing recommendations involves an exhaustive review of published literature including standard text books, vaccine trials, recommendations of various countries, World Health Organization (WHO) position papers, literature from the vaccine industry, post-marketing surveillance reports, cost-effective analysis, epidemiology of disease in India and if available Indian studies on vaccine efficacy, immunogenicity and safety. If knowledge gaps are present then expert opinion is sought to fill the gaps. The existing national immunization schedule and government policies are also considered. These recommendations of IAPCOI are meant primarily for pediatricians in office practice as best individual practice guidelines. In addition, IAPCOI also submits its recommendations on incorporation of various new vaccines in the national immunization schedule.

The IAPCOI has categorized the available licenced vaccines in two broad groups

1. Vaccines recommended by IAP for routine use.
2. Vaccines to be used in special circumstances only.

Recommendations on new vaccines licensed and available are based on the likely epidemiology and disease burden, vaccine efficacy, safety and cost in the Indian context. It is important to note that these recommendations are based on the available data and consensus opinion. This being a dynamic process, the guidelines may change from time to time as new information is available.

A complete information on the disease and its likely outcome along with the benefits of the vaccine must be given to the parents while prescribing and using the vaccine in a given child.

Table 2: IAP recommended vaccines (2011)

IAP recommended vaccines for routine use		Vaccines under special circumstances
BCG	Hib	Rabies
OPV	Hep B	Influenza
IPV	MMR	PPSV23
DTwP/DTaP	HPV	Japanese Encephalitis
DT	PCV	Meningococcal
Td	Hepatitis A	Cholera
Tdap	Chicken Pox	Yellow Fever
Measles	Rotavirus vaccine	
Typhoid		



BCG: Bacillus Calmette Guerin; OPV: Oral poliovirus vaccine; DTwP: Diphtheria, tetanus, whole cell pertussis; DT: Diphtheria and tetanus toxoid; TT: Tetanus toxoid; Hep B: Hepatitis B vaccine; MMR: Measles, mumps, rubella vaccine; Hib: Hemophilus influenzae type 'b' vaccine; IPV: Inactivated poliovirus vaccine; Td: Tetanus, reduced dose diphtheria toxoid; Tdap: Tetanus, reduced dose diphtheria & acellular pertussis vaccine; HPV: Human papilloma virus vaccine; PCV pneumococcal conjugate vaccine; DTaP: Diphtheria, Tetanus, acellular pertussis vaccine; PPV 23: 23 valent pneumococcal polysaccharide vaccine.

Details of individual vaccines, basis for their recommendation and position in the immunization schedule is given in chapter on individual vaccines.

Table 3: IAP Immunization Time Table 2011; IAP recommended vaccines for routine use

Age (completed weeks/ months/years)	Vaccines
Birth	BCG OPV0 HepB 1
6 weeks	DTwP1/DTaP1 OPV1*/ OPV1 + IPV1 Hib1 HepB2 Rotavirus 1 ** PCV 1
10 weeks	DTwP2/ DTaP2 OPV2*/ OPV2 + IPV2 Hib 2 Rotavirus 2 PCV 2
14 weeks	DTwP3/ DTaP3 OPV3*/ OPV3 + IPV3 Hib3 Rotavirus 3 HepB3** PCV 3
9 months 12 months	Measles Hepatitis A 1
15 months	MMR1 Varicella PCV booster
16 to 18 months	DTwP B1/ DTaP B1 OPV4*/ OPV4 + IPV B1 Hib B1



Age (completed weeks/ months/years)	Vaccines
18 months	Hepatitis A 2
2 years 5 years	Typhoid 1# DTwP B ₂ / DTaP B ₂ OPV5 MMR2\$ Typhoid 2 Varicella 2 \$\$
10 to 12 years	Tdap/Td& HPV^

* OPV alone if IPV cannot be given

*# Rotavirus vaccine (2/3 doses depending on the brand at 4-8 weeks interval)

** The third dose of Hepatitis B can be given at 6 months

\$ The second dose of MMR vaccine can be given at any time 4-8 weeks after the first dose

\$\$ Varicella (2nd dose may be given any time 3 months after the 1st dose)

Typhoid revaccination every 3 years

& Tdap preferred to Td, followed by repeat Td every 10 years

^ Only females, three doses at 0, 1-2 (depending on brands) and 6 months

For details regarding recommendations please refer to individual vaccines



INDIVIDUAL VACCINES

BACILLUS CALMETTE GUERIN (BCG) VACCINE

Background

The exact burden of childhood tuberculosis in India is unknown but it is believed to constitute 15-20% of all tuberculosis cases. It is also estimated that childhood tuberculosis causes $\geq 10\%$ of all childhood hospital admissions in developing countries such as India. Prevention of childhood tuberculosis is thus an important priority, but is unfortunately difficult because of the limited efficacy of the BCG vaccine.

Vaccine

BCG vaccine is derived from the bovine tuberculosis strain and was first developed in 1921. It was the result of painstaking efforts by the French microbiologist, Albert Calmette, and the veterinary surgeon, Camille Guerin, who performed 231 repeated subcultures over 13 years. It continues to be the only effective vaccine against tuberculosis. The two common strains in use are Copenhagen (Danish 1331) and Pasteur, of which the former was produced in India at the BCG Laboratories, Guindy, Tamil Nadu till recently. BCG induces cell-mediated immunity, but the protective efficacy is a matter of debate and is very difficult to quantify. BCG has an efficacy of 50-80% for prevention of miliary and meningeal form of the disease. Protective efficacy for pulmonary tuberculosis is 50%.

The vaccine contains 0.1-0.4 million live viable bacilli per dose. It is supplied as a lyophilized (freeze-dried) preparation in vacuum sealed, multi-dose, dark colored ampoules or 2 ml vials with normal saline as diluent. The vaccine is light sensitive and deteriorates on exposure to ultra violet rays. In lyophilized form, it can be stored at 2 to 8° C for up to 12 months without losing its potency. The long necked, BCG ampoule, should be cut carefully by gradual filing at the junction of its neck and body, as sudden gush of air in the vacuum sealed ampoule may lead to spillage of the contents. Diluent should be used for reconstitution. Sterile normal saline may be used if diluent is not available. As the vaccine contains no preservative, bacterial contamination and consequent toxic shock syndrome may occur if kept for long after reconstitution. The reconstituted vaccine should be stored at 2 to 8°C, protected from light and discarded within 4-6 hours of reconstitution. The recommended dose is 0.1 ml or 0.05 ml as suggested by the manufacturer of the vaccine. Dose does not depend on the age and weight of the baby. Injection of BCG should be strictly intradermal, using a tuberculin syringe and a 26G / 27G needle. The convex aspect



of the left shoulder at level of deltoid insertion is preferred for easy visualization of the BCG scar and for optimum lymphatic drainage. Other sites such as thigh should be avoided. The selected site may be swabbed clean using sterile saline and local antiseptics should be avoided. A wheal of 5 mm at the injection site indicates successful intradermal administration of the vaccine. Subcutaneous administration of BCG is associated with an increased incidence of BCG adenitis. The injected site usually shows no visible change for several days. Subsequently, a papule develops after 2-3 weeks, which increases to a size of 4-8 mm by the end of 5-6 weeks. This papule often heals with ulceration and results in a scar after 6-12 weeks. The ulcer at vaccination site may persist for a few weeks before formation of the final scar. No treatment is required for this condition. Secondary infection at the vaccination site may require antimicrobials. Ipsilateral axillary/cervical lymphadenopathy may develop a few weeks/months after BCG vaccination. Antitubercular therapy is of no benefit in such situations and should not be administered. The nodes regress spontaneously after a few months. It should also be noted that if fine needle aspiration cytology of the nodes is carried out, stain for acid-fast bacilli may be positive. These are bovine vaccine bacilli and should not be misconstrued as being suggestive of tuberculous disease. In some children, the nodes may even liquefy and result in an abscess. Surgical removal of the nodes or repeated needle aspiration is the treatment of choice; again antitubercular therapy is not recommended. Disseminated BCG infection is extremely unusual but may occur in children with cellular immunodeficiency. BCG should be avoided in the immunocompromised, especially those with cellular immunodeficiency; it may however be given at birth to children born to HIV positive mothers. BCG may be given with all vaccines on the same day or at any interval with the exception of Measles/ Measles Mumps Rubella (MMR) vaccine where a gap of 4 weeks between the two vaccines is recommended.

Recommendations for use

The recommended age of administration is at birth (for institutional deliveries) or at 6 weeks with other vaccines. Catch up vaccination with BCG is recommended till the age of 5 years. Routine tuberculin testing prior to catch up vaccination is not necessary. BCG may be repeated once in children less than 5 years of age in the absence of a reaction/ scar presuming that BCG has not been taken up (even though most patients with absent reactions/ scars have shown *in vitro* evidence of cell mediated immunity against tuberculosis). Here again, tuberculin testing prior to administration of the second dose of BCG is not necessary.



POLIO VACCINES

Background

The availability of two effective vaccines against poliomyelitis for the past five decades has ensured remarkable decline in the global burden of disease. They were developed in the USA during 1950s, first the inactivated polio vaccine (IPV) by Jonas Salk and later the live oral polio vaccine (OPV) by Albert Sabin. The Global Polio Eradication initiative was launched in 1988 using oral polio vaccine (OPV) as the eradication tool and employing a four pronged strategy comprising high routine immunization coverage, supplementary immunization activities (SIA's)/ pulse immunization, AFP surveillance and "Mop- up" immunization. The initiative was hugely successful with reduction of polio cases from 350,000 in 1988 to less than a 1000 cases in 2010. Only four countries India, Pakistan, Nigeria and Afghanistan remain endemic today and wild virus type 2 has not been isolated since 1999. In 2005, new monovalent polio vaccines (mOPV type 1 and type 3) were licensed and used to enhance the impact of supplementary immunization activities (SIAs) in the key remaining reservoirs of wild polio. Despite the use of mOPVs and the intensification of the global eradication efforts in 2007, indigenous wild poliovirus type 1 (WPV1) and 3 (WPV3) transmission has continued in geographically limited areas of four countries: Nigeria, India, Pakistan and Afghanistan. The challenge of interrupting the residual WPV transmission in these areas has been compounded by the recurrent exportation of WPV from northern Nigeria and northern India into previously polio-free areas within and outside their borders. While mOPVs have provided the GPEI with much more potent tools for rapidly building population immunity, optimizing the balance of mOPVs has proven much more difficult than originally anticipated, leading to alternating outbreaks of type 1 and 3 poliovirus in certain settings and prompting the fast-track development of a completely new 'bivalent' OPV (bOPV). With intelligent use of mOPVs and bOPV, the total number of wild polio cases was reduced to 41 in year 2010 in India.

Vaccines

OPV

OPV is a trivalent vaccine consisting of a suspension of attenuated poliovirus types 1, 2 and 3 grown in monkey kidney cell cultures and stabilized with magnesium chloride. It is presented in a buffered salt solution, with light pink colour indicating the right pH. It is a very heat sensitive vaccine having a shelf life of 2 years at a temperature of -20°C, 6 months at 2 to 8°C and 1-3 days at room temperature. OPV should be stored at -20°C at the state and district level and in the freezer at the clinic level. The vaccine must reach the outreach facility at 2 to 8°C in vaccine carriers



with ice packs. Multiple freeze thaw cycles should be avoided as the virus loses its potency. After thawing, it should be kept at temperatures between 2°C and 8°C for a maximum of 6 months. In recent years, all manufacturers are required to attach a 'vaccine vial monitor' to follow its journey through time-temperature sequences. The monitor changes colour if the vial goes through unacceptable time-temperature exposure. The dose is 2 drops orally.

When OPV is given by mouth, the vaccine viruses reach the intestines where they must establish infection (vaccine virus "take") before an immune response may occur.

A peculiarity of OPV, unlike the IPV, is marked variation in its immunogenicity amongst different regions of the world. In general immunogenicity is excellent in developed countries. On the contrary, in the developing countries around the tropical and subtropical belt, the immunogenicity is quite low.

Data from the composite of Vellore studies in 1970s and 1980s suggest that seroconversion rates after three doses of OPV average 65%, 96% and 63% for Types I, II and III respectively. Multiple doses of OPV are necessary before 90-95% of children develop immune responses to all three poliovirus types.

The onset of action of OPV is faster as compared to inactivated poliovirus vaccine (IPV) and thus OPV is the vaccine of choice for outbreak control.

AFP surveillance data, systematically generated since launch of GPEI, suggests that several Indian children particularly from Uttar Pradesh (UP) and Bihar develop paralytic poliomyelitis despite having received 15-20 doses of OPV. A case control study based on AFP surveillance data from India has estimated the per dose efficacy of trivalent OPV in India as 13% to as low as 9% in UP. This poor efficacy is attributed to high population densities, malnutrition, poor sanitation that increase the risk of infection with other enteroviruses and NOT due to poor vaccine potency due to breaks in cold chain.

Monovalent OPVs (mOPVs) and bivalent OPV (bOPV) are presumably 2.5–3 times more efficacious than trivalent OPV, as competition between different polio viruses is eliminated. Henceforth, monovalent OPV containing type 1 and type 3 virus have been introduced in India since 2005 and bivalent OPV containing type 1 and type 3 virus since 2010 for pulse immunization.

A rare but serious adverse effect associated with OPV is vaccine associated paralytic poliomyelitis (VAPP). VAPP occurs due to loss of attenuating mutations and reversion to neurovirulence during replication of the vaccine virus in the gut. VAPP is defined as those cases of AFP which have residual weakness 60 days after the onset of paralysis and from whose stool samples, vaccine-related poliovirus but no wild polio



virus is isolated. VAPP may occur in the vaccine recipient (recipient VAPP, occurring within 4-40 days of receiving OPV) or contact of the vaccine recipient (contact VAPP). The risk of VAPP is higher with the first dose that “takes”, with P2 virus and in patients with B cell immunodeficiency. In industrialized countries, the risk of VAPP decreases sharply (>10-fold) with subsequent OPV doses, whereas in developing countries, this decline is more gradual, probably as a consequence of lower vaccine effectiveness. The incidence of VAPP has been estimated at 4 cases per million (1/1 000 000) birth cohort per year in countries using OPV. The incidence of VAPP in developed countries, such as USA, has been reported to be 1 per 2.4 million doses distributed and 1 per 750,000 with first dose. The risk of VAPP in India has been estimated to be 1 per 4.1 to 4.6 million doses distributed and 1 per 2.8 million first dose recipient risk. This lower risk of VAPP has been attributed to maternal antibodies, birth dose of OPV, early immunization with OPV and most importantly lower “take” of the vaccine (as only the vaccine that takes up can cause VAPP). Nevertheless the absolute numbers of VAPP are significant and it is estimated that 181 cases of VAPP occurred in India in 1999.

A recently recognized unanticipated major problem with the use of OPV is the emergence of Vaccine Derived Polio Viruses (VDPVs). They arise due to mutation and recombination in the human gut and are 1-15% divergent from the parent vaccine virus. The functional definition of VDPV, as isolates showing >1% nucleotide substitutions in VP1, was derived from the observation that all VDPVs were >1% divergent from Sabin Vaccine virus sequence. Data is being collected to know if isolates with <1% changes (5 to 9) can also be labeled as VDPV or pre-VDPV. These viruses, like those causing VAPP, are neurovirulent but additionally are transmissible and capable of causing outbreaks. They have been classified into three groups: circulating VDPV (cVDPV) VDPV with evidence of virus circulation in the population causing two or more paralytic cases, iVDPV- VDPV in the immunodeficient person and VDPV of ambiguous origin (aVDPV)- VDPV isolated from environmental sources or evidence of circulation not established. During 2000–2009, 13 outbreaks of cVDPVs were reported from 13 countries in 3 continents, with at least 421 cases. There was a large outbreak in Nigeria caused by cVDPV type-2. In each of these incidents, immunity gaps were identified as potential risk factors, and OPV was used to control the outbreak. These cVDPV events demonstrate the importance of achieving and maintaining high polio immunization rates. Risk factors for outbreaks due to cVDPV include dropping immunization coverage (both routine and SIA's), high population densities, tropical conditions and previous eradication of wild virus. In India, total number of 24 VDPV were reported between April 2009 and January 2010. Type 1 VDPV was isolated from two AFP cases of which one was



from an immuno-deficient child. Type 2 VDPV was isolated from 22 AFP cases. One was from an immuno-deficient child. No VDPV case has been reported since February 2010 after a round of tOPV. A total of 3 cases of Type 2 VDPV were reported (2 from Uttar Pradesh and 1 from Tamilnadu) in the year 2010. Recognition of VDPVs is the primary reason why synchronous stopping of OPV use globally and continuing to vaccinate against polio with IPV is mandatory in the post polio eradication scenario.

OPV is contraindicated in immunodeficient patients (especially humoral immunodeficiencies) and their household contacts.

Inactivated polio vaccines (IPV)

IPV is formaldehyde killed poliovirus, grown in monkey kidney cell/human diploid cells. Old IPV contained 20, 8 and 32 D antigen units of types 1, 2 and 3 polioviruses respectively. All currently used IPV vaccines are enhanced potency IPV (eIPV) which contain 40, 8 and 32 D antigen units of type 1, 2 and 3 respectively. Currently the term IPV means eIPV. The vaccine should be stored at 2 to 8°C and the dose is 0.5 ml intramuscularly/subcutaneously. It is highly immunogenic. Its immunogenicity is dampened by the presence of maternal antibody in the very young infant, especially up to the age of 8 weeks. Seroconversion rates are 90-100% after two doses given after the age of 2 months and at 2 months interval or in the EPI schedule of three doses at 6, 10 and 14 weeks. A third dose, given after a suitable interval boosts the antibody levels and ensures the perpetuation of immunity for decades and more. IPV can be administered along with all other childhood vaccines and can be used in combination with DTwP/ DTaP, Hib and Hep B vaccines without compromising seroconversion or increasing side effects. The vaccine is very safe. As IPV contains trace amounts of streptomycin, neomycin and polymyxin B, allergic reactions may be seen in individuals with hypersensitivity to these antimicrobials.

Several countries have shifted from all OPV to sequential OPV- IPV schedules and all IPV schedules with elimination of wild polio. IPV will be indispensable in the post eradication era when OPV has to stop but “vaccination against polio” cannot stop.

Mucosal immunity and Herd effect with OPV and IPV

It was widely believed that OPV mimics natural infection, spreads widely in the community and immunizes children in community (contact immunization), and produces excellent mucosal immunity to protect not only from disease but also from subsequent infection. Due to these attributes, it was believed that it would eliminate transmission of wild polio virus when 3 dose tOPV coverage reaches 80-85% (Herd Effect).



Immunocompetent individuals infected by poliovirus develop protective immunity through humoral (circulating antibody) responses and mucosal (secretory immunoglobulin A) immune responses. The presence of neutralizing antibody against polioviruses is considered a reliable correlate of protection against poliomyelitis. Mucosal immunity in polio refers to the resistance to mucosal infection by wild polioviruses due to prior infection with WPV or immunizing experience with polio vaccines. Mucosal immunity decreases the replication and excretion (shedding) of the virus, and thus provides a potential barrier to its transmission. If OPV induces good mucosal (gut) immunity then fully immunized children should not participate in transmission of wild polio virus. But that is not the case, WPV1 infection and fecal shedding has been documented in older immunized children who are in contact with under -5 children with polio. Polio cases continue to occur in well immunized communities. OPV induces a high nasopharyngeal and duodenal IgA response which was thought to be an absolute marker of gut mucosal immunity; however, now we know that IgA is a marker of gut infection and there are other mechanisms for mucosal immunity besides IgA. Secondly it has been shown in animal studies done in Vellore that repeated infections are necessary to induce sufficient mucosal immunity and it is not necessary that an OPV dose will cause infection every time because of poor uptake of OPV in developing countries. Finally, there is evidence that gut immunity for polio wanes with time; this coupled with high force of wild poliovirus transmission (dictated by inoculum size and/or repetitiveness of exposure) and persistence or reintroduction of wild poliovirus, would set the stage for large scale polio outbreaks in well immunized populations after a period of control of disease.

In contrast to OPV, IPV produces excellent humoral immunity as well as local pharyngeal immunity. In a study from Vellore, monkeys given 3 doses of IPV resisted infection after oral inoculation with wild poliovirus for up to 12 months. This can be explained by the fact that though IPV induces only low levels of Ig A antibodies, it generates strong humoral immunity (IgG) and it has been postulated that the spill over of Ig G antibodies has inhibitory influence on local infection. So ultimately the degree of mucosal immunity more closely correlates with the titer of homologous humoral antibodies. Mucosal immunity is good when vaccine efficacy is high as in case of IPV, bOPV or mOPV than t OPV.

Herd effect with polio vaccines

The phenomenon of immunized individuals affecting the epidemiology of infection (and consequently disease) in the unimmunized segment of population is referred to as herd effect. Higher the vaccine efficacy and coverage, greater the herd effect. In industrialized countries, two factors contribute to a high herd effect: 1. There is an



excellent gut immunity due to a high OPV immunogenicity and 2. contact immunization of the non – immunized children due to spread of the vaccine virus from the vaccines. Both these attributes are weak in developing countries. This herd effect seen in the industrialised countries is not visible in India and is evident by the following facts: 1. Repeated doses of OPV have to be given to the same group of children, with virtually 100% coverage, before wild virus transmission could be stopped 2. The median age of polio in India has not shifted to the right and remained stationary at 12-18 months from prior to introducing immunization till now. On the contrary, IPV with its high immunogenicity and efficacy, induces high levels of antibodies which spill over to the gut and thus prevent transmission potential of immunised individuals besides protecting them. Thus contrary to the conventional teaching, IPV exhibits a demonstrable herd effect.

Recommendations for use

IAPCOI recommends continuing OPV use for birth dose, for routine immunization at 6, 10 and 14 weeks, 18-24 months and at 5 years and on all NID's and SNID's. The IAPCOI also recommends offering additional use of IPV with OPV in all children in the schedule discussed below. Any of the currently licensed brands may be used. The recommendation for combined use of OPV and IPV is for the following reasons:

- Excellent and highly predictable immunogenicity, efficacy and safety of IPV
- OPV use should be continued at present in concordance with the government policy of using OPV for polio eradication
- Better mucosal immunity of OPV and IPV combination schedule as compared to IPV alone.
- The risk of VAPP with this combined OPV and IPV schedule is extremely low as the child receives OPV at the time when he/she is protected against VAPP by maternal antibodies. Subsequently he/she is protected from VAPP by IPV. Even if we adopt an all IPV schedule, the child may still be at a small risk for VAPP through exposure to the oral polio vaccine virus through contacts/ environment before he/she receives his/her first dose of IPV.
- OPV and IPV used simultaneously in combination in the trials in Gambia, Oman, Thailand and Pakistan have shown higher levels of seropositivity as compared to all OPV or IPV alone schedules. In the Gaza strip combined IPV-OPV use reduced the incidence of paralytic polio from 10 to less than 2 cases per 100 000 persons in the first 3 years and it further reduced to 0.16 per 100 000 cases in the next 5 years.



- Furthermore, the concurrent use of OPV may compensate for somewhat inferior seroresponse (particularly against types 1 & 2 serotypes) of IPV when used in accelerated 6, 10, and 14 week schedule.

Dose and Schedule

Child who has not received any polio vaccination so far

OPV at birth, OPV and IPV at 6, 10 and 14 weeks. OPV and IPV at 15-18 mths and OPV at 5 years. OPV on all NID's and SNID's. An alternative to this schedule is birth dose of OPV, OPV at 6 weeks, OPV and IPV at 10 weeks, OPV at 14 weeks and IPV at 18 weeks, OPV and IPV at 15 - 18 months, OPV at 5 years and OPV on all NID's and SNID's. In this schedule though the number of IPV doses have reduced from 4 to 3 but it a) is logistically more demanding as number of visits increase b) is not feasible if combination vaccines are chosen.

Child who has completed primary series of OPV

IPV may be offered as catch up vaccination for children less than 5 years of age who have completed primary immunization with OPV. IPV can be given two doses at 2 month interval. OPV need not be given with these IPV doses. OPV should be given with the first and 2nd boosters of DTP and on all NID's and SNID's.

Immunodeficient children and their close contacts

IPV should be the preferred vaccine especially in patients with B cell immunodeficiency if resources permit. OPV should be avoided. The schedules are as discussed earlier with the exception that a second booster dose of IPV at 5 years is also recommended.

Combination vaccines containing IPV will be discussed separately.

Recommendations for 'End game' and 'Post-eradication' vaccine strategy

In the current scenario, the combined OPV and IPV schedule strives to provide the best of protection to an individual child while not deviating from the national immunization policies.

For the public program, while mOPV1 is a sharper tool against WPV 1, bOPV seems to be adequate against WPV 1 and WPV 3; hence there may not be any more need for mOPV3. Thus, the key to success lies in intelligent and imaginative use of the three OPVs, *i.e.* mOPV1, bOPV and tOPV, against WPV types 1 and 3, and circulating Vaccine Derived Polio Virus (cVDPV) types 1, 2 and 3.

IAP-Polio Eradication Committee (IAP PEC) advocates bOPV for all Supplementary



Immunization Activity (SIAs), the number of National Immunization Days (NIDs) fixed as 3 in the lowest season; and consideration for strategic use of IPV to improve gut immunity in highly endemic regions if need arises.

There is no unanimity on the universal use of any poliovirus vaccine including IPV as far as post-eradication era is concerned. WHO has not issued any guidelines and left it to individual member country to design their own vaccination strategy.

The IAPCOI believes that the risks of leaving large population without any protection against future polio outbreaks are grave. Therefore, the only safe option is to introduce IPV and achieve high coverage before discontinuing OPV. While many countries resorted to abrupt switching from OPV to IPV, all of them had, and continued to have, very high vaccination coverage- an unlikely prospect in India as of now. Thus, India can also discontinue OPV irrespective of its continued use in other countries, provided sufficient steps (using IPV) are taken to protect children from any imported vaccine-derived viruses.

Hence, IAPCOI recommends introduction of IPV in routine immunization in southern states free of wild polio, to facilitate OPV cessation. This should be followed gradually by universal use of IPV in RI all over the country (when UP and Bihar are also polio free).

OPV used thereafter should be confined to three-annual pulses through NIDs, until we are certain that WPV transmission has truly stopped.

IAPCOI believes there is a need to chalk out a clear strategy on how to deal with the issues like OPV cessation plans, global synchronization versus regional/national synchronization, duration of AFP surveillance, tackling of future outbreaks of both wild and vaccine viruses, role of IPV in controlling future outbreaks of cVDPVs, development of safe and affordable IPV *etc.* IAPCOI thinks that there is a need to develop country-specific economic models for employing universal IPV during post-eradication era.

DIPHTHERIA, TETANUS & PERTUSSIS VACCINES

DTwP VACCINE

Background

The morbidity and mortality due to diphtheria, tetanus and pertussis has reduced significantly in India since introduction of the whole cell vaccines in EPI. However coverage with 3 doses of the whole cell vaccine DTP stands at 55% with booster coverage being even lower, the need of completing the schedule and boosters should be stressed upon by the pediatrician.



Vaccine

Popularly known as triple antigen, DTwP is composed of tetanus and diphtheria toxoids as well as killed whole cell pertussis bacilli adsorbed on insoluble aluminium salts which act as adjuvants. The content of diphtheria toxoid varies from 20 to 30 Lf and that of tetanus toxoid varies from 5 to 25 Lf per dose. The vaccines need to be stored at 2 to 8°C. These vaccines should never be frozen, and if frozen accidentally, should be discarded. The dose is 0.5 ml intramuscularly and the preferred site is the anterolateral aspect of the thigh. The immunogenicity (protective titer for diphtheria ≥ 0.1 IU/ml and for tetanus ≥ 0.01 IU/ml) and effectiveness against diphtheria/ tetanus of three doses of the vaccine exceeds 95%. Disease may occur in vaccinated individuals but is milder. The efficacy of the vaccine against pertussis is lower and as per data from international trials ranges from 70-90% (exception the US Connaught whole cell vaccine which is now withdrawn). Immunity against all three components wanes over the next 6-12 years and thus regular boosting is needed.

Most adverse effects are due to the pertussis component. Minor adverse effects like pain, swelling and redness at the local site, fever, fussiness, anorexia and vomiting are reported in almost half the vaccinees after any of the 3 primary doses. Serious adverse effects have been reported with DTwP vaccines but are rare. The frequency of these side effects/ 1000 doses is 0.2 - 4.4 for fever more than 40.5°C, 4 - 8.8 for persistent crying, 0.06 - 0.8 for hypotonic hyporesponsive episodes (HHE), 0.16 - 0.39 for seizures and 0.007 for encephalopathy. The frequency of systemic reactions reduces and that of local reactions increases with increasing number of doses. Children with history of a reaction following vaccination are more likely to experience a reaction following future doses. Catastrophic side effects such as sudden infant death syndrome (SIDS), autism, chronic neurologic damage, infantile spasms, learning disorders and Reye's syndrome were attributed to use of the whole cell vaccine in the past. It has now been proved beyond doubt that the whole cell pertussis vaccine is not causally associated with any of these adverse events.

Absolute contraindications to any pertussis vaccination (including DTwP vaccine) is history of anaphylaxis or development of encephalopathy within 7 days following previous DTwP vaccination. In case of anaphylaxis, further immunization with any diphtheria/ tetanus/ pertussis vaccine is contraindicated as it is uncertain which component caused the event. For patients with history of encephalopathy following vaccination, any pertussis vaccine is contraindicated and only diphtheria & tetanus vaccines may be used. Events such as persistent inconsolable crying of more than 3 hours duration/ hyperpyrexia (fever $\geq 40.5^{\circ}$ C)/ HHE within 48 hours of DTwP administration and seizures with or without fever within 72 hours of administration of



DTwP are considered as precautions but not contraindications to future doses of DTwP because these events generally do not recur with the next dose and they have not been proven to cause permanent sequelae. Progressive/evolving neurological illnesses, is a relative contraindication to first dose of DTwP immunization. However DTwP can be safely given to children with stable neurologic disorders.

Recommendations for use

The standard schedule is three primary doses at 6, 10 and 14 weeks and two boosters at 15-18 months and 5 years. Early completion of primary immunization is desirable as there is no maternal antibody for protection against pertussis. The schedule for catch up vaccination is three doses at 0, 1 and 6 months. The 2nd childhood booster is not required if the last dose has been given beyond the age of 4 years. DTwP is not recommended in children aged 7 yrs and older due to increased risk of side effects. It is essential to immunize even those recovering from diphtheria, tetanus and pertussis as natural disease does not offer complete protection.

DTaP VACCINE

Background

The introduction of the whole cell vaccines paid rich dividends in terms of decline in disease morbidity and mortality. Once disease rates declined, concern over minor, serious and “devastating” adverse effects of the pertussis component of the whole cell vaccines led to development of the acellular pertussis vaccines in Japan in 1981. These were licensed in the US in 1996 and have now replaced the whole cell vaccines in many developed countries.

Vaccine

The components of pertussis bacilli used for preparation of the acellular vaccines include pertussis toxin (PT) as the essential component with or without filamentous hemagglutinin (FHA), pertactin (PRN) and fimbrial hemagglutinins 1, 2 & 3 (FIM). Commercially available vaccines vary in number of components, quantity of components and method of inactivation of the components. Currently available aP vaccines in India include five component vaccines, three component vaccines and a two component combination vaccine. The vaccines should be stored at 2 to 8°C and the recommended dose is 0.5 ml intramuscularly. The efficacy and duration of protection with DTaP vaccines against diphtheria/ tetanus and pertussis is similar to that afforded by the whole cell vaccines. There is considerable controversy on the relative efficacy of different acellular vaccines with varying number of components.



The efficacy is influenced not only by number of components but also by quantity of antigen and method of inactivation. Even monocomponent vaccines with only PT have performed well in national programs. Review of clinical trial data and experience from field use in national programs indicates that all currently licensed acellular pertussis vaccines have similar efficacy. All DTaP vaccines show better efficacy against severe disease than mild disease.

The DTaP vaccines score over the whole cell vaccines in terms of adverse effects. Broadly speaking the incidence of both minor and major adverse effects is reduced by two thirds with the acellular vaccines. The incidence of adverse effects is similar with all currently licensed DTaP vaccines. The absolute contraindications to DTaP vaccines are same as those for whole cell vaccines and include history of anaphylaxis/encephalopathy following past pertussis vaccination. Serious adverse events following previous pertussis vaccination (listed in DTwP section) though less likely as compared to DTwP may still occur with DTaP and are similarly considered as precautions while using the vaccine.

Recommendations for use

DTaP vaccines are not more efficacious than DTwP vaccines, but have fewer adverse effects. It must also be remembered that serious adverse effects are rare phenomena even with the whole cell vaccine unlike popular belief. The IAPCOI therefore unequivocally endorses the continued use of DTwP vaccine in EPI because of its proven efficacy and safety. The use of DTaP vaccine in office practice should be following one to one discussion with parents on a named child basis. The DTaP vaccines may be preferred to DTwP vaccines in those children with history of severe adverse effects following DTwP vaccines or children with neurologic disorders, if resources permit. The schedule is same as with DTwP vaccines. Like DTwP vaccines, DTaP vaccines must not be used in children 7 years or older because of increased reactogenicity. All licensed DTaP vaccines are of similar efficacy and safety as of currently available data and any one of them may be used. DTaP combination vaccines will be discussed separately.



TETANUS TOXOID (TT)

Background

Antibodies to tetanus decline over time and hence regular boosting is needed to ensure adequate levels of antibodies during any apparent/inapparent exposure to tetanus bacilli/ toxin.

Vaccine/Toxoid

TT containing 5 Lf of toxoid is one of the most heat stable and commonly used vaccines. The vaccine should be stored between 2 to 8°C and the dose is 0.5 ml intramuscularly. Administration of boosters more frequently than indicated leads to increased frequency and severity of local and systemic reactions as the preformed antitoxin binds with the toxoid and leads to immune complex mediated reactions.

Recommendations for use

The role of stand alone TT vaccines is diminishing and replacement with Td/ Tdap is recommended for more comprehensive protection. In individuals who have completed primary and booster vaccination with DTwP/ DTaP, TT boosters every 10 years provide sufficient protection.

TT in pregnancy

WHO has evolved exhaustive guidelines for administration of TT in pregnant women and recommends replacement of TT with Td in a phased manner. For pregnant women who have not been previously immunized, two doses of TT at least one month apart should be given during pregnancy so that protective antibodies in adequate titers are transferred to the newborn for prevention of neonatal tetanus. The first dose should be administered at the time of first contact/ as early as possible and the second dose of TT should be administered 1 month later and at least 2 weeks before delivery. A single dose of TT would suffice for subsequent pregnancies that occur in the next 5 years; thereafter, 2 doses of TT would again be necessary. Women, who have received 5 doses of TT over a period of at least 2.5 years, get lasting protection for their reproductive years. For women who have received 3 primary doses in infancy, two doses during the 1st pregnancy are indicated. The 2nd pregnancy requires 1 more dose and gives lasting protection for the reproductive years. For women who have received three doses and 1 booster in childhood, 1 dose each in the first and second pregnancy provide lasting protection. In women who have received 3 primary doses and the two childhood boosters only 1 dose in the first pregnancy provides lasting protection. For women who have received an additional



adolescent booster, in addition to the 5 childhood doses, no further doses are necessary in pregnancy.

TT in wound management

All patients presenting with skin wounds/ infections should be evaluated for tetanus prophylaxis. Cleaning of the wound, removal of devitalized tissue, irrigation and drainage is important to prevent anaerobic environment which is conducive to tetanus toxin production. The indications for TT and Tetanus immunoglobulin (TIG) are as below. Again replacement of TT with Td/Tdap is recommended.

History of Tetanus Toxoid doses	Clean, Minor Wounds		All Other wounds	
	TT/Td	TIG*	TT/Td	TIG*
Unknown, ≤ 3 , immunodeficient	Yes	No	Yes	Yes
≥ 3 doses	No**	No	No***	No

Including, but not limited to, wounds contaminated with dirt, feces, soil, saliva; puncture wounds; avulsions; and wounds resulting from missiles, crushing, burns, and frostbite.

*TIG: Tetanus immunoglobulin (250 - 500 IU IM)

**Yes, if more than 10 years since last dose

***Yes, if more than 5 years since last dose

Evidence suggests that tetanus is highly unlikely in individuals who have received 3 or more doses of the vaccine in the past and who get a booster dose during wound prophylaxis, hence passive protection with TIG is not indicated in these patients irrespective of wound severity unless the patient is immunocompromised. For children who are completely unimmunized, catch up vaccination should be provided by giving three doses of TT at 0, 1 and 6 months. For partially immunized children, catch up vaccination entails administration of at least 3 doses of TT including previous doses received. Children with unknown / undocumented history should be treated as unimmunized. It is recommended that the TT booster doses administered at the time of wound management and for catch up vaccination be replaced with DTwP/ DTaP/ Td/ Tdap depending on the age of the child and nature of previous doses received for more comprehensive protection.

DT VACCINE

This vaccine comprises of diphtheria and tetanus toxoid in similar amounts as in DTwP/DTaP, should be stored at 2 to 8°C and the dose is 0.5 ml intramuscularly. It is



recommended in children below 7 years of age where pertussis vaccination is contraindicated. Studies with DTwP in school aged children have shown no serious adverse events attributable to the vaccine. Additionally, boosting of pertussis immunity is important to protect against childhood pertussis. Henceforth, the IAPCOI recommends DTwP/DTaP as the 2nd childhood booster and the Government of India has also replaced DT with DTwP for the 2nd childhood booster.

Td VACCINE

Background

Studies show that diphtheria antibody levels decline over time resulting in increasing susceptibility of adolescents and adults to diphtheria. However, good childhood vaccination coverage (at least 70%) provides herd effect by reducing circulation of toxigenic strains and prevents outbreaks in adults despite susceptibility. When childhood vaccination programs break down as happened in the former Soviet Union in the early 1990s, massive outbreaks of diphtheria involving primarily adults have occurred. Thus it is desirable to regularly boost adult immunity against diphtheria in addition to tetanus every 10 years. The DTwP, DTaP and DT vaccines cannot be used in children aged 7 years and above due to increased reactogenicity due to the higher diphtheria toxoid and pertussis components.

Vaccine

Td contains the usual dose of tetanus toxoid and only 2 units of diphtheria toxoid, is stored at 2 to 8°C and is administered intramuscularly in a dose of 0.5 ml.

Recommendations for use

This vaccine is indicated as replacement for DTwP/DTaP/DT for catch up vaccination in those aged above 7 yrs (along with Tdap) and as replacement for TT in all situations where TT is given.

Tdap VACCINE

Background

Immunity against pertussis following primary/booster DTwP/DTaP vaccination wanes over the next 6-12 years. Surveillance studies from the developed world, chiefly US, have shown a gradual increase in adolescent and adult pertussis cases over the past decade. This has been attributed to more awareness, better diagnosis and a real increase in pertussis cases due to loss of vaccine induced/natural immunity



further reduced by lack of natural boosting. Adolescent/ adult pertussis is responsible for considerable morbidity/ loss of working days and is a reservoir for disease transmission to unvaccinated/ incompletely vaccinated neonates and young infants. Henceforth, several developed countries have instituted routine booster immunization of adolescents and adults with standard quantity tetanus toxoid and reduced quantity diphtheria and acellular pertussis vaccine (Tdap) instead of Td. The standard strength DTwP and DTaP vaccines cannot be used for vaccination of children 7 years and above due to increased reactogenicity.

Around 22,616 cases of pertussis were reported in India in 2006. This probably reflects a fraction of actual disease incidence as DTwP3 coverage in India is only 55% and coverage with the 1st and 2nd booster even lower with wide interstate variations. There is no data on the incidence of adolescent and adult pertussis in India but is perceived to be significant, especially in those states where childhood immunization coverage is good and reduced natural circulation of pertussis leads to infrequent adolescent boosting.

Vaccine

In India, currently two brands of Tdap are licensed. It contains tetanus toxoid 5 Lf, diphtheria toxoid 2 Lf and the three acellular pertussis components namely, pertussis toxin 8 µg, filamentous hemagglutinin 8 µg and pertactin 2.5 µg. It contains aluminium hydroxide as adjuvant and no preservative. The vaccine should be stored between 2 to 8°C, must not be frozen. The dose is 0.5 ml IM intramuscularly. Immunogenicity studies have shown that antibody response to a single dose of Tdap booster in previously vaccinated children/adolescents is similar to that following 3 doses of full-strength DTwP or DTaP vaccines. Vaccine efficacy against clinical disease exceeds 90%. Commonest side effect with Tdap is pain at the local injection site in about 70% of vaccinees, followed by redness and swelling. Systemic side effects like fever, headache and fatigue are rarely seen. Serious adverse events have not been reported. The contraindications are serious allergic reaction to any component of the vaccine or history of encephalopathy not attributable to an underlying cause within 7 days of administration of a vaccine with pertussis component.

Recommendations for use

There is no reason to believe that the disease burden of pertussis is low in adolescents in India. A safe and efficacious vaccine is available. The IAPCOI therefore recommends offering Tdap vaccine instead of Td/TT vaccine in all children/adolescents who can afford to use the vaccine in the schedule discussed below. It also recommends that studies aiming to determine the serosusceptibility to pertussis



and prevalence of pertussis in children/ adolescents/ adults presenting with prolonged cough be conducted.

- In those children who have received all three primary and the two booster doses of DTwP/DTaP, Tdap should be administered as a single dose at the age of 10-12 years. Catch up vaccination is recommended till the age of 18 years. A single dose of Tdap may also be used as replacement for Td/TT booster in adults of any age if they have not received Tdap in the past. Earlier it was recommended to observe a gap of 2-5 years between Tdap and previous TT/Td vaccines to decrease local adverse reactions. While longer intervals between Tdap and TT/Td would decrease local reactions, the benefit of protection against pertussis outweighs the potential risk of adverse events. Hence it is now recommended that Tdap can be given regardless of time elapsed since the last vaccine containing tetanus toxoid or diphtheria toxoid.
- It is also acceptable to use Tdap as a replacement for TT/Td in wound management of children aged 10 and above if they have not received Tdap in the past, and at least 5 years have elapsed since receipt of Td/ TT vaccine.
- In children who have missed the 2nd booster of DTwP/DTaP and who are 7 years of age or more, Tdap single dose is recommended at the time of presentation.
- In children who have not completed primary immunization with DTwP/DTaP and are more than 7 years of age, 1 dose of Tdap and 2 doses of Td at 0, 1 and 6 months respectively are recommended.
- The single booster dose of Tdap may be followed by Td boosters every 10 years. There is no data at present to support repeat doses of Tdap (Austria is an exception where Tdap is recommended every 10 years). No tetanus prophylaxis is required for minor wounds if less than 10 years have elapsed since receipt of Tdap. No tetanus prophylaxis is required for major wounds if less than 5 years have elapsed since receipt of Tdap; if more than 5 years (but less than 10 years) have elapsed a single dose of TT may be given.
- In the absence of sufficient data on the efficacy, immunogenicity and duration of protection against pertussis with Tdap used as 2nd childhood booster, the IAPCOI does not recommend the use of Tdap vaccine as an alternative to DTaP/DTwP for the 2nd childhood booster in children below the age of 7 years at present.

MEASLES, MUMPS & RUBELLA VACCINES

Several combinations for protection against Measles, Mumps and Rubella are available. These include monovalent Measles, Mumps and Rubella vaccines, MR



vaccine and MMR vaccine. Monovalent Mumps vaccine is not available in India.

MEASLES VACCINE

Background

Measles, a potentially eradicable disease, is no longer endemic in western countries and the 2005 goal set by the World Health Assembly (WHA) to halve measles deaths worldwide, compared to 1999 levels, has been achieved. This has been made possible by a multi pronged strategy including improved routine coverage, provision of a second dose through routine immunization or periodic supplementary immunization activities, careful surveillance and appropriate case management.

WHA has now endorsed the global goal of reducing the measles death by 90% by 2010 compared to 2000 levels. However, measles continues to be an important cause of childhood morbidity and mortality in India. At a workshop convened jointly by Government of India, WHO, and UNICEF on Measles, in May 2007, it was estimated that between 100,000 and 160,000 children die from Measles in India each year and that over 90% of deaths occur in 10 states – Uttar Pradesh (UP), Bihar, Rajasthan, Madhya Pradesh, Jharkhand, Assam, West Bengal, Andhra Pradesh (AP), Orissa and Gujarat. Unfortunately, Measles vaccination coverage continues to be poor since its introduction in EPI in 1985.

A recent vaccination coverage survey in India showed overall 71% coverage for Measles vaccine (given during 9 to 12 months of age). Accepting 85% vaccine effectiveness for vaccination at 9 months, actual protection was offered to only 60% of annual birth cohorts ($71\% \times 85\% = 60\%$). In other words, 40% remained susceptible to Measles. As per District Level Health Survey (2007-08), state like Uttar Pradesh has just 47% coverage for Measles vaccine.

Vaccine

A safe, effective and reasonably inexpensive vaccine is available against Measles for the past 5 decades. All currently used vaccines are live attenuated vaccines. Most of the currently used live attenuated Measles vaccine strains originate from the original Edmonston strain and include Schwarz, Edmonston Zagreb, Moraten and Edmonston-B strains. Indian vaccines are usually formulated from the Edmonston Zagreb strain grown on human diploid cells or purified chick embryo cells. Each dose contains at least 1000 infective units and has no preservative. It is supplied freeze-dried in single dose or multidose vials with distilled water as a diluent. The vaccine may be stored frozen or at 2-8°C (shelf life 2 years). Reconstituted vaccine



is destroyed by light and is very heat labile (loses 50% potency at 20°C and 100% at 37°C after 1 hour) and is susceptible to contamination as it does not have any preservative. For these reasons, reconstituted vaccine should be protected from light, kept at 2-8°C and used within 4-6 hours of reconstitution. This is particularly applicable to multidose vials. The dose is 0.5 ml subcutaneously or intramuscularly, preferably over the upper arm / anterolateral thigh. Immunogenicity depends on the age of administration, due to interference by preexisting maternal antibodies. Seroconversion rates are around 60% at the age of 6 months, 80-85% at the age of 9 months and beyond 95% at the age of 12-15 months. While antibody titers wane over the years, Measles specific cellular immunity persists and provides lifelong protection. Secondary vaccine failures rarely occur. Immunogenicity is lower in the immunocompromised including HIV. In HIV infected infants, superior seroconversion rates are seen at 6 months as compared to 9 months due to progressive immunodeficiency with age. Vaccine efficacy studies from India have reported varying efficacies ranging from 60-80% when given at the age of 9 months. Adverse reactions, apart from local pain and tenderness, include a mild Measles like illness 7-12 days after vaccination in 2-5% of the vaccinees. Thrombocytopenic purpura may occur at a frequency of 1/30,000 vaccinees. Though depression of cell mediated immunity may occur, it recovers within 4 weeks and is considered harmless even for those with early HIV or latent/ unrecognized tuberculosis. There is no data to support causal relationship between Measles vaccine and encephalitis, GBS, subacute sclerosing encephalitis and autism. There is no transmission of the vaccine virus from the vaccinees to the contacts. Measles vaccine has been the cause of several infant deaths in several states of India due to toxic shock syndrome(TSS) and use of succinylcholine instead of distilled water as the diluents. Measles vaccine vial can get contaminated when the cap is punctured, leading to bacterial growth in the vial as it does not contain preservative. Bacteria like staphylococci excrete several exotoxin and can cause severe shock in recipients. TSS can be prevented by adhering to injection safety and if reconstituted multidose Measles vaccine is used within 4-6 hours. Left over doses after this period must be discarded. The vaccine is contraindicated in the severely immunocompromised, in those with history of severe allergic reactions to the constituents and in pregnancy. The vaccine should be administered to those with HIV infection unless severely immunocompromised as here the benefits outweigh the risks. The vaccine may be given to those with history of egg allergy. The vaccine may be given along with all childhood vaccines with the exception of BCG vaccine.



Recommendations for use

Vaccine immunogenicity and efficacy are best when the vaccine is administered beyond the age of 12 months. However in India a significant proportion of Measles cases occur below the age of 12 months. Hence in order to achieve the best balance between these competing demands of early protection and high seroconversion, completed 9 months of age has been recommended as the appropriate age for Measles vaccination in India. In case of an outbreak, however, the vaccine can be given to infants as young as completed 6 months. Administration of the vaccine within 2 days of exposure protects and/or modifies the severity of clinical disease. The vaccine should be given irrespective of prior history of Measles as any exanthematous illness is often confused as Measles. In view of about 15% cases of primary vaccine failures with the first dose of the vaccine, an additional dose of Measles vaccine preferably as MMR vaccine at the age of 15 months is required for durable and possibly lifelong protection against Measles.

For reducing Measles mortality in the country, National Technical Advisory Group on Immunization (NTAGI), reviewed data on Measles epidemiology and case fatality rate, and has recommended the following:

- A second dose of Measles vaccine should be introduced in the Universal Immunization Program (UIP) at the time of DPT booster dose (at 18 months of age) in states with >80% evaluated coverage with the first dose of Measles vaccine
- Catch-up Measles vaccination campaigns should be implemented for children up to age 10 years in states with <80% evaluated coverage with the first dose of Measles vaccine and that detailed action plans for these SIAs should be finalized immediately in states with low coverage and high Measles mortality burden. IAPCOI endorses NTAGI recommendations.

RUBELLA VACCINE

Background

Rubella *per se* is a mild exanthematous illness but if acquired in the first trimester of pregnancy can lead to disastrous consequences in the fetus/ new born such as abortion, stillbirth, mental retardation, congenital heart disease, blindness and cataract. Hence the objective of vaccination against rubella is protection against congenital rubella syndrome (CRS). Developed countries have remarkably reduced the burden of CRS by universal immunization against rubella. It is essential that when immunization against rubella is instituted, more than 80% coverage is achieved.



Indiscriminate use of Rubella vaccine (monovalent or as a constituent of MMR) in young children, through public health measures with sub-optimal coverage of the target population, may be counter-productive as it may shift the epidemiology of Rubella to the right with more clinical cases occurring in young adults leading to paradoxical increase in cases of CRS. This has been shown to occur using mathematical models. Direct evidence from some Latin American countries and Greece also corroborates these concerns. There is paucity of reliable data on occurrence of CRS in India. Other developing countries have incidence rates of 0.6-4.1 per 1000 live births. WHO estimates that 100,000 cases of CRS occur in developing countries alone. Cost benefit studies in countries with routine immunization coverage $\geq 80\%$ show that benefits of Rubella vaccine outweigh the costs particularly when combined with Measles vaccination.

Vaccine

Rubella vaccine is currently derived from RA 27/3 vaccine strain grown in human diploid/chick embryo cell cultures. The vaccine is available in freeze dried form that should be stored frozen or at 2-8°C and needs to be reconstituted with sterile diluent prior to use. The reconstituted vaccine must be protected from light, stored at 2-8°C and used within 6 hrs of reconstitution. The dose is 0.5 ml subcutaneously. A single dose of vaccine provides lifelong protection in 95% of the vaccinees. Apart from local side effects, a mild rash may develop in 5% of the vaccinees. Joint symptoms such as arthralgia and arthritis may occur 1-3 weeks following vaccination, especially in susceptible post pubertal females, but is usually mild. Immune thrombocytopenic purpura may occur in a frequency of 1 per 30,000 vaccinated children. The vaccine is contraindicated in the severely immunocompromised and in pregnancy. Pregnancy should be avoided for 3 months after vaccination but babies born to women inadvertently vaccinated in pregnancy do not exhibit an increased risk of congenital malformations. Hence, accidental vaccination in pregnancy is not an indication for medical termination of pregnancy.

Recommendations for use

IAPCOI recommends the use of MMR vaccine instead of monovalent rubella vaccine so as to provide additional protection against Mumps and Measles. Recommendations for use of MMR are discussed later.



MMR VACCINE

Background

Globally, most countries use MMR vaccine instead of monovalent vaccines. The epidemiology of Measles and Rubella has been discussed earlier. Mumps is a mild disease in childhood but can occasionally result in complications such as deafness, meningoencephalitis and orchitis. The burden of Mumps has been reduced in developed countries following use of MMR vaccines. Like Rubella, indiscriminate use of Mumps vaccine can result in shift of epidemiology to the right and an increase in infection rates in adolescents and adults with greater complications.

Vaccine

Formulations from different manufacturers have different strains of the vaccine virus. Mumps vaccine virus strains include Leningrad-Zagreb, Leningrad-3, Jeryl Lynn, RIT 4385 or Urabe AM9 strains and are grown in chick embryo/human diploid cell cultures. MMR vaccines are supplied in lyophilized form and should be frozen for long-term storage. In the clinic, these vaccines can be stored at 2 to 8°C. The vaccines should be protected from light. Reconstituted vaccine should be stored at 2-8°C, protected from light and used within 4-6 hours. The dose is 0.5ml given subcutaneously. The vaccine can be given along with all other childhood vaccines except BCG vaccine. The immunogenicity and efficacy against Measles and Rubella has been discussed earlier. Seroconversion rates against Mumps are more than 90% but clinical efficacy and long term protection with single dose is 60-90%; outbreaks have been noted in previously vaccinated populations. Hence two doses are needed for durable protection. Adverse effects due to Measles and Rubella components have been discussed earlier. Five percent of children can get fever more than 39°C 7-12 days following vaccination and febrile seizures may occur. Aseptic meningitis can rarely occur 2-3 weeks following vaccination but is usually mild. Transient parotitis may occur. The virus does not spread from vaccinee to contacts. There is now incontrovertible evidence that there is no causal relationship between MMR vaccine and autism, inflammatory bowel disease, GBS and many other neurological complications. MMR is contraindicated in patients with severe immunodeficiency, pregnancy and those with history of serious allergy to vaccine or its components. The vaccine should be given with caution after weighing risks versus benefits in patients with history of thrombocytopenic purpura and should be preferably avoided in those where thrombocytopenia followed previous vaccination with Measles/MMR. The vaccine may be safely given in those with history of egg allergy.



Recommendations for use

For the purposes of universal immunization, the vaccine should be introduced in those areas where immunization coverage is at least 80% and can be sustained on a long term basis, failing which an epidemiologic shift and increase in CRS may occur. For this reason MMR vaccine has been introduced in those Indian states where Measles coverage is at least 70%. Simultaneously, a system for surveillance for CRS and catch up immunization for all adolescent girls should also be instituted. The MMR vaccine in EPI improves protection against Measles by immunizing those who have missed Measles vaccine or failed to seroconvert to the first dose of vaccine, should reduce burden of CRS and provides added protection against mumps.

For office practice the IAPCOI recommends offering MMR vaccine to all children. This use of MMR in the private sector is unlikely to impact the epidemiology of Rubella at present but must be carefully monitored. Two doses are recommended one at the age of 12-15 months and second at school entry (4-6 years) or at any time 8 weeks after the first dose. The second dose of MMR vaccine is to protect children failing to seroconvert against primarily Mumps and less commonly against Rubella (primary vaccine failures). In a child aged 12 months or older, who has not received Measles vaccine, 2 doses of MMR at 8 weeks interval suffices; monovalent Measles vaccine is not required. Catch up vaccination with two doses of the vaccine should be given to all those not previously immunized (with no upward age limit) and especially to health care workers, adolescent girls and students travelling for studies overseas. All the currently licensed preparations of MMR vaccine are safe and effective and any one may be used.

HEMOPHILUS INFLUENZAE TYPE B (Hib) CONJUGATE VACCINES

Background

Capsulated *H. influenzae* has six serotypes of which type b is most important. *Haemophilus influenzae type b* (Hib) is an important invasive pathogen causing diseases such as meningitis, bacteremia, pneumonia, cellulitis, osteomyelitis, septic arthritis and epiglottitis. Most of invasive Hib disease occurs in children in the first two years of life and natural protective immunity is acquired by the age of 3-4 years. Non capsulated Hib disease including bronchitis, otitis media, sinusitis and some pneumonia is not amenable to prevention at present and can occur at all ages. The burden of Hib disease is underestimated in India as cultures are often not sent, the organism is difficult to culture especially when antibiotics have been administered and as a large proportion of pneumonia may be non bacteremic. Data from the



Invasive Bacterial Infections Surveillance (IBIS) group from six referral hospitals in India show that Hib is a common cause of meningitis in India.

Global burden of Hib disease

In spite of the availability of an effective vaccine against Hib since more than a decade, Hib continues to be a leading cause of mortality and morbidity worldwide, especially in developing countries.

As per the WHO estimates, 1.575 million under five children died of pneumonia in 2008. Child Health Epidemiology Reference Group (CHERG) publication in 2008 estimated that as of 2000, 155.84 million episodes of “clinical” pneumonia occur annually world over of which 151.76 million episodes occur in developing countries. These large figures are for “clinical” pneumonia which is based on WHO definitions of clinical pneumonia and not severe pneumonia. Nevertheless, 24-36% of these clinical pneumonia episodes are radiologically proven (using WHO definition) *i.e.* 38-50 million episodes; and 6-12% of total clinical pneumonia episodes are severe pneumonia (needing hospitalization) *i.e.* 11-20 million episodes annually. Based on various methods of cultures, 10-30% of hospitalised pneumonia occur due to *H influenzae B*.

A recently published data reported that Hib caused about 8.13 million serious illnesses worldwide in 2000 (uncertainty range 7.33-13.2 million) and estimated that Hib caused 371000 deaths (2,47,000-5,27,000) in children aged 1-59 months, of which 8100 (5,600-10,000) were in HIV-positive and 3,63,000 (2,42,000-5,17,000) in HIV-negative children. Hospital-based studies show that Hib is a major cause of bacterial meningitis and/or pneumonia in the Philippines, India, Thailand, Malaysia, Indonesia and Vietnam.

Indian burden

There was paucity of data regarding the Hib burden in the 1980s. Various studies conducted since then reveal the substantial Hib burden in India.

During 1993-1997, a prospective surveillance of acute infections caused by *H. influenzae* was carried out in 6 academic referral Indian hospitals. The study included 5798 patients aged 1 month to 50 years who had diseases likely to be caused by *H. influenzae*; 75% of the patients were aged <5 years. A total of 125 *H. influenzae* infections were detected, 97% of which were caused by Hib. Of 125 isolates, 108 (86%) were from children aged <5 years, and 11 (9%) were from adults aged >18 years. Sixty-two percent of the patients had meningitis. The case-fatality rate was 11% overall and 20% in infants with Hib meningitis.



In 1995, Bahl et al conducted a hospital based study on 110 children < 5 years on severe and very severe pneumonia, and it was found that 19% cases were due to Hib.

In a hospital based study conducted in Delhi by Patwari et al, in 1996, found 15% of 132 children < 12 years suffered from pneumonia due to Hib.

A prospective surveillance study was carried out during 1997 and 1999 in hospitals for cases of Hib meningitis from 5 administrative areas of an Indian district (Vellore, Tamil Nadu) with 56,153 children under 5 yr of age, over a 24 month period. In infants 0-11 months of age, the incidence of Hib meningitis was 32 per 100,000 (95%CI 16 to 67) and in the 0-23 month group, it was 19 (95%CI 8 to 37).

A preparatory surveillance for pneumonia and meningitis among children less than 2 years done for a vaccine probe study was conducted at Chandigarh, Vellore and Kolkatta from July 2005 to December 2006. Out of 17951 children it was found that severe clinical pneumonia ranged from 2717 to 7890 per 100,000 child-years, while suspected meningitis ranged from 1971 to 2433 per 100,000 child-years.

The WHO estimates for the year 2008 show that 1.828 million children under 5 years die annually in India alone of which 20.3% mortality death is due to pneumonia. These statistics coupled with the evidence of large number of Hib pneumonia brought out in the above studies highlights the urgency to take effective measures against Hib disease in India.

In April 2008, the Hib and Pneumococcal subcommittee of National Technical Advisory Group on Immunization (NTAGI) in India reviewed the existing Indian, regional and global data on Hib disease epidemiology, vaccine safety and efficacy and cost-effectivity. It concluded that the disease burden of Hib is sufficiently high in India to warrant prevention by vaccination, the vaccine is safe and efficacious. It strongly recommended its immediate introduction in India's UIP.

Vaccine

All Hib vaccines are conjugated vaccines where the Hib capsular polysaccharide (polyribosyl ribitol phosphate or PRP) is conjugated with a protein carrier so as to provide protection in the early years of life when it is most needed. Currently available vaccines include HbOC (carrier CRM197 mutant *C. diphtheria* toxin protein), PRP – OMP (carrier *N meningitidis* protein outer membrane complex) and PRP- T (carrier tetanus toxoid). PRP- D has been withdrawn due to relatively poor efficacy. HbOC and PRP-T vaccines show only a marginal increase in antibody levels after the first dose with a marked increase after the second and even better response



after the third dose. On the other hand, PRP-OMP shows an increase in antibody level after the first dose itself with only marginal increases after the second and third doses. The onset of protection with PRP-OMP is thus faster. Additionally, while 3 doses of HbOC and PRP-T are recommended for primary vaccination, only 2 doses of PRP-OMP are recommended for this purpose. Only HbOC and PRP-T are currently available in India. The vaccines should be stored at 2 to 8°C and the recommended dose is 0.5 ml intramuscularly. Efficacy trials have demonstrated 90-100% efficacy against culture proven invasive Hib disease for 1 year after vaccination. A trial in Gambian infants has shown 21% protection against episodes of severe pneumonia. The serologic correlate of protection at the time of exposure has been fixed at 0.15 µg/ml and that for long term protection as 1µg/ml. Side effects are mild and usually local. Developed countries where the vaccine was introduced for universal immunization have witnessed virtual elimination in Hib disease with no serotype replacement. The vaccine has also been shown to impart herd protection by reducing nasopharyngeal carriage. A notable exception in the Hib success story was an increased incidence of Hib disease in vaccinated children between the years 1999-2003 in the UK occurring after a remarkable initial decline in Hib disease in the early 1990's. Most of the cases of invasive Hib disease occurred in the late 2nd year of life. The major factor responsible for this phenomenon was omission of the 2nd year booster. Vaccine induced immunity wanes over time and reduced carriage of the organism in the environment compounds the problem by lack of natural boosting. It is also now recognized that immunological memory is insufficient for protection against Hib disease. Hence a booster dose is mandatory for sustained protection.

Recommendations for use

The IAPCOI recommends offering the Hib vaccine to all children. The Government of India's (Gol) decision to introduce Hib vaccine in EPI in a phased manner was challenged in the court of laws in a PIL (public interest litigation) on the grounds that India does not have significant Hib disease burden to warrant use of Hib vaccine in the EPI. However, after hearing the NTAGI's stand on the issue, the Gol has decided to introduce the vaccine in 2 states to begin with and gradually use it in the remaining states.

Schedule and doses

The vaccination schedule for Hib consists of three doses when initiated below 6 months, 2 doses between 6-12 months and 1 dose between 12-15 months, with a booster at 18 months. For children aged more than 15 months a single dose may



suffice. The interval between two doses should be at least 4 weeks. As Hib disease is essentially confined to infants and young children, catch up vaccination is not recommended for healthy children above 5 years. However, the vaccine should be administered to all individuals with functional/ anatomic hyposplenism irrespective of age. Hib vaccines are now used mostly as combination vaccines with DTwP/ DTaP/ Hep B/ IPV, details of which will be discussed separately.

HEPATITIS B (Hep B) VACCINE

Background

In India, 1-4% of individuals are chronic carriers of Hepatitis B Virus (HBV). Infection with HBV may occur perinatally (vertical transmission), during early childhood (the so-called horizontal spread), through sexual contact or nosocomially. It should be noted that, in our country, horizontal route (*e.g.* child to child) and the vertical route (*i.e.* mother to child) are the major routes of transmission of hepatitis B. The risk of infection in a child born to a Hepatitis B positive mother ranges from 10-85% depending on the mother's HBeAg status.

Younger the age of acquisition of HBV infection, higher the chances of becoming a chronic carrier. It is believed that as many as 90% of those who are infected at birth go on to become chronic carriers and upto 25% of chronic carriers will die of chronic liver disease as adults. Infection with HBV is one of the most important causes of chronic hepatitis, cirrhosis of liver and hepatocellular carcinoma. These outcomes are all preventable by early childhood immunization. It is for this reason that the World Health Organization has recommended universal Hepatitis B vaccination.

Vaccine

The plasma derived Hep B vaccine is no longer available. The currently available vaccine containing the surface antigen of Hepatitis B is produced by recombinant technology in yeast and adjuvanted with aluminium salts and preserved with thiomersol (thiomersol free vaccines is also available). Hep B vaccine is available as single and multidose vials and should be stored at 2 to 8°C. The vaccine should not be frozen; frozen vaccine should be discarded. The dose in children and adolescents (aged less than 18 years) is 0.5 ml/ 10 µg and in those 18 yrs and older is 1 ml/ 20 µg. It should be injected intramuscularly in the deltoid/ anterolateral thigh. Gluteal injections should be avoided due to low immunogenicity. The vaccine is extremely safe and well tolerated. The classical schedule is 0, 1 and 6 months. The vaccine is highly immunogenic and seroconversion rates are greater than 90% after a three dose schedule. Seroconversion rates are lower in the elderly, the



immunocompromised and those with chronic renal failure. Four doses at 0, 1, 2 and 12 months of double dose may be given in these patients. Routine testing for anti HBsAg levels 1 month after completion of the immunization schedule is recommended in children born to HBsAg positive mothers, health care workers and those with co morbidities. Antibody titers greater than 10 mIU/ml signify a response and are considered protective. Non responders should be tested for Hepatitis B carrier status. If found to be negative, the same three dose schedule should be repeated. 50% of non responders may respond to the second series; the rest are permanently susceptible. Routine boosters are not needed in healthy children and adults. Studies have shown that individuals who had responded to the vaccination series and had levels of 10 mIU/ml after vaccination are protected against hepatitis B disease for life even if the levels drop to below protective levels or are undetectable later. This is due to immune memory. In the immunocompromised and those with co morbidities such as chronic renal disease, levels should be checked periodically and booster vaccination given whenever levels drop to below protective levels.

Hepatitis B Immunoglobulin (HBIG)

HBIG provides passive immunity and is indicated along with Hep B vaccine in management of perinatal/ occupational/ sexual exposures to Hepatitis B in susceptible individuals. The dose of HBIG in adults is 0.06 ml/kg and in neonates/ infants 0.5 ml. HBIG should be stored at 2 to 8°C and should not be frozen. HBIG provides temporary protection lasting 3-6 months. HBIG should never be given intravenously. HBIG is also used alone following exposure to Hepatitis B in patients who are non responders to Hepatitis B vaccination (genetic reasons/ immunocompromised status). In this situation two doses of HBIG 1 month apart are indicated.

Recommendations for use

The hepatitis B vaccines are of public health importance. The government of India has initiated hepatitis B vaccination since June 2002 with expansion in a phased manner.

For office practice, the IAPCOI recommends offering hepatitis B vaccine to all children.

Hep B vaccine may be given in any of the following schedules:

- (i) Birth, 1 and 6 months
- (ii) Birth, 6 and 14 weeks
- (iii) 6, 10 and 14 weeks
- (iv) Birth, 6 weeks, 6 months
- (v) Birth, 6 weeks, 10 weeks, 14 weeks



Immunologically 0 – 1 – 6 months schedule of hepatitis B immunization has been most widely used and proven to be ideal with high antibody titers at the end of the vaccination. However Hep B vaccine is a T-cell dependent vaccine and the titers at the end of immunization schedule may not be important so far as it is well above the protective level. There would occur anamnestic response with the titers going up, should there occur contact with the virus again in future. Also now that Hep B vaccination is integrated into the existing immunization program (EPI) in India, due to operational issues at a national level one has to piggy back on the available contacts for routine immunization *i.e.* DTP which is given at 6, 10 and 14 weeks of age. At the same time, birth dose has to be given to cover for the vertical route. Hence IAPCOI recommends 0 – 6 – 14 wks schedule for public health. In case birth dose has been missed, 6 – 10 – 14 wks schedule can be followed. In office practice, one can still use 0 – 4/6wks – 6 months schedule. As of now, from the data available, none of the above schedules needs a booster.

Catch up vaccination with Hep B vaccine as a 0, 1, 6 schedule should be offered to all children/ adolescents who have not been previously vaccinated with Hep B vaccine. This is to address problems related to horizontal mode of transmission of the virus. Prevacination screening with anti HBsAg antibody is not cost effective and is not recommended. Catch up vaccination is particularly important for contacts of HBsAg positive patient. Prevacination screening for HBsAg should be done in these contacts.

All available brands of Hepatitis B vaccine are equally safe and effective and any may be used. Interchange of brands is permitted but not routinely recommended. Combination vaccines containing Hep B are discussed separately.

Management of an infant born to Hepatitis B positive mother

Pregnant women should be counseled and encouraged to opt for HBsAg screening. If the mother is known to be HBsAg negative, Hep B vaccine can be given along with DTP at 6, 10 and 14 weeks/6 months as there is no special requirement to start vaccination at birth itself. The 6-10-14 wks schedule may be easier to implement in the context of the national immunization program as higher vaccination coverage may be achieved with earlier administration of vaccines.

If the mother's HBsAg status is not known, it is important that Hep B vaccination should begin within a few hours of birth so that perinatal transmission can be prevented. Any one of the following schedules may be used for this purpose; birth, 6 and 14 weeks or birth, 6 wks and 6 months.



If the mother is HBsAg positive (and especially HBeAg positive), the baby should be given Hepatitis B Immune Globulin (HBIG) along with Hep B vaccine within 12 hours of birth, using two separate syringes and separate sites for injection. The dose of HBIG is 0.5 ml IM. HBIG may be given upto 7 days of birth but the efficacy of HBIG after 48 hours is not known. Two more doses of Hep B vaccine at 1 month and 6 months are needed. The closely spaced schedule should not be used. If HBIG is not available (or is unaffordable), Hep B vaccine may be given at 0, 1 and 2 months with an additional dose between 9-12 months. The efficacy of prophylaxis with both HBIG and Hep B vaccine is 85-95% and that with Hep B vaccine alone (1st dose at birth) is 70-75%. All infants born to HBsAg positive mothers should be tested for HBsAg and anti HBsAg antibodies at the age of 9-15 months to identify carriers/ non responders.

Hepatitis B vaccination should be routinely offered to persons in high-risk settings that includes health care workers; public safety workers; trainees in blood or blood-contaminated body fluid health care fields in schools of medicine, dentistry, nursing, laboratory technology, and other allied health professions.

Adults with risk factors for HBV infection can begin and should be administered on a 0-, 1-, and 6-month schedule.

An accelerated schedule may be required as

Dose 1 of the series at any visit

Dose 2 At least 4 wk after dose 1

Dose 3 At least 8 wk after dose 2 and at least 16 wk after dose 1

Post Exposure Prophylaxis to Prevent Hepatitis B Virus Infection

Most health care workers (HCW) working around patients or biological samples stand the risk of accidental exposure to blood and blood-borne pathogens. An exposure to infected blood, tissue or other potentially infectious body fluids can occur by either cut/ needle-stick injury or contact with mucous membrane or damaged skin. In case of exposure of the health worker one has to assess whether the health worker has been immunized earlier or not and one has to find the HBsAg status of the source. Depending on that the protocol is as follows:

HBsAg-Positive Exposure Source

- Persons who have written documentation of a complete hepatitis B vaccine series and who did not receive postvaccination testing should receive a single vaccine booster dose.



- Persons who are in the process of being vaccinated but who have not completed the vaccine series should receive the appropriate dose of Hepatitis B immune globulin (HBIG) and should complete the vaccine series.
- Unvaccinated persons should receive both HBIG and Hepatitis B vaccine as soon as possible after exposure (preferably within 24 hours). Hepatitis B vaccine may be administered simultaneously with HBIG in a separate injection site. The Hepatitis B vaccine series should be completed in accordance with the age-appropriate vaccine dose and schedule.

Exposure Source with Unknown HBsAg Status

- Persons with written documentation of a complete Hepatitis B vaccine series require no further treatment.
- Persons who are not fully vaccinated should complete the vaccine series.
- Unvaccinated persons should receive the Hepatitis B vaccine series with the first dose administered as soon as possible after exposure, preferably within 24 hours. The vaccine series should be completed in accordance with the age-appropriate dose and schedule.

COMBINATION VACCINES

Background

A combination vaccine consists of two or more separate immunogens that have been physically combined in a single preparation. These immunogens may pertain to the many antigens/ serotypes of the given pathogen (e.g. poliovirus vaccines) or of multiple pathogens (e.g. DTP vaccine). This concept differs from that of simultaneous vaccines, which, although administered concurrently, are physically separate. The combining of multiple related or unrelated antigens into a single vaccine is not a new concept. Several combination vaccines have been in use including the trivalent Influenza vaccines, Diphtheria, Pertussis and Tetanus toxoids (DTwP, DTaP, DT, Td, Tdap), the Polio vaccines, MMR and Meningococcal vaccines. Additionally several other multivalent vaccines have been recently introduced including the Pneumococcal, Rotavirus and HPV vaccines. Further discussion on combination vaccines here refers to vaccines against multiple pathogens combined in a single injection. The advantages of combination vaccines are multiple and include fewer injections, reduced burden on the cold chain, reduced requirement of syringes & needles and easier record keeping. The concern is stability of the product and immune interference between the various antigens leading to suboptimal immunogenicity.



Combination vaccines currently licensed in India

DTwP+ Hib, DTwP+ Hep B, DTwP+Hib+ HepB

These are available in two forms. 1) As ready to use liquid preparations: DTwP+ Hep B, DTwP+Hib, DTwP+Hep B+ Hib and 2) When lyophilized Hib needs to be reconstituted with DTwP/ DTwP + Hep B from the same manufacturer: DTwP + Hib, DTwP+ Hib + Hep B. Though the antibody response to Hib is reduced in these combination vaccines as compared to separate administration, most subjects attain the seroprotective level of 1 µg/ml and there is no reduced efficacy against Hib disease. The antibody responses to Diphtheria, Pertussis, Tetanus and Hep B are unchanged. The liquid and the lyophilized formulations have similar immunogenicity and safety for both primary and booster immunization.

DTaP+Hib, DTaP+Hib+IPV

Currently the DTaP/Hib is available as lyophilized Hib which needs to be reconstituted with liquid DTaP just prior to administration. DTaP (2 component)+Hib+IPV is available as a ready to use formulation. Antibody responses to Diphtheria, Pertussis, Tetanus and (if applicable) Polio are satisfactory and comparable to those obtained after administration as separate doses. The primary concern and debate with these vaccines is Hib immunogenicity as studies showed a significant reduction in Hib titer/ percentage of children achieving the long term protective level of 1 µg/ml, when these combination vaccines are used as compared to separate administration of Hib vaccines in primary immunization. This reduction in Hib immunogenicity is not noted when these vaccines are used for booster vaccination even in subjects who had been administered combination vaccines for primary immunization. The reduction in Hib antibody titers was noted across all studies with different formulations of DTaP (exception Canadian five component DTaP vaccine) and different Hib conjugate vaccines and was more significant when vaccination was administered earlier in life and in premature babies. Studies with the five component Canadian vaccine combination vaccine with Hib did not show reduced Hib immunogenicity. Experts did not attach much significance to lower Hib immunogenicity of these combination vaccines as the serologic correlates of protection for Hib were derived from studies with the polysaccharide vaccines, which provided poor quality antibodies and no immunologic memory. Hence DTaP+ Hib combination vaccines were initially licensed in Europe for both primary and booster immunization but in the USA only for booster vaccination. An increased incidence of Hib disease was noted in the UK but not in other European countries following shift to DTaP+ Hib combination vaccines. This was initially attributed to the lower immunogenicity of the combination vaccine but later conclusively attributed to other factors mainly non administration of a booster



dose at 18 months. The US FDA and ACIP has approved DTaP (5 component) + IPV+ Hib combination vaccine for primary immunization (June 2008).

HepA+ HepB

Available in adult formulation and pediatric formulation. The recommended schedule is three doses at 0, 1 and 6 months. These combination vaccines show acceptable and comparable immune response against Hep A and Hep B as compared to separate administration. A rapid immunization schedule particularly suitable for travelers at 0, 7 and 21 days has acceptable short and long term efficacy. The adult formulation may also be used effectively in children aged 1-15 years as two doses at 0 and 6 months.

Internationally available combination vaccines

DTwP+IPV, DTwP+IPV+Hib

These vaccines are available internationally and show acceptable immunogenicity (against all components) and safety. These vaccines are potentially of immense importance in the Indian EPI to facilitate a shift from OPV to IPV as polio eradication nears.

DTaP+IPV, DTaP+HepB, DTaP+IPV+Hep B, DTaP+Hib+HepB, DTaP+IPV+HepB+Hib

These quadrivalent, pentavalent and hexavalent combination vaccines show acceptable and comparable immunogenicity against Diphtheria, Pertussis, Tetanus and Polio. The responses against Hib are lower as discussed earlier. The Hep B antibody titers following primary immunization are also lower than when HepB is administered separately which is believed to be due to close spacing of the doses at 1 mth interval rather than immune interference. The hexavalent vaccines are available internationally in two different formulations; one is lyophilized Hib which needs to be reconstituted with liquid DTaP+IPV+Hep B and the other as a ready to use liquid vaccine.

MMRV vaccine

A combination MMR and varicella vaccine was licensed in USA in 2005 for healthy children aged 12 months to 12 years. The antigen content of varicella is higher than single antigen varicella vaccine. The vaccine demonstrates comparable immunogenicity and efficacy against all components but greater side effects of fever and rash as compared to separate administration of the vaccines. Post marketing surveillance reports indicate an increased (double) risk of febrile seizures following



the receipt of this vaccine as compared to separate MMR and varicella vaccines. Another combination MMRV vaccine licensed in Europe is with comparable immunogenicity and efficacy but an increased risk of fever as compared to separate administration of vaccines.

HepA+ typhoid

These vaccines particularly for use in travelers to endemic countries show comparable immunogenicity and safety as compared to separate administration of vaccines.

HepB+Hib

These vaccines show acceptable immunogenicity against Hib and Hep B as compared to separate administration of vaccines

Recommendations for use

The IAPCOI concludes that all currently licensed combination vaccines in India have an immunogenicity, efficacy and safety profile comparable to separately administered vaccines as of currently available data. However the manufacturer's recommendation for mixing the vaccines in the same syringe should be strictly followed.

TYPHOID VACCINES

Background

Enteric fever (typhoid and paratyphoid) is a major public health problem in India and for which reliable epidemiologic data is available. Population based studies from urban slum population in India suggest that overall incidence of typhoid fever ranges from 266 to 980 per 100,000 person years. The incidence is highest in those aged below 15 years and is considerable even between the ages of 1-5 years. This data does not include the additional burden of paratyphoid fever. The risk of mortality may be under estimated in active surveillance studies. Increasing prevalence of antimicrobial resistance and need for hospitalization are other problems associated with enteric fever. All these factors have made vaccines against typhoid and paratyphoid fever of immense importance in our country.



Vaccine

Several vaccines have been available against typhoid/ paratyphoid fever:

Whole cell inactivated typhoid/ paratyphoid vaccines (TA/TAB)

These were the earliest vaccines available. These vaccines were best suited for developing countries as they were efficacious in children as young as 6 months, inexpensive, provided protection against both typhoid and paratyphoid and had efficacy at least as good as the currently available vaccines. However, increased reactogenicity led to discontinuation of use of these vaccines and they are no longer available. For further details please refer to earlier editions of the book.

Oral Live Attenuated Ty21a Vaccine

Salmonella typhi Ty21a is a live attenuated strain with a mutation in gal E gene and lacks the enzyme UDP-gal 4 epimerase. It is genetically stable and is not known to revert to virulence. It provides protection by inducing local gut immunity but there is no biological marker of this vaccine. The vaccine is supplied in an enteric coated formulation as the bacteria are acid labile as capsules or liquid formulation. Efficacy drops over time and the cumulative efficacy at three years of 3 doses of the capsule formulation against culture confirmed typhoid fever has been reported as 48% in a Cochrane metanalysis. The liquid formulation has superior efficacy but is not available commercially. The vaccine should be stored at 2-8°C. The commercially available capsular form can only be given to children five years of age and above as the capsules have to be swallowed intact. Three doses on alternate days on an empty stomach with a cool liquid are recommended. The vaccine should not be given during diarrhoea and antimicrobials active against typhoid bacillus should not be used 3 days before and 3 days after oral typhoid vaccine administration as these may interfere with the vaccine "take". The vaccine may be administered with all other childhood vaccines including live vaccines. Protection begins within a week after completion of the course. Revaccination is recommended every 3-7 years. No adverse effects were noted in clinical trials. The vaccine should be avoided during pregnancy and in the immunocompromised (may be given in HIV infected with CD4 count more than 200 cells/ μ l). This vaccine is currently not available in India.

Vi-capsular polysaccharide vaccine

The vaccine contains highly purified antigenic fraction of Vi-capsular polysaccharide antigen of *S typhi* which is a virulence factor of the bacteria. Each dose contains 25 μ g of purified polysaccharide in 0.5 ml of phenolic isotonic buffer for intramuscular or subcutaneous use. The vaccine should be stored at 2-8°C and should not be



frozen. The vaccine is stable for 6 months at 37°C and for 2 years at 22°C. Since it is a pure polysaccharide vaccine, it is not immunogenic in children below 2 years of age and has no immune memory. The biological marker is anti Vi antibodies and 1 µg/ml is proposed as the serologic correlate of protection. The vaccine does not interfere with the interpretation of the WIDAL test. Efficacy drops over time and the cumulative efficacy at 3 years against culture confirmed typhoid fever is reported as 55%. In a recently published cluster randomized effectiveness trial conducted in over 40,000 subjects in urban slums of Kolkata, the overall effectiveness of the vaccine at 2 years follow up was 61%, and in children below 5 years was 80%. Interestingly the herd protection of 44% was noted in unvaccinated children in the vaccinated cluster as compared to the control cluster. The Vi polysaccharide vaccine is recommended for use as a single dose in children aged 2 years and above and can safely be given with all other childhood vaccines. Revaccination is recommended every 3 years. The adverse effects are mild and include pain and swelling at injection site. The vaccine is contraindicated only in those with previous history of hypersensitivity to the vaccine and can be safely given in the immunocompromised including HIV infected.

Vi conjugate typhoid vaccines

The limitations of the currently available typhoid vaccines include non effectiveness below the age of 2 years, limited efficacy of around 60%, T cell independent response which lacks immune memory and is not boostable and finally no protection against paratyphoid fever. Conjugation of the Vi antigen with a protein carrier is hence desirable as it would induce a T cell dependent immune response. Conjugation of Vi antigen with non toxic recombinant *Pseudomonas aeruginosa* exotoxin A (rEPA) has been evaluated in safety, immunogenicity and efficacy trials in Vietnam. Two doses administered 6 weeks apart showed immunogenicity superior to Vi polysaccharide vaccine and a cumulative 3 year efficacy of 89% in 2-5 year old children. Another conjugate vaccine which has been recently licensed in India has Vi antigen conjugated with tetanus toxoid. In a couple of unpublished immunogenicity studies done in 150-200 subjects aged 12 weeks and more, a satisfactory immune response was seen (four fold rise in antibody titers or an ELISA level higher than the threshold 1 µg/ml) in all subjects following a single dose of the vaccine. The vaccine was well tolerated with no major local or systemic side effects. No data on duration of immunity and efficacy is available. The manufacturer recommends 2 doses of 0.5 ml intramuscularly at an interval of 4 - 8 weeks, followed by a booster every 10 years. In children aged less than 2 years an extra booster 2 - 2 1/2 years after the first dose is recommended additionally. Since the immunogenicity trial assessed response to only single dose, did not assess duration of immunity, the dosing schedule



seems extremely arbitrary. The extrapolation of efficacy of the vaccine from the Vietnamese trial is invalid due to fundamental differences between the two vaccines, age groups and dosing schedule. In view of these issues, the committee does not recommend the use of this conjugated vaccines at present.

New conjugate vaccines wherein Vi antigen has been conjugated to CRM 197 as well as bivalent conjugate vaccines with CRM 197 (*S. typhi* and *S. paratyphi A*) are under clinical development.

Recommendations for use

The public health burden of enteric fever in India is huge. Improvements in hygiene and sanitation are still a distant dream. The Vi polysaccharide vaccine has been demonstrated to have reasonable efficacy in the Indian setting and is available. The IAPCOI therefore recommends the immediate inclusion of the Vi polysaccharide vaccines in the national immunization schedule. Cost effectiveness studies demonstrate that administration of a single dose of the polysaccharide vaccine in the age group of 2-15 years will be highly cost effective (\$160 per DALY averted.)

For office practice, the IAPCOI recommends the administration of the currently available Vi polysaccharide vaccine 0.5 ml IM every three years beginning at the age of 2 years. A child with history of suspected/ confirmed enteric fever may be vaccinated 4 weeks after recovery if he/she has not received the vaccine in the past 3 years.

As mentioned earlier, the committee does not recommend the use of the currently available conjugated typhoid vaccine. It also stresses the need for development of new vaccines against typhoid and paratyphoid fever.

HUMAN PAPILLOMA VIRUS (HPV) VACCINES

Background

Prevalence of HPV infection in general population of India is about 7.9%. HPV infections are primarily transmitted by sexual contact, even with a single sexual act. HPVs are highly transmissible, and most sexually active men and women will acquire an HPV infection at some time in their lives. Whereas most HPV infections are transient and benign, persistent genital infection with certain viral genotypes can lead to the development of anogenital precancers and cancers. The lag period between infection with oncogenic HPV and invasive cervical cancer is 15-20 years. 100 serotypes of HPV have been discovered of which 15-20 are oncogenic. It is well recognized that HPV is a necessary cause of cervical cancer. Analysis of 932



specimens from women indicated that 99.7% of cervical cancers and over 90% of their precursor lesions (squamous intra-epithelial lesions) contain HPV DNA. In India, high-risk HPV types were found in 97% of cervical cancers.

Types 16 and 18 account for 70% of the cases of invasive cervical cancer globally. A meta-analysis of human papillomavirus type distribution from India showed that in invasive cervical carcinoma (ICC), HPV16 was the predominant type (64.8%), followed by HPV18, 45, 33, 35, 58, 59 and 31. The estimated HPV 16/18 positive fraction was 78.9% in women with Invasive Cervical Cancer (87.7% in North and 77.2% in South India), 61.5% with high squamous intra-epithelial lesion, 30.8% with low squamous intra-epithelial lesion and 3.9% in women with normal cytology/histology. There was no difference in overall HPV prevalence in cervical cancer between North and South India. However, HPV16 and 45 appeared to be more prevalent in North India, while HPV35 appeared to be more prevalent in South India. It is estimated that HPV16/18 vaccines will provide over 75% protection against ICC in South Asia. Oncogenic HPV serotypes have also been implicated in causation of anal, vulvar, vaginal, penile and oropharyngeal cancers. Additionally, non-oncogenic HPV serotypes 6 and 11 are responsible for more than 90% of anogenital warts and most recurrent respiratory papillomatosis.

Incidence of cervical cancer

Globally, cancer of the cervix uteri is the second most common cancer among women with an estimated 529,409 new cases and 274,883 deaths in 2008. About 86% of the cases occur in developing countries, representing 13% of female cancers.

Cancer incidence is generally expressed as Age Adjusted or Age Standardised Incidence Rates (AAR) per 100,000 persons according to world standard population. Globally the AAR is 15.3 per 100,000. The AAR for Indian women is 27 per 100,000. The cumulative lifetime risk for Indian woman of getting the disease is 2.8 as compared to the global figure of 1.6. India has a population of 366.58 million women aged 15 years and older who are at risk of developing cervical cancer. Current estimates indicate that every year 1,34,420 women are diagnosed with cervical cancer and 72,825 die from the disease. Based on the data of the Population Based Cancer Registries (PBCRs), the estimated number of new cancers during 2007 in India was 90,708. Cancer of the cervix accounted for 16 per cent of all cancers in women in the urban registries in 2005. All the urban Population Based Cancer Registries (PBCR) at Bangalore, Bhopal, Chennai, Delhi and Mumbai have shown a statistically significant decrease in the AARs of cervical cancer. However, since over 70 per cent of the Indian population resides in the rural areas, cancer cervix still constitutes the number one cancer.



As per the Hospital Based Cancer Registries (HBCR), cancer of cervix constitutes between 11.4 (Thiruvananthapuram) to 30.7 per cent (Chennai) of all cancers in women.

Mortality

The cumulative risk of death due to cervical cancer in Indian women is 1.7 as compared to 0.9 in the women world over. The crude mortality rate expressed as deaths per 100,000 women per year is 12.8. This is also higher as compared the world crude mortality of 8.2.

The relative five year survival reported some time earlier averaged 48.7 per cent. Additionally, cervical cancer may occur early and strike at the productive period of a woman's life.

There is no data on the burden of anogenital warts in the general community; warts have been reported in 2-25.2% of STI clinic attendees in India.

The comparative data on incidence, cumulative risk of disease and death is summarized in the table.

	World	India
Annual no of cases	529828	134420
Annual no of deaths	275128	72825
Incidence rate/ 100000 women	15.3	27
Incidence of death/ 100000w	7.8	15.2
Cumulative risk of disease	1.6	2.8
Cumulative risk of death	0.9	1.7

GLOBOCON Estimates of Cervical Cancer in Indian population

HPV Vaccines

HPV infections are restricted to the intraepithelial layer of the mucosa and do not induce a vigorous immune response. Approximately half of all women infected with HPV develop detectable serum antibodies, but these antibodies do not necessarily protect against subsequent infection by the same HPV type. The best characterized and most type specific HPV antibodies are those directed against the L1 protein of the virus.

Two vaccines have been licensed globally; a quadrivalent and a bivalent vaccine. Both are manufactured by recombinant DNA technology that produces non-infectious virus like particles (VLP) comprising of the HPV L1 protein, the major capsid protein of HPV. The mechanisms by which these vaccines induce protection have not been fully defined but seem to involve both cellular immunity and neutralizing immunoglobulin G antibodies. Clinical trials with both vaccines have used efficacy against cervical intraepithelial neoplasia (CIN) 2/3 and adenocarcinoma *in situ* (AIS)



caused by HPV strains contained in the concerned vaccine as primary end points. Regulatory authorities have accepted the use of CIN grade 2 or 3 (CIN2–3) and AIS as clinical end points in vaccine efficacy trials instead of invasive cervical cancer.

Both vaccines do not protect against the serotype with which infection has already occurred before vaccination.

However, it is well established that if a woman is infected with a particular HPV type, she may clear the infection but not necessarily produce an adequate and long lasting immune response towards it and will therefore be susceptible to a future infection with the same type. Therefore, vaccination may offer future protection even against the serotype that a woman may currently/ previously be infected with. Both vaccines have been licensed in several countries world over.

These vaccines are equally safe and both have shown nearly complete protection against precancerous lesions and other anogenital pathology caused by the respective vaccine related HPV types during the 8-9 years of observation so far. The consistency of these observations strongly suggests that similar high rates of protection can be expected also against cervical cancer.

Quadrivalent vaccine available in India is a mixture of L1 proteins of HPV serotypes 16, 18, 6 and 11 with aluminium containing adjuvant. Each 0.5 mL dose of this vaccine contains 20 µg of HPV-6 L1 protein, 40 µg of HPV-11 L1 protein, 40 µg of HPV-16 L1 protein and 20 µg of HPV-18 L1 protein adsorbed onto 225 µg of the adjuvant. Clinical trials with three doses at 0, 2 and 6 months in more than 16,000 women aged 16-26 years from 5 continents including Asia have shown 99% efficacy at a median follow up of 3 years against types 16, 18 related CIN- 2/3 and AIS in per protocol analysis (women who received all three doses of the vaccine and who remained uninfected with vaccine HPV type at onset and for 1 month after completion of the vaccine schedule). Additionally, 99-100% efficacy was seen against vaccine type related genital warts, vaginal intraepithelial neoplasia (VaIN) and vulvar intraepithelial neoplasia (VIN). Follow up studies in a subset of participants over 5 years show persistent protection, and good response to booster immunization indicative of immune memory. Immunogenicity studies in females 9-15 years showed antibody titers non-inferior to those aged 16-26 years. Local adverse effects reported were pain at the injection site in 83% of vaccinees (mainly mild – moderate intensity) and swelling and erythema in 25%. Systemic adverse effects such as fever was reported in 13% of vaccinees. No serious vaccine related adverse events have been reported either in trials or post marketing surveillance studies.

The bivalent vaccine is a mixture of L1 proteins of HPV serotypes 16 and 18 with



AS04 as an adjuvant. The efficacy of the bivalent HPV vaccine in the prevention of vaccine-related HPV types CIN2–3 was assessed in a phase III study that included 18 644 women aged 15–25 years. Clinical trials (PATRICIA trial) with three doses at 0, 1 and 6 months in more than 18000 women globally has shown 92.9% efficacy against type 16/18 related CIN2/3 and AIS at 34.9 month follow up in modified intention to treat analysis (included women who were at baseline negative for HPV DNA of vaccine type virus and who received at least 1 dose of the vaccine). Follow up studies in a subset of participants over 7.3 years show no evidence of waning immunity. Local side effects reported were pain (mild and moderate intensity) in 90% and swelling and erythema in 40%. Systemic side effects such as fever were seen in 12%. No serious vaccine related adverse effects were observed.

HPV vaccine safety

The safety and efficacy of these vaccines have been documented in numerous studies and endorsed by numerous international and national regulatory agencies.

Clinical trials of both HPV vaccines conducted in India prior to licensure, demonstrated high immunogenicity and a good safety profile, confirming the findings reported in other countries. These have been approved by the Drug Controller General of India (DCGI) for general use.

In a demonstration project conducted by PATH, in the large cohorts of girls vaccinated in Andhra Pradesh and Gujarat, six deaths were reported in the weeks or months following HPV vaccination. None of these deaths was causally associated with the vaccine.

To date, no deaths have been causally associated with HPV vaccination in India or elsewhere. Experience with the HPV vaccines used in the post-licensure observational study confirms the good safety profile reported in clinical trials.

In its 2009 position paper on HPV vaccination, the World Health Organization stated that “WHO’s Global Advisory Committee on Vaccine Safety (GACVS) concluded that both vaccines had good safety profiles.”

Recommendations for use

The IAPCOI recommends offering HPV vaccine to all females in the schedules discussed below. Since protection is seen only when the vaccine is given before infection with HPV, the vaccine should preferably be given prior to sexual debut. The vaccine should preferably be introduced to parents as a cervical cancer preventing vaccine and not as a vaccine against a sexually transmitted infection (STI). Vaccines



are not 100% protective against cervical cancer and not a replacement for periodic screening. Hence screening programs should continue as per recommendations. Need for boosters and potential for serotype replacement would be known in future. Both the available vaccines are equally efficacious and safe for protection against cervical cancer and precancerous lesions as of currently available data. The quadrivalent vaccine additionally protects against anogenital warts.

Dose and Schedule

The vaccines should be stored at 2 to 8°C and must not be frozen. The dose is 0.5 ml intramuscular in deltoid. The recommended age for initiation of vaccination is 10-12 years. As of current licensing regulations in India, catch up vaccination is permitted up to the age of 45 years. Three doses at 0, 2 and 6 months are recommended with the quadrivalent vaccine (minimum interval between 1st and 2nd dose is 4 weeks and second and third dose is 12 weeks) and 0, 1 and 6 months with the bivalent vaccine. HPV vaccines can be given simultaneously with other vaccines such as Hepatitis B and Tdap. As a precaution against syncope following any vaccine in adolescents, the vaccinee should be counseled prior to vaccination, vaccine be administered in a sitting/ lying down position and the patient observed for 15 minutes post vaccination. Both vaccines are contraindicated in those with history of previous hypersensitivity to any vaccine component and should be avoided in pregnancy. The vaccines may be administered in the immunocompromised but immunogenicity and efficacy may be lower. At present, there is no data to support use of boosters.

Cervical cancer is responsible for significant morbidity/ mortality in Indian women and affects women of all socio economic strata. Compliance with cervical Papanicolaou (PAP) smear screening is low in India. The currently available vaccines are safe and efficacious. The HPV vaccines are thus of public health importance. However, cervical cancer prevention is not a public health priority and the programmatic feasibility and economic sustainability need to be given due consideration before including the HPV vaccine in NIP.



PNEUMOCOCCAL VACCINES

Pneumococcal disease burden

S. pneumoniae is responsible for 15-50% of all episodes of community acquired pneumonia, 30-50% of all cases of acute otitis media and a significant proportion of bacterial meningitis and bacteremia. It is estimated that 50% of the 2 million deaths due to pneumonia globally every year are attributable to *S pneumoniae*. Ninety serotypes of *S. pneumoniae* have been described of which a handful are responsible for most cases of invasive pneumococcal disease (IPD). According to a recent publication, seven serotypes (1, 5, 6A, 6B, 14, 19F, 23F) were the most common globally. These serotypes were most common in both Africa and Asia, and accounted for 58%-66% of IPD in every region. Serotype 14 was the most common serotype accounting for 12%-29% of IPD in each region. Serotype 6B ranked second in every region, except Africa (ranked fifth); when combined with serotype 6A, this serogroup accounted for 14%-18% of IPD across regions. Serotypes 1, 5, and 14 together accounted for 28%-43% of IPD across regions. Serotypes 23F and 19F were responsible for 9%-18% of IPD overall. Based on year 2000 incidence and mortality estimates, these seven serotypes accounted for 300,000 deaths in Africa and 200,000 deaths in Asia.

Children under the age of 2 yrs are at greatest risk for invasive pneumococcal disease.

Estimates of IPD incidence for developing countries are difficult to obtain. It is estimated that for every case of meningitis, there are 10 times more cases of bacteremia, 100 times more cases of non-invasive pneumonia and 1000 times more cases of acute otitis media (AOM). 90% of bacteremia, 30-50% of severe community acquired pneumonia, 30-45% of pyogenic meningitis and 30-60% of all bacterial AOM are estimated to be caused by pneumococcus. The mortality rate of invasive disease is 6% - 20% and there are long term sequels like CNS sequel in survivors of meningitis and deafness in children with recurrent AOM.

Prevalence of pneumococcal disease in India - Data is scanty

Mortality

Globally, according to WHO estimates published in 2009, 826000 (582000-926000) under five children died of pneumococcal disease. Of these, 449000 [316000-501000] (61%) occurred in ten African and Asian countries.

Around 142000 under five children died of pneumococcal diseases in India, highest among this list of ten countries.



Pneumonia mortality in under five children (WHO estimates: 2005-06)

18% of 8.795 million *i.e.* 1.575 million globally

20.3% of 1.829 million deaths *i.e.* 0.371 million in India

WHO estimates that 50% of these pneumonia deaths occur due to pneumococcus *i.e.* 0.8-1.0 million deaths every year

Pneumococcal serotype distribution

As far as pneumococcal serotypes distribution is concerned, sparse India specific data has been published since Invasive Bacterial Infection Surveillance (IBIS) study done in 1993-1997. Results of the IBIS study in patients with Invasive Pneumococcal Disease (IPD) indicate that serotypes 6, 1, 19, 14, 4, 5, 45, 12, 7, 23 are the most prevalent with serotypes 1 and 5 accounting for 29% of invasive pneumococcal disease. The same study now continues as South Asian Pneumococcal Alliance (SAPNA) project and the serotype distribution has not changed much with time. According to this study, the most prevalent serotypes in India are 6B, 20, 16 and 1. The results of SAPNA study were based only on the report of 11 samples from India taken between October 2006 to March 2007. Further, serotypes 20 and 16 form the miniscule group. Even in IBIS study, they did not get any mention below 5 yrs of age and constituted only 1-4% above 5yrs of age.

Pneumococcal vaccines

Till recently only 7-valent pneumococcal conjugate vaccine (PCV7) and unconjugated pneumococcal polysaccharide vaccine (PPSV 23) were available in India. However, in mid 2010, a new 13-valent conjugate vaccine (PCV13) was launched in India. PCV 13 has replaced PCV 7 world over, including India. Another PCV, a 10-valent pneumococcal conjugate vaccine (PCV 10) is now available internationally and soon will be available in India too.

Pneumococcal polysaccharide vaccine

The unconjugated pneumococcal polysaccharide vaccine is a 23 valent vaccine (PPSV 23) containing the following serotypes – 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F. It is a T cell independent vaccine that is poorly immunogenic below the age of 2 yrs, has low immune memory, does not reduce nasopharyngeal carriage and does not provide herd immunity. It has at best 70% efficacy against prevention of invasive pneumococcal disease in the high-risk population but offers no protection against non bacteremic pneumonia/otitis media. It is stored at 2 to 8°C and the dose is 0.5 ml subcutaneous/



intramuscularly. It is a safe vaccine with occasional local side effects. Not more than two life time doses are recommended, as repeated doses may cause immunologic hyporesponsiveness.

Pneumococcal conjugate vaccines

Conjugate pneumococcal vaccines (PCV) were developed primarily to address the problem of low immunogenicity of the polysaccharide vaccine in children below the age of 2 who are at high risk for pneumococcal disease. Conjugation of the pneumococcal polysaccharide of varying number of serotypes has been done with diphtheria toxoid cross-reactive material 197 (CRM197) protein, protein D of non capsulated Hib, DT and TT and finally Men OMP.

PCV 7

Till recently only PCV7 was available. It covered 7 serotypes namely 4, 6B, 9V, 14, 18C, 19F and 23F. Efficacy of PVC 7 in the landmark randomized controlled NCKP trial in the US in around 40, 000 children is summarized in the table 1.

Table 1: *Efficacy of PCV7 in US (data from NCKP trial, 2000).*

Type of pneumococcal disease	% protection over 5 years
IPD VT	95%
IPD any serotype	89%
Clinical pneumonia	4%
Radiological pneumonia	30%
Otitis Media	6%
Tympanoplasty Tube Placement	20%

(IPD=Invasive pneumococcal diseases, VT=Vaccine type)

PCV7 was licensed in the USA in the year 2000, and in Europe in 2001. By December 2009, PCV7 was licensed in approximately 100 of 193 member states of the WHO. In addition, it had been included in the routine or national immunization programs or was widely used in 42 of these countries.

Impact of PCV 7

Over nearly a decade, PCV7 has demonstrated high efficacy against invasive pneumococcal diseases caused by vaccine serotypes in children younger than 2 years of age. Its effectiveness has been confirmed under routine use in the USA, Canada and several European countries. Of note, disease surveillance and several



studies showed that indirect population protection outweighs the direct protection of immunized subjects. A substantial impact of PCV7 was also confirmed on community-acquired pneumonia and AOM. A limited increase in IPD caused by non-PCV7 serotypes, particularly 19A serotype has been registered to date, but in most countries, this is far below the magnitude of the beneficial reduction in IPD due to vaccine serotypes.

The safety profile of PCV7 is well defined on the basis of the vaccine's pre-licensure clinical evaluation and nearly one decade of post-licensure experience, with more than 300 million doses having been distributed worldwide since the year 2000.

PCV 9 & PCV 11

These two products, though had shown their efficacies in clinical trials in developing country settings and also amongst HIV-infected populations, are no longer in active development owing to diminished immunogenicity of few serotypes and interference with co-administered other pediatric vaccines.

Newer PCVs

There is some rationale for inclusion of each individual serotype in new PCVs since each of the serotypes has its own 'personality'. Serotype 1 may be responsible for more than 10% of all IPD cases in children less than 5 years of age. Moreover, serotype 1 is often reported as the leading cause of pneumonia and pneumonia with empyema. In the least-developed countries of the world, outbreaks of serotypes 1 and 5 (so-called epidemic serotypes) are important causes of childhood disease. As described above, these two serotypes account for 29% of IPD in India (18.9% in underfive children). The pediatric serotypes, such as 6A and 19A, are characterized by their ability to colonize the nasopharynx of young children. These serotypes have a tendency to develop reduced susceptibility to commonly used antibiotics, such as penicillin G and macrolides. 6A and 19A constitute around 10% of all pneumococcal serotypes even in India. Serotype 6A has become more complex with the newly identified 6C and 6D, and according to few reports 6A provides better cross protection against the entire 6 group than 6B alone.

According to 2008 ANSORP data, 19A is on rise in most Asian countries. Amongst 1637 invasive *S. pneumoniae* isolates collected from 10 Asian countries, 91 were serotype 19A. Of the 91 samples of 19A, only 3 were from India and constituted 13% of the pneumococcal isolates causing invasive pneumococcal disease from India. In the USA, Active Bacterial Core surveillance (ABCs) data showed that the incidence of IPD due to serotype 19A increased from 0.8 to 2.5 cases per 100,000 population between 1998 and 2005. Increasing rates of 19A infection, often by multi-antibiotic-resistant strains, are now reported from many regions in the world. As far as serotype



3 is concerned, the invasive infections caused by this serotype are more commonly seen in older children than in the very young and it is often associated with pulmonary necrosis and severe pneumonia. Serotype 3 is a hard nut to crack for PCV developers due to its poor immunogenicity and non-boostability. Serotype 3 pneumococci are abundantly capsulated, making the bacteria less sensitive to immune interactions. Attempts are made to make it more immunogenic with the use of better adjuvants.

Serotype 7F IPD rates are currently increasing in some countries. This serotype is only rarely resistant to commonly used antibiotics.

a. PCV 13

Vaccine Composition

PCV13 was developed as a successor to the currently registered PCV7. PCV13 contains polysaccharides of the capsular antigens of *S. pneumoniae* serotypes 1, 5, 7F, 3, 6A and 19A, in addition to the 7 polysaccharides of the capsular antigens of 4, 6B, 9V, 14, 18C, 19F and 23F present in the PCV7, individually conjugated to a nontoxic diphtheria cross-reactive material (CRM) carrier protein (CRM197). A 0.5-mL PCV13 dose contains approximately 2.2 μg of polysaccharide from each of 12 serotypes and approximately 4.4 μg of polysaccharide from serotype 6B; the total concentration of CRM197 is approximately 34 μg . The vaccine contains 0.02% polysorbate 80 (P80), 0.125 mg of aluminum as aluminum phosphate (AlPO₄) adjuvant, 5mL of succinate buffer, and no thimerosal preservative. Except for the addition of six serotypes, P80, and succinate buffer, the formulation of PCV13 same as that of PCV7.

Serological correlates of protection

Any new pneumococcal conjugate vaccine has to meet the following two criteria laid down by the WHO for its licensure:

1. IgG (for all common serotypes collectively and not individually) of equal to or more than 0.35 mcg/ml measured by the WHO qualified Elisa technique.
2. Opsonophagocytic activity with OPA titers of 1:8 or higher.

Evaluation of PCV13 immunogenicity in clinical trials

There are no efficacy trials with PCV13 as it is unethical to conduct placebo controlled efficacy trials using any new PCV when already a proven PCV7 vaccine is available and recommended for use in children. Consequently, the immune response induced by the new pneumococcal conjugate vaccine was used to provide an assessment of the protective efficacy of the vaccine.



In the first pivotal trial conducted in US, responses to shared serotypes 6B and 9V and new serotype 3 did not meet this criterion. For serotypes 6B and 9V, however, the differences were small. The non-inferiority criterion was not met for the response to serotype 3 even after the 4th dose of PCV 13. However, PCV13 elicited functional antibodies (OPA titers of 1:8 or higher) to all 13 vaccine serotypes in all pivotal trials. Overall, PCV 13 met almost all the WHO non-inferiority criteria for licensure.

The immunogenicity study, performed in France, looked at the antibody responses to PCV13 booster dose among toddlers who received 3 doses of either PCV7 or PCV13. The 3 groups received PCV 13 and PCV7 in PCV7+PCV7, PCV13+PCV13 and PCV7+PCV13 in primary + booster schedule. The antibody responses were comparable across the groups and thus supported the ability to substitute PCV13 for PCV7 at any point in the immunization schedule for protection against the seven common serotypes. For the six additional serotypes, the IgG and OPA responses in the 7v/13v group were comparable to the post-infant series with 13v. However, significantly lower IgG and OPA responses were seen for serotypes 1, 5 and 6A in the 7v/13v group compared with the group that received all four doses of PCV13 for all doses.

Adverse reactions after administration of PCV13 in clinical trials

The incidence and severity of local reactions at the injection site and systemic reactions were comparable to PCV7. The data suggest that the safety profiles of PCV13 and PCV7 are comparable.

Clinical trials of PCV 13 in India

Preliminary reports presented at the 7th International Symposium on Antimicrobial Agents and Resistance, Bangkok, Thailand, 2009, from one cohort (Pune and Mumbai) of a multicentric immunogenicity and safety trial of PCV13 in India, when given with routine vaccines to infants, found satisfactory responses for both the shared as well as additional serotypes. Responder rates to PCV13 and PCV7 1 month after the third dose were similar between groups for all 7 serotypes common to both vaccines, with $\geq 80.4\%$ of subjects achieving anticapsular IgG-binding antibody concentrations $\geq 0.35 \mu\text{g/mL}$ while responder rates for the 6 additional serotypes were 79.4% to 99.0% and were greater than the respective responses in the PCV7 group. However, as with pivotal immunogenicity trials, the IgG seroresponse rates and GMCs for serotype 3 were the lowest (79.4% and $0.6 \mu\text{g/mL}$, respectively) amongst all additional serotypes. Immune profile of serotype 3 following PCV13 is similar to 11-valent PHiD-CV (POET study) *i.e.* lower titres post booster as compared to post primary. Serotype 3 efficacy of PCV13 not demonstrated as yet.



Vaccine Administration

PCV13 is administered intramuscularly as a 0.5-mL dose and is available in latex-free, single-dose, prefilled syringes. PCV13 can be administered at the same time as other routine childhood vaccinations, if administered in a separate syringe at a separate injection site. The safety and efficacy of concurrent administration of PCV13 and PPV23 has not been studied, and concurrent administration is not recommended.

b. PCV-10

Vaccine Composition

PCV10 is now available internationally, though not in India, and covers 3 additional serotypes besides the PCV7 *i.e.* 1, 5, and 7F. Three different carrier proteins are used in this formulation (Table 2).

Table 2: Antigen concentration of different serotypes and carrier proteins used in the development of PCV10.

Serotypes	1, 5, 6B, 7F, 9V, 14, 23F	4	18C	19F
Antigen concentration	1 mcg	3 mcg	3 mcg	3 mcg
Carrier proteins	Non-typeable <i>H. influenzae</i> (NTHi) Protein D		Tetanus Toxoid	Diphtheria Toxoid

The choice of non-typeable *Haemophilus influenzae* Protein D as main carrier protein in PCV 10 was driven in part to avoid carrier-mediated suppression and possible bystander interference with co-administered vaccines. PCV10 is a preservative-free vaccine and adsorbed on aluminium phosphate.

Evaluation of PCV10 immunogenicity in clinical trials

Its immunogenicity, safety and reactogenicity profile is comparable to the currently licensed pneumococcal vaccine, and compatibility with major childhood vaccines has been demonstrated in co-administration studies.

There are no efficacy trials with PCV10. PCV10 was tried in pivotal non-inferiority trials compared with PCV7. Overall PCV10 was found to be non-inferior to PCV7. However post-primary 3 doses seroconversion for > 0.35 mcg/ml by ELISA was inferior for two serotype *i.e.* 6B and 23F and GMC for all 7 common serotypes were inferior to shared serotypes compared to PCV7. Seroconversion by OPA > 1:8 was sub-optimal for types 1 and GMC were lesser for five of seven common serotypes as well as for types 1 and 5. However, post-booster immune responses at 15 months seroconversion > 0.35 mcg/ml by ELISA and OPA > 1:8 were equal to that observed



by PCV7, but GMC by ELISA were lesser for four of seven shared serotypes and by OPA for five of seven shared serotypes.

However, other studies comparing PCV10 with PCV7 in EPI schedule of 6-10-14 weeks have not shown much difference between these two vaccines. PCV-10 has also shown good immunogenicity and safety in Mali and the Philippines when administered to infants at 6, 10 and 14 weeks of age.

The safety and reactogenicity profiles of the PCV10 and PCV 7 are comparable.

PCV10 is now licensed for active immunization of infants and children from 6 weeks up to 2 years of age in several European countries, Canada, Australia and Latin America but not in USA. It is expected to be licensed soon in India too.

Predecessor of PCV10, PCV11 demonstrated efficacy against non-typable Hib (around 35% efficacy in POET trial). However, studies are needed to assess the potential advantages of protein D as a carrier and the potential efficacy of this new vaccine against *H. influenzae*.

Recently, a double-blind, individually randomized study known as COMPAS trial (Clinical Otitis Media and Pneumonia Study) was conducted in few countries of Latin America (Argentina, Columbia and Panama) to quantify the (combined) impact of PCV-10 on all-cause pneumonia. This three-year trial which was started in 2007, enrolled 24,000 subjects and provided three primary doses of PCV-10 at 2, 4, 6 months plus one booster at 15-18 months alongside other routinely administered infant vaccines. The main objectives of this trial is to demonstrate efficacy of PCV-10 against community acquired pneumonia (CAP), clinical acute otitis media (AOM), AOM due to NTHi, and nasopharyngeal carriage of pneumococci and NTHi. The results are expected by the end of 2011. This study will generate the first PCV efficacy data in Latin America. It will also generate the first efficacy data with the new generation of PCVs.

Clinical trials in India

A phase III, single-blinded, randomised, controlled study immunogenicity and safety profile of a 3-dose primary vaccination with PCV-10 was studied at four centers (Vellore, Ludhiana, Pune, and Kolkata) in Indian infants, between March 2009 and November 2009.

According to preliminary results, one month post-dose III, for each of the 10 vaccine pneumococcal serotypes, at least 98.3% of subjects vaccinated with PCV-10 had antibody concentration of ≥ 0.2 $\mu\text{g/mL}$ (equivalent to the threshold of 0.35 $\mu\text{g/mL}$ as measured by the non-22F inhibition ELISA used by the WHO) except for serotypes



23F (89.5%) and 6B (77.7%) and at least 95.7% of subjects had OPA titres ≥ 8 , except for serotypes 1 (90.5%) and 6B (84.5%). All subjects except one (99.6%) were seropositive for antibodies against protein D (≥ 100 EL.U/mL).

Recommendations for use

A. For public use

Looking at the enormous pneumonia disease and mortality burden, pneumococcus being the number one cause of these severe pneumonia cases and deaths, and the effectiveness of PCV on pneumonia burden and child mortality, WHO in 2007 recommended to include PCV in the National Immunization Program (NIP) of any country with under-5 MR of $> 50/1000$ live births or absolute child deaths of $> 50,000$ per year. With under-5 MR of 72/1000 live birth and nearly 2 million under-five deaths per year, India merits to include PCV in NIP with high priority. There are 72 GAVI eligible countries which can apply for GAVI support for inclusion of live saving vaccines in NIP at a nominal cost sharing of few US dollars per dose by these countries. India has shown intent to include PCV in NIP by 2012-13 when PCV10/PCV13 will become available, which will cover $> 75\%$ of prevalent serotypes of pneumococcus as seen in children. PCV 13 is available now in India and PCV-10 is on the verge of introduction. Both PCV10 and PCV13 are likely to prevent even more cases of pneumococcal pneumonia and deaths due to better serotypes coverage. Inclusion of PCV is likely to reduce child deaths and help India achieve millennium developmental goal 4.

However, on the other hand, there are many issues to confront with before introducing PCVs in NIP of the country. Unlike the African countries, the major burden of disease syndrome caused by pneumococci in India is pneumonia not meningitis. Hence, until the vaccines have good effectiveness at mass level against pneumonia; the desired impact of introduction of PCVs cannot be obtained. Further, there is an urgent need to carry out community based surveys to establish exact disease burden of various syndromes caused by pneumococci and to establish an effective surveillance system to monitor prevalence of different serotypes. A watch on prevalence of multi-drug resistance will also prove fruitful to design future strategies to tackle pneumococcal diseases. Studies are urgently needed to document efficacy of newer PCVs and shortened schedule especially on pneumonia incidence. Without institution of an effective surveillance system like ABCs, we will not be able to keep a vigil on issues like serotype replacement and impact of mass use of PCVs on pneumococcal disease burden. Indigenous production of new pneumococcal vaccines like protein based vaccines should be explored and pursued aggressively.



Shortened vaccination schedule for public use consideration

One exciting prospect will be to study a shortened vaccination schedule with these newer, better formulations as this will moderately cut down the cost incurred on pneumococcal mass vaccination program.

PCV7 has been introduced into the '2 + 1' (two infant doses plus a booster) national vaccination schedule in several European countries and is now used in more than 50% of EU countries. Consequently, the immunogenicity was carefully assessed in the PCV13 development program and the immunogenicity after two doses in infants has been documented in four studies. The proportion of infants achieving a pneumococcal anticapsular polysaccharide IgG concentration of at least 0.35 µg/ml 1 month after the second dose ranged from 79.6 to 98.5% across 11 of the 13 vaccine serotypes. Smaller proportions of infants achieved this antibody concentration threshold for serotype 6B (27.9–57.3%) and 23F (55.8–68.1%) for all studies using a 2-, 4-month regimen, compared with 58.4% for serotype 6B and 68.6% for 23F for a study using a 3-, 5-month regimen. However, after the booster dose, all vaccine serotypes including 6B and 23F had immune responses consistent with adequate priming with a two-dose primary series. As for PCV7, the recommended immunization series for PCV13 consists of four doses (3 plus 1). Alternatively, when PCV13 is given as part of a routine infant immunization program, a series consisting of three doses (2 plus 1) may be given. Effectiveness of 1 dose of PCV13 was estimated as 48%, 2 doses 87% and 2+1 doses 100%. One dose catch up for toddlers showed 83% effectiveness. Similarly, trials with PCV-10 are also currently undergoing to assess efficacy of 2+1 catch-up schedule in unprimed individuals. However one should refrain from using 2+1 schedule for individual in office practice and can be used only in NIP.

B. For individual use

I. High risk children

Children at high risk of pneumococcal disease are listed in Table 3. The IAPCOI recommends offering both PCV and PPV 23 to all high-risk children in schedules discussed below. The PCV vaccines provide robust immune response and immune memory while PPV 23 provides expanded serotype coverage. If PCV can not be given, at least PPV 23 should be given to high-risk children above 2 years of age.

II. Healthy children

According to most recent estimates, PCV-13 covers around 73% and PCV-10 approximately 66% of prevailing pneumococcal serotypes in the region



(pneumoADIP report, 2009). Though more data is needed before making judgment on the suitability of one formulation over other, both the products appear to be almost providing equal protection against the prevailing pneumococcal disease. While PCV-13 offers wider serotype coverage, PCV-10 promises to provide better protection against otitis media.

Doses and Vaccination schedules

1. PCV-13

A. No previous PCV 7/PCV 13 vaccination

The vaccination schedule of PCV13 is essentially the same as PCV7, *i.e.* 4-dose schedule as followed for PCV7, administering doses at ages 6, 10, 14 weeks and a booster at 12-15 month (Table 4).

Following are additional recommendations concerning PCV 13 use:

1. For children who have begun a series of PCV7, replace all remaining doses with PCV13.
2. For children who have completed a 4-dose or other age-appropriate series of PCV7:
 - a. Give one additional dose of PCV13 to all healthy children who have not yet reached their fifth birthday.
 - b. Give one additional dose of PCV13 to children with underlying medical conditions (see Table 3) that increase their risk for developing pneumococcal disease or complications who have not yet reached their sixth birthday.
3. For children ages 6 through 18 years with functional or anatomic asplenia, including sickle cell disease, HIV infection or other immunocompromising condition, cochlear implant or CSF leak, consider giving one dose of PCV13 regardless of previous history of PCV7 or pneumococcal polysaccharide vaccine (PPSV).

General instructions

- Routine use of PCV13 is not recommended for healthy children aged more than 5 years.
- Minimum age for administering first dose is 6 weeks.
- Minimum interval between two doses is 4 weeks for children vaccinated at age <12 months whereas for those vaccinated at age >12 months, the minimum interval between doses is 8 weeks.



B. Children Vaccinated Previously with PCV7 or PCV13

These infants and children who are in various stages of PCV vaccination (*i.e.*, unvaccinated, begun a series of PCV7 or PCV13 but not yet completed, or have completed a series of PCV7) can complete their vaccination with PCV-13 as shown in Table 5.

2. PCV-10

The recommendations for the primary vaccination of unvaccinated infants and children are essentially the same as described above for PCV-13. It is recommended that subjects who receive a first dose of PCV 10 should complete the full vaccination course with the same formulation.

C. Vaccination schedule for high-risk children

Administration of PPSV23 after PCV7 or PCV13/PCV 10 among children aged 2–18 years who are at increased risk for pneumococcal disease should be undertaken as per following instructions:

- 1 Children aged ≥ 2 years with underlying medical conditions (Table 3) should receive PPSV23 after completing all recommended doses of PCV13. These children should be administered 1 dose of PPSV23 at age ≥ 2 years and at least 8 weeks after the most recent dose of PCV.
- 2 Children who have received PPSV23 previously also should receive recommended PCV13/PCV10 doses.
- 3 Children aged 24–71 months with underlying medical conditions who received any incomplete schedule of 3 doses of PCV7 before age 24 months should receive 1 dose of PCV13/PCV 10 followed by 1 dose of PPSV23 administered ≥ 8 weeks later.
- 4 Children aged 24–71 months with underlying medical conditions who received <3 doses of PCV7 before age 24 months should receive a series of 2 doses of PCV13/PCV 10 at an interval of 8 weeks, followed by 1 dose of PPSV23 administered ≥ 8 weeks later.
- 5 When elective splenectomy, immunocompromising therapy, or cochlear implant placement is being planned; PCV13/PCV 10 and/or PPSV23 vaccination should be completed at least 2 weeks before surgery or initiation of therapy.



Revaccination with PPSV23 among Children at Highest Risk

A second dose of PPSV23 is recommended 5 years after the first dose of PPSV23 for children who have anatomic or functional asplenia, including SCD, HIV infection, or other immunocompromising condition. No more than two PPSV23 doses are recommended.

Table 3: Children at high risk for pneumococcal disease

Risk Group	Condition
Immunocompetent children	Chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure)
	Chronic lung disease (including asthma if treated with prolonged high-dose oral corticosteroids)
	Diabetes mellitus
	Cerebrospinal fluid leak
	Cochlear implant
Children with functional or anatomic asplenia	Sickle cell disease and other hemoglobinopathies
	Congenital or acquired asplenia, or splenic dysfunction
Children with immunocompromising conditions	HIV infection
	Chronic renal failure and nephrotic syndrome
	Diseases associated with treatment with immunosuppressive drugs or radiation therapy (e.g., malignant neoplasms, leukemias, lymphomas, and Hodgkin disease; or solid organ transplantation)
	Congenital immunodeficiency (includes B-(humoral) or T-lymphocyte deficiency; complement deficiencies, particularly C1, C2, C3, and C4 deficiency; and phagocytic disorders (excluding chronic granulomatous disease)



Table 4: Recommended schedule for use of PCV-13/PCV10 among previously unvaccinated infants and children by age at time of first vaccination

Age at first dose	Primary PCV13/PCV10 series*	PCV13/PCV10 booster dose†
6wks–6 mos	3 doses	1 dose at 12–15 mos
7–11mos	2 doses	1 dose at 12–15 mos
12–23mos	2 doses	NA
24–59 mos in healthy children	1 dose	NA
24–71mos in children with certain chronic diseases or immunocompromising conditions	2 doses	NA

Abbreviation: NA = not applicable

* Minimum interval between two doses is 4 weeks for children vaccinated at age <12 months whereas for those vaccinated at age > 12 months, the minimum interval between doses is 8 weeks.

Minimum age for administration of first dose is 6 weeks.

† Administered at least 8 weeks after the previous dose.

Table 5: Recommended schedule for administering doses of PCV-13 to children by PCV vaccination history and age

Child's age now	Vaccination History of PCV7 and/or PCV13	Recommended PCV13 Schedule
6 wks through 6 mos	0 dose	3 doses, 4 wks apart; 4th dose at age 12-15 mos.
	1 dose	2 doses, 4 wks apart; 4th dose at age 12-15 mos
	2 doses	1 dose, at least 4 wks after the most recent dose; 4th dose at age 12-15 mos
7 through 11 mos	0 doses	2 doses, 4 wks apart; dose 3 at age 12-15 mos
	1 or 2 doses before age 7 mos	1 dose at age 7-11 mos, with a second dose at age 12-15 mos (8 wks later)
12 through 23 mos	0 doses	2 doses, at least 8 wks apart
	1 dose before age 12 mos	2 doses, at least 8 wks apart



Child's age now	Vaccination History of PCV7 and/or PCV13	Recommended PCV13 Schedule
	1 dose at or after age 12 mos	1 dose, at least 8 wks after the most recent dose
	2 or 3 doses before age 12 mos	1 dose, at least 8 wks after the most recent dose
	4 doses of PCV7 or other age-appropriate, complete PCV7 schedule	1 supplemental dose, at least 8 wks after the most recent dose
24 through 59 mos (healthy)	Unvaccinated or any incomplete schedule	1 dose, at least 8 wks after the most recent dose
	4 doses of PCV7 or other age-appropriate, complete PCV7 schedule	1 supplemental dose, at least 8 wks after the most recent dose
24 through 71 months (with risk factor)	Unvaccinated or any incomplete schedule	2 doses, one at least 8 wks after the most recent dose and another dose at least 8 weeks later
	Any incomplete schedule of 3 doses	1 dose, at least 8 wks after the most recent dose
	4 doses of PCV7 or other age-appropriate complete PCV7 schedule	1 supplemental dose, at least 8 wks after the most recent dose

HEPATITIS A VACCINES

Background

Hepatitis A virus (HAV) infection is a relatively benign infection in young children. As many 85% of children below 2 years and 50% of those between 2-5 years infected with HAV are anicteric and may just have non-specific symptoms like any other viral infection. On the contrary, hepatitis A in adults is symptomatic in 70% to 95% with a mortality of 1%. The disease severity increases irrespective of age, in those with underlying chronic liver disease.

Countries are classified as low/ intermediate or highly endemic for Hepatitis A. In countries with high endemicity, most individuals acquire natural infection in childhood and burden of disease including incidence of outbreaks is low. As a shift occurs towards intermediate endemicity due to improvements in hygiene and sanitation, a certain proportion of children remain susceptible till adulthood. Thus burden of



symptomatic disease and incidence of outbreaks paradoxically increase. India which earlier was a highly endemic country is now shifting to intermediate endemicity. Seroprevalence studies show susceptibility in 30-40% of adolescents and adults belonging to the high socioeconomic class with regional differences (seropositivity in Kerala being lower than other states). Studies also show a reduction in cord blood seropositivity (indicative of young adult seronegativity) for HAV over the year. Several outbreaks of hepatitis A in various parts of India have been recorded in the past decade; children from rural and semi-urban areas of the state of Maharashtra (2002-2004), an explosive outbreak among adults from Kerala involving 1,137 cases (2004) and over 450 cases in children and adults in Shimla (2007). An increasing contribution of Hepatitis A to fulminant hepatic failure has also been noted.

Vaccines

Inactivated vaccines

Most of the currently available vaccines are derived from HM 175/GBM strains and grown on MRC5 human diploid cell lines. The virus is formalin inactivated and adjuvanted with aluminum hydroxide. The vaccine is stored at 2-8°C. The vaccines are given in a two dose schedule, 6 months apart intramuscularly. The manufacturer's recommendation for dosage should be followed. The serologic correlate of protection is 20 mIU/ml. Protective antibodies are seen in 95-100% 1 month after the 1st dose and almost 100% after the second dose. The protective efficacy is around 90-100% and onset of protection is 2 weeks – 1 month after the 1st dose of the vaccine. The vaccine efficacy is lower in the elderly, immunocompromised, those with chronic liver disease, in transplant recipients and those with pre existing maternal antibodies. The vaccine may be safely given with other childhood vaccines and interchange of brands is permitted though not routinely recommended. Immunity is lifelong due to anamnestic response and no boosters are recommended at present in the immunocompetent. Adverse reactions are minor and usually include local pain and swelling.

A liposomal adjuvanted hepatitis A vaccine derived from the RG-SB strain, harvested from disrupted MRC-5 cells and inactivated by formalin is now available. The liposome adjuvant is immunopotentiating reconstituted influenza virosome (IRIV) composed of phosphatidylcholine, phosphatidylethanolamine and hemagglutinin from an H1N1 strain of influenza virus. The efficacy and safety profile is nearly similar to the other inactivated vaccines.

Combination Hep A and Hep B vaccines are also available to be used in those who have not been vaccinated for Hep B previously. These are available in both adult



and pediatric formulations and are discussed separately under combination vaccines.

Live attenuated vaccine

This vaccine is derived from the H2 strain of the virus attenuated after serial passage in Human Diploid Cell (KMB 17 cell line). It has been in use in China since the 1990's in mass vaccination programs. The vaccine meets requirements of the Chinese drug authority and the WHO. It is also now licensed and available in India. The recommended dose is 1 ml SC (10 (6.5) CCID₅₀/ml) in children aged 1-15 years. Immunogenicity studies with single dose show seroconversion rates of more than 98% 2 months after vaccination and persistence of protective antibodies in more than 80% of vaccines at 10 year follow up. The mean geometric mean titers achieved with the live vaccines are almost 10 fold lower as compared to the inactivated vaccines. Uncontrolled studies from China with single dose of the vaccine show an efficacy of almost 100% sustained over 10 years despite decline in seroprotection rates and antibody titers. However recent controlled studies with 2 doses of the live vaccine from China have shown higher antibody titers and better seroprotection rates over follow up as compared to controls who received single dose. Two immunogenicity studies from India in 143 and 505 children respectively have demonstrated > 95% seroconversion with single dose of the live attenuated vaccine with persistence of antibodies over follow up. Thirty month follow up data of 137 subjects in the 1st study demonstrates an immunogenicity of 87.8% with a GMT of 92.02mIU/mL at 30 months after a single dose of live attenuated Hepatitis A vaccine. In the multicentric study of 505 children the seroconversion ranged from 95% at 6 weeks to 98% at 6 months. The geometric mean titer (GMT) of anti-HAV antibody at 6 weeks and 6 months were 81.04 mIU/mL (95% CI-70.67-92.85) and 150.66 mIU/mL (95% CI-127.23-162.88), respectively following the vaccination. No horizontal transmission or serious adverse effects have been noted with the live vaccine. The live vaccine is not effective as post exposure prophylaxis. Some studies have reported inability of single dose of the live vaccine to protect against subclinical infection.

Recommendations for use

The hepatitis A vaccine may be offered to all healthy children with special emphasis in risk groups as enumerated below

- Patients with chronic liver disease
- Carriers of Hep B & Hep C
- Congenital or acquired immunodeficiency
- Transplant recipients



- Adolescents seronegative for HAV who are leaving home for residential schools
- Travelers to countries with high endemicity for Hepatitis A
- Household contacts of patients with acute Hep A virus infection within 10 days of onset of illness in the index case. It may not always be effective under such circumstances when the contact has had the same source of infection as the index patient.

If a decision to administer the vaccine is taken any of the licensed vaccines may be used as all have nearly similar efficacy and safety (exception post exposure prophylaxis, immunocompromised patients where only inactivated vaccines may be used). Two doses 6 months apart are recommended for all vaccines. The manufacturers of the live attenuated vaccine claim that a single dose is sufficient for long term protection. Since controlled studies from China demonstrate superiority of two dose schedule vs single dose schedule and since long term serologic data from India with single dose of the live vaccine is still not available, the IAPCOI recommends two doses of even the live attenuated vaccine. All Hep A vaccines are licensed for use in children aged 1 year or older. In its earlier publications the committee had recommended initiation of hepatitis A vaccination at the age of 18 months, so that interference with maternal antibodies is minimized. However new data suggests decline in the adult seropositivity rates especially in those belonging to the high socioeconomic status. Consequently babies may be born with no maternal antibodies. Immunogenicity studies also show that antibody titres achieved with vaccination at 12 months are comparable to those achieved at 18 mths- 2 years. In light of these facts, the committee now recommends initiating Hepatitis A vaccine at the age of 12 months. For catch up vaccination, pre vaccination screening for Hepatitis A antibody is recommended in children older than 10 years as at this age the estimated seropositive rates exceed 50%.

VARICELLA VACCINE

Background

Chickenpox caused by the varicella zoster virus (VZV) is usually a self limiting and benign illness in children. The incidence of complications is higher in neonates, adults, pregnant women and the immunocompromised. Varicella is a highly contagious disease and in the absence of a vaccination program it affects nearly every person by mid-adulthood in most populations. The epidemiology of varicella differs between temperate and tropical climates. In tropical climates, VZV seroprevalance reflects a higher mean age of infection and higher susceptibility among adults as compared to



temperate climates. There is little data on the health burden of varicella in developing countries. However, as in tropical climates, higher proportion of varicella cases may occur among adults, varicella morbidity and mortality may be higher than that described in developed countries. A seroprevalence study from India reported 15% seronegativity and susceptibility to varicella in adults.

Vaccine

Takahashi et al developed a live attenuated vaccine from the Oka strain in Japan in the early seventies. Varicella vaccines, in use today, are all derived from the original Oka strain but the virus contents may vary from one manufacturer to another. The recommended dose is 0.5 ml subcutaneously and the minimum infectious virus content should be 1000 Plaque Forming Units. It is available as a lyophilized vaccine, storage requirements vary with the brand of the vaccine and manufacturer instructions should be followed. It should be protected from light and needs to be used within 30 minutes of its reconstitution. The vaccine may be given with all other childhood vaccines. Vaccination induces both humoral and cellular immunity. Immunogenicity studies report overall seroprotection rates of 86% following single dose of the vaccine (immunogenicity reducing with increasing age) and persistence of protective antibodies for up to 10 years after vaccination. Pre licensure efficacy and post licensure effectiveness studies have shown the efficacy of a single dose of the vaccine to range from 70-90% against any disease and $\geq 95\%$ against combined moderate and severe disease for 7-10 years after vaccination. Administration of 2 doses three months/ 4-6 years apart improves seroprotection rates to 99% and results in higher GMT's by at least 10 fold. This translates to superior efficacy of 98.3% against any disease/ 100% against moderate/ severe disease and reduces incidence of breakthrough varicella as compared to single dose by 3.3 fold. Administration of the 2nd dose at 3 months following the first dose or at 5 years has similar efficacy. Vaccine failure with single dose is mainly primary as most cases of breakthrough disease happen within 5 years of vaccination and efficacy of single dose or two doses are similar at 10 years following vaccination. The observed vaccine failure after 1 dose of vaccine may be explained in most probability as that immunized children either do not develop humoral immunity to VZV at all or that there is an initial immune "burst" of immunity that is enough to generate a positive gpELISA result but is inadequate to generate a sustained memory T cell response leading to waning of immunity over a period of time.

Breakthrough varicella is defined as varicella developing more than 42 days after immunization and usually occurs 2-5 years following vaccination. Breakthrough disease in 70% of instances is typically mild, with <50 skin lesions, predominantly



maculopapular rather than vesicular rash, low or no fever, and shorter (4-6 days) duration of illness. It may go unnoticed /undiagnosed resulting in more opportunities to infect others due to failure to isolate these cases. Nevertheless, breakthrough varicella is contagious, may be severe, can result in outbreaks and has occasionally caused deaths in the immunocompromised. Some of the risk factors for vaccine failure and breakthrough disease include young age at vaccination (≤ 15 months), increasing time since vaccination, receipt of steroids within 3 months of breakthrough disease, initiation of vaccination in older children and adolescents and administration of vaccine within 28 days of MMR vaccine but not on the same day. Adverse reactions, documented carefully in prelicensure/ postlicensure studies, include local reactions such as pain, redness and swelling at vaccination site, injection site rash, fever and a systemic varicella like rash in around 5 %. Transmission of the vaccine virus from vaccinees to contacts is rare especially in the absence of a vaccine related rash in the vaccinees. However, vaccine recipients who develop a rash should avoid contact with persons without evidence of immunity who are at high risk for severe complications. Herpes zoster in vaccine recipients is known to occur due to both the vaccine virus and the wild virus; however the overall incidence of herpes zoster in vaccinated children was noted to be much lower than unvaccinated children in pre licensure trials. The side effect profile is similar with the 2 dose schedule. The vaccine is contraindicated during pregnancy, in those with clinically manifested HIV infection and in the immunocompromised (exceptions listed below). When used in adult females, pregnancy should be avoided for 3 months after vaccination.

Recommendations for use

The IAPCOI recommends offering the vaccine to all healthy children with no prior history of varicella with special emphasis in all children belonging to certain high risk groups as enumerated below:

- Children with humoral immunodeficiencies.
- Children with HIV infection but with CD4 counts 15% and above the age related cut off.
- Leukemia but in remission and off chemotherapy for at least 3-6 months.
- Children on long term salicylates. Salicylates should be avoided for at least 6 weeks after vaccination.
- Children likely to be on long term steroid therapy. The vaccine may be given at any time if the children are on low dose steroids / alternate day steroids but only 4 weeks after stopping steroids if the patients have received high dose steroids (≥ 2 mg/kg) for 14 days or more.



- In household contacts of immunocompromised children.
- Adolescents who have not had varicella in past and are known to be varicella IgG negative, especially if they are leaving home for studies in a residential school/college.
- Children with chronic lung/heart disease.
- Seronegative adolescents and adults if they are inmates of or working in the institutional set up e.g. school teachers, day care center workers, military personnel and health care professionals.
- For post-exposure prophylaxis in susceptible healthy non pregnant contacts preferably within 3 days of exposure (efficacy 90%) and potentially up to 5 days of exposure (efficacy 70%, against severe disease 100%).

The vaccines are licensed for age 12 months and above. However the risk of breakthrough varicella is lower if given 15 months onwards. Hence the IAPCOI recommends administration of varicella vaccine in children aged 15 months or older. After a single dose of varicella vaccine, approximately 15% of vaccines remain at risk of developing a breakthrough varicella disease. These varicella infections in immunized population may raise concern regarding vaccine efficacy and a misunderstanding by physicians or parents who may lose faith in vaccination. Because immunized children who experience breakthrough disease are coinfectd with both wild and vaccine strains of varicella virus, they may be at increased risk of zoster from the reactivated wild-type strain later in life, compared with vaccine recipients who do not experience breakthrough disease.

Two doses of varicella vaccine offer superior individual protection as compared to a single dose. The IAPCOI now recommends two doses of varicella vaccine for children of all age groups. For primary immunization, the first dose should be given at the age of 15 mths and the second dose at 4-6 years. For catch up vaccination, children below the age of 13 years should receive 2 doses 3 months apart and those aged 13 years or more should receive 2 doses at an interval of 4-8 weeks.

A live attenuated vaccine against herpes zoster is now licensed and available in the US but not in India.

Varicella Zoster Immunoglobulin (VZIG)

VZIG provided passive immunity against varicella and is indicated for post exposure prophylaxis in *susceptible* individuals with *significant* contact with varicella/ herpes zoster who are at high risk for severe disease. *Susceptible* is defined as



i) all unvaccinated children who do not have a clinical history of varicella in the past
ii) all unvaccinated adults who are seronegative for anti varicella IgG. Bone marrow transplant recipients are considered susceptible even if they had disease or received vaccinations prior to transplantation. A significant contact is defined as any face-to-face contact or stay within the same room for a period greater than 1 hour with a patient with infectious varicella (defined as 1-2 days before the rash till all lesions have crusted) or disseminated herpes zoster. Patients meeting these two criteria and who are at high risk of developing severe disease as enumerated below merit prophylaxis with VZIG.

- Neonates born to mothers who develop varicella 5 days before or 2 days after delivery. The risk of varicella related death in these infants as per older estimates is likely to be 30% but may be lower. Other full term healthy newborns are not at increased risk for complications and do not merit prophylaxis if exposed to varicella.
- All neonates born at less than 28 weeks of gestation/ with birth weight less than 1000 gms, exposed in the neonatal period.
- All preterm neonates born at more than 28 weeks of gestation and exposed to varicella only if their mothers are negative for anti varicella IgG, exposed to varicella.
- Pregnant women exposed to varicella.
- All immunocompromised children especially neoplastic disease, congenital or acquired immunodeficiency or those receiving immunosuppressive therapies. Patients who received IVIG @ 400 mg/kg in the past 3 weeks are deemed protected.

VZIG should be given as soon as possible but not later than 96 hours following exposure. VZIG reduces risk of disease and complications and duration of protection lasts for 3 weeks. The currently available VZIG is for intravenous use (Varitect) and is administered at a dose of 0.2 – 1ml/kg diluted in normal saline over 1 hour. The efficacy against death in cases where neonatal exposure has occurred is almost 100%. Side effects include allergic reactions and anaphylaxis. Since VZIG prolongs the incubation period, all exposed should be monitored for at least 28 weeks for disease manifestations. The cost of VZIG is prohibitive. If non affordable/ not available, other options with uncertain efficacy include IVIG @ 200 mg/kg or oral acyclovir @ 80 mg/kg/day beginning from the 7th day of exposure and given for 7-10 days.



ROTA VIRUS VACCINES

Background

Rotavirus is a major cause of diarrhea related morbidity and mortality in children worldwide. Rotavirus illness rates are similar in both the developed and developing world and in children of all socioeconomic status.

The disease is spread mostly through person-to-person contact rather than poor hygienic or sanitary conditions. Transmission is by fecal-oral spread, close person-to-person contact and by fomites. Rotaviruses are probably also transmitted by other modes such as respiratory droplets. The increasing role of rotavirus in the etiology of severe childhood diarrhea is likely attributable to the fact that this pathogen is often transmitted from person to person and is difficult to control through improvements in hygiene and sanitation, which have had greater impact on the prevention of diarrhea caused by bacterial and parasitic agents over the past 2 decades.

Rotavirus is an icosahedral RNA virus and seven serogroups have been described (A-G); Group A rotaviruses cause most human disease. The viral outer capsid is made of VP7 and VP4 proteins. The VP7 protein determines the G serotypes and the VP4 protein the P serotypes. Variability of genes coding for the VP7 and VP4 proteins is the basis for classification into genotypes. All G genotypes correspond with serotypes; there are more P genotypes than serotypes. Each rotavirus strain is designated by its G serotype number followed by P serotype number and then P genotype number in square brackets e.g. G1P1A[8]. In the studies by the 'Indian Rotavirus Strain Surveillance Network' from 2005 to 2007, rotavirus was found in approximately 39% of 4243 enrolled patients.

Rotavirus was markedly seasonal in northern temperate locations but was less seasonal in southern locations with a tropical climate. Rotavirus detection rates were greatest among children aged 6–23 months, and 13.3% of rotavirus infections involved children aged <6 months. The study also documents the early incidence of rotavirus disease in India. The most common types of strains were G2P[4] (25.7% of strains), G1P[8] (22.1%), and G9P[8] (8.5%); G12 strains were seen in combination with types P[4], P[6], and P[8] and together comprised 6.5% of strains. In addition to the common G and P serotypes, newer serotypes, mixed forms and untypable serotypes are frequently seen.



Disease burden

Global

Despite the success of oral rehydration solution (ORS) in reducing diarrheal mortality, the annual mortality of rotavirus disease has been estimated at more than 527,000 infant deaths. The majority of these deaths occur in the developing world, especially in the South Asian region and India alone accounts for over a lac of deaths in the underfive children per annum due to rotavirus disease. Rotavirus infections cause 111 million episodes of gastroenteritis for which healthcare is not sought, 25 million clinic visits and more than 2 million hospitalization.

Low and middle income countries

Approximately 99% of deaths occur in these countries and more than half of these are from just six countries of India, Nigeria, Congo, Ethiopia, China and Pakistan. Most of the deaths occur in malnourished infants living in socioeconomically disadvantaged regions in low income countries of Africa and Asia.

In India alone, rotavirus causes more than 120,000 deaths annually, 450,000 hospitalization, 5 million clinic visits and 25 million diarrheal episodes in under five children. The emerging middle income countries of Latin America have lower rotavirus mortality rates. 42% of hospitalized diarrhea is due to rotavirus in Latin America.

High Income Countries

While deaths due to rotavirus are less in the high income countries of North America, Europe, East Asia and Australia, the incidence of disease in young children is similar to that of low and middle income countries.

Health care associated rotavirus infections

31-87% of health care associated gastroenteritis is rotaviral out of which one third are severe. The incidence is 0.3 to 4.8 per 1000 hospital days.

Seasonality of rotavirus infections

In temperate countries, there is a marked seasonal pattern with peaks encompassing winter and spring months when the ambient temperature and humidity is low. Such a marked seasonality is not seen in the tropical countries but the activity is higher during winter months. When minimal seasonality occurs, rotaviruses circulate at a relatively higher level all year round, resulting in children exposed at an early age and experiencing severe illness.



Vaccine

Currently two live oral vaccines are licensed and marketed worldwide, Human monovalent live vaccine and Human Bovine pentavalent live vaccine. A vaccine based on Indian neonatal strains is undergoing clinical trials.

Human monovalent live vaccine, now available in India, is a monovalent attenuated human rotavirus vaccine derived from the human Rota virus strain 89-12 grown in vero cells and contains the G1P1 [8] strain administered orally in a 2-dose schedule to infants of approximately 2 and 4 months of age. Human Bovine pentavalent live vaccine is a Human Bovine reassortant vaccine and consists of five reassortants between the bovine WC3 strain and human G1, G2, G3, G4 and P1A [8] rotavirus strains grown in vero cells and administered orally in a three dose schedule at 2, 4 and 6 months. Both the available vaccines have shown excellent protective efficacy against severe rotavirus gastroenteritis in trials conducted mainly in Latin America, Europe, and the United States. Large phase 3 double blind placebo controlled trials with both vaccines in around 70,000 infants (11 countries mainly US, Finland for Human Bovine pentavalent live vaccine and Latin America and Finland for Human monovalent live vaccine) have shown 85-98% efficacy against severe rotavirus gastroenteritis and 42-59% efficacy against hospitalization due to diarrhea of any cause. Both vaccines have been demonstrated to be extremely safe with no increased risk of intussusception as compared to placebo. Similar high efficacy extends into the second year of follow up with the vaccine. Results from a recent trial with Human monovalent live vaccine in 10,000 infants in Hong Kong, Singapore and Taiwan showed efficacy and safety similar to that seen in earlier trials mentioned above. Both vaccines have been licensed and introduced into the national immunization program of several countries worldwide. Human Bovine pentavalent live vaccine has also been reported to reduce the number of hospitalizations and emergency room visits by 95% and to lower the number of office visits by 87%, up to two years post vaccination in Europe, due to serotypes G1 to G4. It was found that the vaccine prevented severe rotavirus gastroenteritis both in infants who received two doses or three of the vaccine with vaccinated children being 61 percent less likely to develop severe rotavirus infection.

Rotavirus vaccines' efficacy in developing countries

In Malawi, the effectiveness of Human monovalent live vaccine was 49 percent, compared to about 77 percent in South Africa. This study showed that a rotavirus vaccine significantly reduces the episodes of severe rotavirus gastroenteritis in African children during the first year of life. The overall efficacy of the vaccine was lower



than that observed in European studies and Latin American studies and possible reasons include poor nutritional status, co-infections with other enteric pathogens, interference by breastfeeding due to presence of high levels of antirotavirus neutralizing antibodies in breastmilk, and interference by maternal antibody or by coadministration of the oral poliovirus vaccine, which may reduce rotavirus antibody levels. Herd immunity has been shown to be induced by rotavirus vaccines (as an indirect effect) by reducing the exposure of unvaccinated persons to the organism. Thus, introduction of the vaccine into countries is likely to have a greater effect than that predicted on the basis of the efficacy trials.

Human Bovine pentavalent live vaccine also was reported to reduce the number of cases of severe rotavirus gastroenteritis by nearly half (48 percent) in infants evaluated in developing countries in Asia (Bangladesh and Vietnam) and by 39 percent in infants evaluated in developing countries in Africa (Ghana, Kenya, and Mali) through nearly two years of follow-up. This is the first study demonstrating efficacy for any rotavirus vaccine in developing countries in Asia. If only homotypic protection is induced 22.1% strains would be covered by Human Monovalent vaccine and 47.9% by Human Bovine pentavalent live vaccine. However reports from across the globe like Europe, Latin America, Asia and Africa indicate cross protection across genotypes with use of human monovalent vaccine.

In one of the recent studies conducted in India, the seroconversion rate was reported to be comparable with the results obtained from other studies done in the developing countries (*i.e.* Latin America, South Africa, Bangladesh). Studies show no interference between rotavirus vaccines and other childhood vaccines including IPV, pneumococcal, Hib, DTaP and Hep B. Data is insufficient for pertussis immunity. Immunogenicity studies about simultaneous administration of rotavirus vaccines with OPV are available for Human monovalent live vaccine and Human Bovine pentavalent live vaccine, which show no reduction in immunogenicity against polio and no significant reduction in immunogenicity against rotavirus. Additionally, studies in South Africa and Bangladesh show no reduction in efficacy of Rotavirus vaccines against severe rotavirus gastroenteritis when co administered with OPV.

Thus the rotavirus vaccines which had shown very good efficacy in the developed nations have now been documented to have acceptable efficacy in the low, low middle and high middle income countries. The number of episodes of diarrhea prevented per 100 person years is higher in these low and middle income countries due to higher disease burden as compared to that in the high income countries.



Recommendations for use

Based on their review of the evidence, Strategic Advisory Group of Experts (SAGE) recommends the inclusion of rotavirus vaccination of infants into all national immunization programmes. In countries where diarrheal deaths account for $\geq 10\%$ of mortality among children aged < 5 years, the introduction of the vaccine is strongly recommended. SAGE concluded that efficacy and effectiveness data from a rotavirus vaccine study performed in a population from one of the strata can be extrapolated for use of the same vaccine in populations in the same stratum. The use of specific interventions against rotavirus, such as newly available vaccines, would help prevent much of this large disease and economic burden.

The IAPCOI acknowledges the morbidity and mortality burden of rotavirus and need for a rotavirus vaccine. Such a vaccine would be most needed in the national immunization program as the disease consequences are the most serious in the underprivileged. Given the minimal impact that water and sanitation measures have had on the burden of rotavirus in developing areas, there is wide agreement that effective vaccination represents the most promising prevention strategy against the disease. Though the efficacy of rotavirus vaccines in developing countries was not as high as seen in Latin America, European or US study, it was significant and quite encouraging as overall 5 episodes/100 infant-year of severe rotavirus disease needing hospitalization were prevented by vaccine in the African study using Human monovalent live vaccine, as compared to estimated 1 episode/100 infants-year prevented in most of the western trials. Similarly Human Bovine pentavalent live vaccine in Bangladesh and Vietnam prevented 3 episodes/100 infants-year and 2 episodes/100 infants-year in African study. This is due to higher burden of disease in community in developing countries as compared to developed world. Most of the high disease burden countries including India are eligible for GAVI support to include such vaccines in NIP with nominal cost sharing of few US cents per dose by these countries.

Dose and schedule

Vaccination should be strictly as per schedule discussed below, as there is a potentially higher risk of intussusception if vaccines are given to older infants. Vaccination should be avoided if age of the infant is uncertain. There are no restrictions on the infant's consumption of food or liquid, including breast-milk, either before or after vaccination. Vaccines may be administered during minor illnesses. Though there is limited evidence on safety and efficacy of rotavirus vaccines in preterm infants, vaccination should be considered for these infants if they are clinically stable and at least



6 weeks of age as preterms are susceptible to severe rotavirus gastroenteritis. Vaccination should be avoided in those with history of hypersensitivity to any of the vaccine components or previous vaccine dose. Vaccination should be postponed in infants with acute gastroenteritis as it might compromise efficacy of the vaccine. Immunocompromised infants are susceptible to severe and prolonged rotavirus gastroenteritis but safety and efficacy of either of the two vaccines in such patients is unknown. Risks versus benefits of vaccination should be considered while considering vaccination for infants with chronic gastrointestinal disease, gut malformations, previous intussusception and immunocompromised infants.

Human monovalent live vaccine

Human monovalent live rotavirus vaccine contains one strain of live attenuated human strain 89-12 (type G1P1A (8)) rotavirus. It is provided as a lyophilized powder that is reconstituted before administration. A fully liquid formulation is available in the international market and will be available in India in near future. Each 1- ml dose of reconstituted vaccine contains at least 10^6 median culture infective units of virus. The vaccine contains amino acids, dextran, Dulbecco's modified Eagle medium, sorbitol and sucrose. The diluent contains calcium carbonate, sterile water and xanthan. The vaccine contains no preservatives of thiomersal.

The vaccine and the diluents should be stored at 2 to 8°C and must not be frozen. The vaccine should be administered promptly after reconstitution as 1 ml orally. The first dose can already be administered at the age of 6 weeks and should be given no later than at the age of 12 weeks. The interval between the 2 doses should be at least 4 weeks.

Human Bovine pentavalent live vaccine

Human Bovine pentavalent live vaccine contains five reassortant rotaviruses developed from human and bovine parent rota viruses. Each 2-ml vial of vaccine contains approximately 2×10^6 infectious units of each of the five reassortant strains. The vaccine viruses are suspended in the buffer solution that contains sucrose, sodium citrate, sodium phosphated monobasic monohydrate, sodium hydroxide, polysorbate 80, and tissue culture media. Trace amounts of fetal bovine serum might be present. The vaccine contains no preservatives of thiomersal.

The vaccine is available as a liquid virus mixed with buffer and no reconstitution is needed. It should be stored at 2 to 8°C. The recommended schedule is 3 oral doses at ages 2, 4 and 6 months. The first dose should be administered between ages 6–12 weeks and subsequent doses at intervals of 4–8 weeks. The manufacturer does



not recommend re administration of vaccine if a dose is spit out or regurgitated. Regardless of which vaccine is used, the first dose should be given between six weeks and 14 weeks six days of age. Immunization should not be initiated in infants 15 weeks or older because of insufficient safety data for vaccines use in older children. All the doses of either of the vaccines should be completed within 32 weeks of age. Both vaccines should not be frozen. Rotavirus vaccine must not be injected. Programmatic errors have been reported. Large vaccine volume requires full insertion of vial tip into infant's mouth. Contact with infant's mouth contaminates the vial and complicates development of multidose vials.

Special situations

Regurgitation of vaccine

Readministration need not be done to an infant who regurgitates, spits out, or vomits during or after administration of vaccine though the manufacturers of Human monovalent live vaccine recommend that the dose may be repeated at the same visit, if the infant spits out or regurgitates the entire vaccine dose. The infant should receive the remaining recommended doses of rotavirus vaccine following the routine schedule (with a 4-week minimum interval between doses).

Interchangeability of Rotavirus Vaccines

Ideally, the rotavirus vaccine series should be completed with the same product. However, vaccination should not be deferred because the product used for previous doses is unavailable. In such cases, the series should be continued with the product that is available. If any dose in the series was human bovine pentavalent vaccine, or if the product is unknown for any dose in the series, a total of three doses should be administered.

Missed opportunity

It is not necessary to restart the series or add doses because of a prolonged interval between doses with either of the vaccines.

Contraindications

Rotavirus vaccine should not be administered to infants who have a history of a severe allergic reaction (eg, anaphylaxis) after a previous dose of rotavirus vaccine or to a vaccine component. Latex rubber is contained in the currently available human monovalent vaccine oral applicator, so infants with a severe (anaphylactic) allergy to latex should not receive human monovalent vaccine. The human bovine pentavalent vaccine dosing tube is latex-free.



FDA controversy

In March 2010, the FDA recommended that clinicians temporarily stop using Human monovalent live vaccine after it discovered that the vaccine contained DNA sequences from a virus found in pigs called porcine circovirus 1 (PCV1). The virus is not known to cause disease in either pigs or humans, according to the FDA. The FDA later learned that another rotavirus vaccine on the market, Human Bovine pentavalent live vaccine, also contains DNA fragments of both PCV1 and a related virus called PCV2. Though the latter virus can cause a wasting disease in pigs, there is no evidence it causes illness in humans, according to the FDA.

But in May 2010, FDA revoked the recommendation and voiced support for the continued use of rotavirus vaccine, arguing that the vaccine's benefits outweigh the theoretical risks. FDA also commented that the loss of a viable rota virus vaccine from the community will be devastating.

RABIES VACCINES

Background

Rabies is transmitted by bites, scratches, licks on mucous membrane or non intact skin by a rabid animal. Infrequently it may occur due to organ (including cornea) transplantation from a rabies victim. The incubation period usually averages 4-6 weeks but can range from five days to 6 years. The disease is uniformly fatal and only 6 survivors have been reported in world literature. It is estimated that 20,000 people die of rabies in India every year (50% of the world disease burden) and in 95% the dog is the source. Rabies is endemic in all states of India except Andaman, Nicobar and Lakshwadeep island. Vaccination is the only effective modality to reduce the burden of the disease.

Vaccine

The nerve tissue vaccines are no longer available due to poor efficacy and life threatening adverse effect of neuroparalytic reactions. The currently available vaccines are the modern tissue culture vaccines (MTCV) and include Purified Chick Embryo Cell (PCEC) vaccine, Human Diploid Cell Vaccine (HDCV), Purified Vero Cell Vaccine (PVRV), Purified Duck Embryo Vaccine (PDEV). The vaccines are available in lyophilized form with sterile water as diluent, are stable for 3 years at 2 to 8°C and should be used within 6 hours of reconstitution. All tissue culture vaccines have almost equal efficacy and any one of these can be used. These vaccines induce protective antibodies in more than 99% of vaccinees following pre/ post exposure



prophylaxis. The main adverse effects are local pain, swelling and redness and less commonly fever, headache, dizziness and gastrointestinal side effects. Systemic hypersensitivity reactions in vaccinees have been reported with HDCV particularly following booster injections but not with PCEC/ PVRV. Intradermal vaccination may cause more local irritation as compared to the intramuscular route. Along with proper wound care and rabies immunoglobulin (RIG) post exposure prophylaxis is effective in preventing 100% of rabies cases. Failures occur due to delay in initiation or non use of RIG when indicated.

Rabies immunoglobulin (RIG)

RIG contains specific anti rabies antibodies that neutralize the rabies virus and provide passive protection till active immunity is generated. There are 2 types of RIG: (1) Human rabies immunoglobulin (HRIG – dose is 20 U/kg body weight, maximum dose 1500 IU) and (2) Equine rabies immunoglobulin (ERIG – dose is 40 U/kg body weight, maximum dose 3000 IU). HRIG is preferred, but if not available/ unaffordable ERIG may be used. Most of the new ERIG preparations are potent, safe, highly purified and less expensive as compared to HRIG but do carry a small risk of anaphylaxis. As per latest recommendations from WHO skin testing prior to ERIG administration is not recommended as skin tests do not accurately predict anaphylaxis risk and ERIG should be given whatever the result of the test.

RIG is indicated in all cases of category 3 wounds where it should be infiltrated thoroughly into and around the wound. The remaining part if any is to be injected IM into the deltoid region or anterolateral aspect of thigh away from the site of vaccine administration to avoid vaccine neutralization. In case RIG dose (quantity) is insufficient for adequate infiltration of extensive or multiple wound, it may be diluted with equal volume of normal saline so that all the wounds can be thoroughly infiltrated. Adverse reactions include tenderness/stiffness at the injection site, low grade fever; sensitization may occur after repeated injections.

If RIG could not be given when antirabies vaccination was began, it should be administered as early as possible but no later than the seventh day after the first dose of vaccine was given. From the eight day onwards, RIG is not indicated since an antibody response to the vaccine is presumed to have occurred. RIG is also not indicated in individuals who have received pre exposure prophylaxis/ post exposure prophylaxis in the past.

Post exposure prophylaxis (PEP)

Post exposure prophylaxis is a medical emergency and is indicated following a



significant contact (discussed in detail below) with any warm blooded animal. These include dogs, cats, cows, buffaloes, sheeps, goats, pigs, donkeys, horses, camels, foxes, jackals, monkeys, mongoose, bears and others. In case of bites by pet animals, PEP may be deferred only if the pet at the origin of exposure is more than a year old and has a vaccination certificate indicating that it has received at least 2 doses of a potent vaccine, the first not earlier than 3 months of age and the second within 6 to 12 months of the first dose and in the past 1 year. If vaccination is deferred, the pet should be observed for 10 days; if the dog shows any sign of illness during the observation period, the patient should receive full rabies post-exposure prophylaxis urgently. Rabies due to rodent bites has not been reported in India till date and post exposure prophylaxis is not normally recommended for these bites. Post exposure prophylaxis should be initiated as soon as possible and should not be delayed till results of lab tests or animal observation is available. Infancy, pregnancy and lactation are never contraindications for PEP. Persons presenting several days/ months/ years after the bite should be managed in a similar manner as a person who has been bitten recently (with RIG if indicated) as rabies may have a long incubation period and the window of opportunity for prevention remains.

Rabies exposure may be classified as per WHO into three categories.

Table 2: Categories of rabies exposure

Category	Description	Recommended treatment
I	Touching or feeding of animals, licks on intact skin	None if reliable case history is available
II	Nibbling of uncovered skin, minor scratches or abrasions without bleeding, licks on broken skin	Administer vaccine
III	Single or multiple transdermal bites or scratches, contamination of mucous membrane with saliva (<i>i.e.</i> , licks), or exposure to bats	Administer RIG and vaccine immediately

The first step is thorough cleansing of the wound with soap and flushing under running water for 10 minutes. This should be followed by irrigation with a virucidal agent such as 70% alcohol or povidone iodine. Antimicrobials and tetanus toxoid should be given if indicated. RIG should be infiltrated in and around the wound in category 3 bites as discussed earlier. Any suturing of wound should be avoided. When suturing is unavoidable for purpose of hemostasis, it must be ensured that RIG has been infiltrated in the wound prior to suturing. All category 2 and 3 bites merit rabies vaccine. Any of the MTCV may be used intramuscularly in anterolateral thigh or the deltoid. Rabies vaccine should never be injected in the gluteal region. The dose is same at all ages and is 1 ml IM for HDCV, PCEV, PDEV and 0.5 ml for PVRV. The standard



schedule (Essen protocol) is five doses on days 0, 3, 7, 14 and 30, with day '0' being the day of commencement of vaccination. A sixth dose on day 90 is optional and may be offered to patients with severe debility or those who are immunosuppressed. Interchange of vaccines is permitted only in special circumstances but should not be done routinely. If RIG is not available then two doses of the vaccine may be given on day 0 (this is however not a substitute for RIG). If the animal remains healthy over a 10 day observation period, further vaccination may be discontinued. It is however desirable to administer one more dose on day 28 in order to convert to the pre exposure prophylaxis schedule.

Several other schedules of rabies vaccination have been proposed. These include the 2-1-1 intramuscular schedule (Zagreb schedule) – two IM doses on day 1, one IM dose on day 7 and one IM dose on day 21. This schedule is however not approved for use in India. Intradermal vaccination is cost effective alternative to intramuscular vaccination as the dose required is only 0.1 ml. The intradermal schedules have been used successfully in Thailand, Philippines and Sri Lanka. The unit dose of 0.1ml for ID should have at least 0.25 units. Based on the recommendations of the expert group as well as WHO, the Drug Controller General of India (DCGI) has recently decided to allow ID route administration of tissue culture based anti rabies vaccine for post exposure prophylaxis in a phased manner in certain government antirabies centres. The schedules permitted in the 1st phase include the Thai Red Cross Regimen (2-2-2-0-1-1, two intradermal doses on the deltoid on days 0, 3, 7 and 1 dose on day 30 and 90) and the Updated Thai Red Cross Regimen (2-2-2-0-2-0, two doses on days 0, 3, 7 and 30). Another schedule not currently approved by DCGI is the 8 site regimen (8-0-4-0-1-1, 8 intradermal doses on each upper arm, each lateral lower abdominal quadrant, each thighs and each suprascapular regions on day 0, 4 doses on day 7 on each thigh and upper arm and 1 dose on day 30 & 90 on upper arm). Vaccines currently recommended for ID route administration in India are purified vero cell rabies vaccine and purified chick embryo cell vaccine. The intradermal route should not be used for immunocompromised patients and those on chloroquine therapy.

The criteria for selection of Antirabies centre for ID use are:

- a) Attendance of minimum 50 patients per day for post exposure prophylaxis
- b) Has adequately trained staff to give ID inoculation
- c) Can maintain cold chain and ensure adequate supply of disposable syringes and needles.

Intradermal administration is not recommended in individual practice. Also it does not make economic sense to practice it for individual cases.



Pre-exposure prophylaxis

Pre exposure prophylaxis is particularly important where the exposure may be unrecognized (lab) or unreported (children). Pre exposure prophylaxis eliminates need for RIG (awareness, cost and availability of RIG is a problem). It also reduces post exposure prophylaxis to two doses only. Pre-exposure prophylaxis is recommended for certain high risk groups enumerated below.

- Continuous exposure: Lab personnel involved with rabies research and production of rabies biologics. Source and exposure may be unrecognized.
- Frequent exposure: Veterinarians, laboratory personnel involved with rabies diagnosis, medical and paramedical staff treating rabies patients, dog catchers, zoo keepers, forest staff.
- Infrequent exposure
 - Postmen, policemen, courier boys
 - Travelers to rabies endemic countries particularly those who intend to backpack/ trek.
 - Most Indian children are at risk for rabies. Therefore IAPCOI recommends offering pre exposure prophylaxis to children at high risk of rabies exposure after discussion with parents.

Any of the tissue culture vaccines can be given for this purpose. Three doses are given intramuscularly in deltoid/ anterolateral thigh on days 0, 7 and 28 (day 21 may be used if time is limited but day 28 preferred). The intradermal schedule of 0.1 ml of any vaccine by the intradermal route on day 0, 7 and 21/28 is currently not approved by DCGI. Routine assessment of anti rabies antibody titer after completion of vaccination is not recommended unless the person is immunocompromised. It is desirable to monitor antibody titers every 6 months in those with continuous exposure and every year in those with frequent exposure. A booster is recommended if antibody levels fall below 0.5 IU/ml. When serologic testing is not available booster vaccination every 5 years is an acceptable alternative. For re exposure at any point of time after completed (and documented) pre or post exposure prophylaxis, two doses are given on days 0 and 3. RIG should not be used as it may inhibit the relative strength or rapidity of an expected anamnestic response.

INFLUENZA VACCINES

Background

The Influenza virus, an orthomyxovirus, is a single stranded RNA virus. It is capable of causing disease in humans, birds and animals. There are three types of Influenza



viruses A, B & C. The subtypes of type A Influenza virus is determined by haemagglutinin and neuraminidase. The Influenza type A causes moderate to severe illness in all age groups in humans and other animals. The illness caused by type B is usually a milder disease in humans only and primarily affects children. The illness by type C Influenza virus is rarely reported in humans and it does not cause epidemics. The nomenclature of Influenza virus is in order of virus type, geographic origin, strain no, year of isolation and virus subtype. Therefore the nomenclature of the current pandemic Influenza virus is A/California/7/2009/H1N1. Influenza virus is characterized by frequent mutations – antigenic drifts (minor antigenic change, both A & B) and antigenic shifts (major antigenic change, only A). The current human pandemic A/H1N1 is an example of antigenic shift. Vaccines elicit a relatively strain specific humoral response, have reduced efficacy against antigenically drifted viruses and are ineffective against unrelated strains. It is of utmost importance, therefore that vaccine should incorporate the current strain prevalent during that time. The Influenza vaccine is therefore unique as the precise composition has to be changed periodically in anticipation of the prevalent Influenza strain expected to circulate in a given year. The WHO reviews data obtained from its chain of reference laboratories from world over (and also from India) and recommends vaccine composition on a biannual basis in September for the Southern Hemisphere and in February for the Northern Hemisphere. This gives the vaccine manufacturer's 4-6 months to manufacture the vaccine in time for the flu season for the respective hemisphere.

The 20th century pandemics were in 1918 (H1N1), 1957 (H2N2) and 1968 (H3N2). The new virus tends to replace endemic/seasonal Influenza viruses and post-pandemic, it continues to circulate as the new seasonal virus. Thereafter it would exhibit antigenic drift; thus more than one drifted variant may co-circulate. H1N1 virus circulated globally from 1918 till 1957 and was replaced by H2N2 virus; in 1968, H3N2 virus replaced H2N2. The seasonal H3N2 viruses that continue to be isolated globally are descendants of the 1968 pandemic virus. In 1977 a descendant of the 1918 pandemic H1N1 virus reappeared in northern hemisphere; it might have been accidentally released from a laboratory. It slowly established circulation globally; subsequently endemic/seasonal viruses in both hemispheres are H3N2 and H1N1.

The novel Influenza A (H1N1) 2009 virus was first identified by US CDC on 17th April, 2009 in samples from two Californian children. The cause of outbreaks of respiratory illness in Mexico during March and April, 2009 was also the same virus. This virus was transmitted in communities across North America within few weeks and was identified in many parts of the world by May, 2009. On June 11, 2009, the World Health Organization (WHO) declared a worldwide Influenza pandemic, indicating community level transmission of the novel Influenza A (H1N1) virus in several parts



of the world. The transmission of novel Influenza A (H1N1) virus continued in both the Northern & Southern Hemispheres. As of August 2010, 18000 people had died globally due to the pandemic flu. The illness rates were highest in children and young adults (20-40% of the population), the hospitalization rates highest in children below the age of 1. The case fatality rates varied tremendously and were estimated to be between 0.0004- 1.5% (0.05% in US, 0.025% in UK, lowest in children). The risk factors for severe disease and death were pregnancy, morbid obesity, asthma, children below 2; however 25% -30% of those who died had no underlying risk factor. Apart from very rapid transmissibility and high attack rates, the affection of predominantly of children and young adults, sparing of the elderly and deaths in those with no risk factors differentiated pandemic flu from seasonal flu.

As per the data published by office of the Director, Emergency Medical Relief, Directorate General of Health Services, Government of India, New Delhi, till 12th December 2010, of the samples from 2,01,804 persons who have been tested for Influenza A H1N1 46065 (23%) of them have been found positive with 2727 deaths. A study from the National Institute of Virology demonstrated that in India, the severity of pandemic flu was higher than seasonal flu (CFR of 0.89% vs 0.13%) with highest attack rates in those aged below 30 and deaths in those aged 20-50 years. Though WHO has declared that pandemic is over, the virus continues to circulate and causes waves of infections leading to hospitalization and complications in different parts of India even in the second half of 2010. The behavior of the H1N1 (2009) virus as a seasonal virus cannot be reliably predicted. Once the pandemic settles down, the virus is most likely to become the predominant agent of endemic/seasonal influenza. Antigenic changes in seasonal A/H1N1 & H3N2 occur by mutations and genetic recombination between co-circulating viruses of the same subtype. A similar phenomenon is likely to occur with 2009 pandemic Influenza A (H1N1) also, resulting in variants that escape natural or vaccine-induced immunity, to become future seasonal influenza. Reassortment with co-circulating viruses of a different subtype may also occur; the fear is that viruses with greater pathogenicity and efficient transmissibility may thus emerge. Of greatest concern is the possibility of re-assortment with H5N1 in domestic poultry/ducks. Continuous surveillance of Influenza cases, particularly severe or atypical, is essential for the early detection of such variants.



Vaccines

Two types of Influenza vaccines are available –inactivated and live attenuated

Inactivated Influenza Vaccines

- The inactivated Influenza vaccines are produced from virus growth in embryonated hen's eggs and are of three types: whole virus, split product, subunit surface – antigen formulations. Whole virus vaccines are associated with increased adverse reactions, especially in children and are currently not used. Most Influenza vaccines are split-product vaccines, produced from detergent treated, highly purified Influenza virus, or surface antigen vaccines containing purified hemagglutinin and neuraminidase.
- Vaccines are trivalent or monovalent. Trivalent vaccines contain 15 µg of each of WHO recommended two influenza A strains (H1N1 & H3N2) and one influenza B strain. Monovalent vaccines contain 15 µg of novel H1N1 2009 strain. They should be stored at 2 to 8°C and never be frozen. The trivalent vaccines are licensed for use in children aged 6 months and older. The 2010-11 seasonal trivalent vaccines contain A/California/7/2009 (H1N1)-like, A/Perth/16/ 2009 (H3N2)-like and B/Brisbane/60/2008 - like antigens. The A/California/7/2009 (H1N1) – like antigen is derived from a pandemic 2009 influenza A (H1N1) virus. The A/Perth/16/2009 (H3N2) – like antigen is different from the A/Brisbane/10/ 2007(H3N2) – like antigen recommended for the 2009-10 northern hemisphere seasonal influenza vaccine. The Influenza B vaccine strain is same B/Brisbane/ 16/2008 and is not changed compared with the 2009-10 northern hemisphere seasonal Influenza vaccine. Apart from this trivalent vaccine, inactivated monovalent novel H1N1 vaccines were widely used in 2009 and 2010 globally and in India. The dosage schedule is as under.

Dosage & Schedule

Age	6-35 months	3-8 years	From 9 years of age
Dose	0.25 ml	0.5 ml	0.5 ml
No. of doses	1 or 2*	1 or 2*	1

* For children who have not previously been vaccinated a second dose should be given after an interval of at least 4 weeks.

Studies demonstrate that provided there is good antigenic match, the vaccines provide 70-90% efficacy against laboratory confirmed disease in healthy adults, 25-40% reduction in hospitalization in elderly non-institutionalized patients and 40-75% reduction in mortality in Influenza seasons. The ability of a flu vaccine to protect a



person depends on the age and health status of the person getting the vaccine, and the similarity or “match” between the viruses or virus in the vaccine and those in circulation.

Side effects are mild and include fever rash and injection site reactions. The link between currently available Influenza vaccines and Gullian Barré Syndrome (GBS) is equivocal and if present is less than 1 case per million people vaccinated. However, the vaccine should preferably be avoided in patients with history of GBS and who are not at high risk of severe Influenza related complications. The vaccine should be administered with caution in patients with history of severe egg allergy only if expected benefits outweigh risks.

Live Attenuated Influenza Vaccines (LAIV)

The live attenuated Influenza vaccine (LAIV) has been approved by US FDA for use in healthy non-pregnant individuals 2-49 years of age. The vaccine is composed of the live attenuated reassortment of the three WHO recommended strains and is administered as a nasal spray. It is stored at 2 to 8°C. This vaccine has superior efficacy as compared to the inactivated vaccines in young healthy children especially below 5 years of age. However, unlike the inactivated vaccinee it has not been licensed for use in individuals with any chronic disease, pregnant women and children aged less than 2 years due to lack of efficacy and safety studies. This vaccine should also be avoided in children less than 5 years of age with history of reactive airway disease, those with history of hypersensitivity to eggs or vaccines components and those with history of GBS in the past. Side effects include mild fever, runny nose and sore throat. The concurrent use of the vaccine with antiviral has not been evaluated. The vaccine should not be administered for 48 hours after the cessation of antiviral therapy. Antiviral agents should not be administered until two weeks after administration of this vaccine unless medically indicated. If anti viral agents and the LAIV are administered concomitantly, revaccination should be considered. Data are not available on co-administration of LAIV with other vaccines. Nasal discomfort, sneezing, stuffy nose, running nose, loss of smell, red eyes and lacrimation are local reactions. Systemic reactions following LAIV are also known such as headache, chills, fatigue, sore throat, myalgia, arthralgia, irritability, loss of appetite, etc. Most of the reactions are mild and resolve within 2 to 3 days without any sequelae. This vaccine is currently not available in India.

Live Attenuated Monovalent Novel H1N1 2009

Influenza vaccine (Human, live attenuated) Pandemic (H1N1), freeze dried is a live monovalent vaccine for administration by intranasal spray. The Influenza vaccine



contains Influenza virus cultivated on embryonated eggs. Each single dose (0.5 ml) contains A/17/California/2009/38 $> 10^7$ EID₅₀. It is available in form of one dose vial (with 0.5 ml diluent) and five dose vial (with 2.5 ml diluent). The contraindications are same as those of the trivalent attenuated vaccine. The lyophilized vaccine is reconstituted using 2.5 ml of sterile water for inhalation with the vaccine, using the supplied syringe and vial adapter. A dose of 0.5 ml is administered as 0.25 ml per nostril using 0.5 ml or 1 ml syringe and spray device. The spray device creates a fine spray that primarily deposits the vaccine in the nose and pharynx.

Recommendations for use

Whom to give?

In the industrialized world morbidity, absenteeism, economic burden and mortality due to Influenza is well quantified and significant. Hence, the recommendations for use of Influenza vaccine in the western world have been fairly liberal. Following the 2009 novel H1N1 pandemic, ACIP of USA recommended universal Influenza vaccination for the entire population above the age of 6 months.

Till the 2009 pandemic, data on morbidity and mortality of Influenza in India was very limited. A handful of studies showed that Influenza contributed to 5-10% of all ARI's. A single incidence study reported the incidence of Influenza URI to be 10/ 100 child years and that of LRI to be only 0.4/100 child years. Hence in its previous recommendations the IAPCOI advised use of the Influenza vaccine only in children with risk factors for severe disease.

However following the 2009 pandemic the situation has changed. There is much more morbidity and mortality data available now (as mentioned earlier) which shows that at least in India the virulence of the pandemic virus was higher than the seasonal virus (unlike the developed world) and also that young healthy children and adults were disproportionately affected. Hence at such times more liberal use of the vaccine was/is justified, which is also the government policy.

In the current scenario wherein we are entering the post pandemic phase, the IAPCOI recommends using the Influenza vaccine in all children with risk factors as mentioned in table 1 and also wherein the vaccine is desired/ requested by parents (discussing with them the benefits and limitations of the vaccine).



Table 1: *At risk individuals*

- Congenital or acquired immunodeficiency
- Chronic cardiac, pulmonary, hematologic, renal, liver disease and diabetes mellitus
- Children on long term aspirin therapy
- Any neurologic disease that might cause respiratory compromise or impair ability to handle secretions
- Asthma requiring oral steroids

Which vaccine to give?

Trivalent or monovalent

At this time since a substantial proportion of Influenza is due to H3N2 and Influenza B the trivalent vaccines are unequivocally preferred over the monovalent vaccines.

Inactivated Vs live

In those who with underlying risk factors only the inactivated vaccines should be used. In healthy individuals aged 2 years to 49 years either the inactivated or live attenuated vaccines may be used. In India, since the trivalent attenuated vaccine is currently not available the trivalent inactivated vaccine is preferred to the monovalent attenuated vaccine

When to give?

The Influenza vaccines are given before the peak Influenza season. However unlike temperate countries where the peak Influenza season is in winters, in tropical countries like India the illness occurs all year round. The vaccine should therefore be given as soon as the new vaccine is released in the market or at the time of presentation to the health care provider. Data from WHO global Influenza surveillance network in India shows a trend of Influenza peaks in the month of June to September which is related with the monsoon across major parts of the country. It is worth noting that these trends correlate closely with the southern hemisphere Influenza virus circulation and vaccine availability (March-April). The vaccine that is currently available in India is based on the northern hemisphere influenza circulation and it arrives a bit late in the monsoon (August -September) .

How to give?

When the vaccine is used first time, in children 6 months to less than 9 years of age the vaccines (TIV/LAIV) are given as 2 doses, 1 month apart. Only one dose is sufficient at 9 years and above. Revaccination is recommended with a single annual



dose irrespective of age and even if the vaccine antigenic composition does not change.

Pre-pandemic Influenza Vaccine

A pre-pandemic vaccine is produced in advance of a pandemic. Such a vaccine based on the currently circulating avian H5N1 influenza virus likely to cause a pandemic and has the ability to raise immune protection against potential drift H5N1 strains. Pre-pandemic vaccines therefore might play a critical role in pandemic preparedness planning, with experts citing that immunization with such stockpiled vaccines in advance or at the onset of a pandemic is the most effective strategy for protecting entire populations. Recently European Commission has granted license for H5N1 adjuvanted pre-pandemic vaccine for all 27 EU member states.

CHOLERA VACCINES

Background

Cholera is an important public health problem in developing countries with poor sanitation and hygiene as well as in displaced populations. The predominant strain is *V. cholerae* O1 (classical and El tor biotype); while *V. cholerae* O139 is an emerging strain. As per WHO estimates, the annual burden of cholera is estimated to be 3-5 million cases with 100,000-130,000 deaths. Cholera is endemic in India where only 25% of the population has access to piped water supply and sanitation. A recent meta analysis reports 22,000 cases a year in India (probably a gross underestimate) of which most is *V. cholerae* O1 El tor biotype. Although cases have been reported from almost all states and Union territories the maximum burden is in West Bengal, Orissa, Chattisgarh, Andaman and Nicobar island and Assam. In a longitudinal community base surveillance study in urban slums of Kolkata, the overall incidence was around 1.6/1000 person years with the highest incidence seen in children below the age of 2 yrs (8.6/ 1000 py) followed 6.2 in the age group 2-5 years and 1.2 in those aged above 5 years.

Vaccines

The parenteral killed vaccine which had a 3 month efficacy of 45% is no longer recommended. The WC-rBS vaccine available internationally as Dukoral and widely used in travelers is a vaccine comprising of killed *V. cholerae* O1 with recombinant b subunit of cholera toxoid. It is an oral vaccine (with buffer), has to be stored at 2-8°C and is administered as 2 doses 1 week apart. It is licensed for those aged 2 years and above. The efficacy of the vaccine is 85-90% for all ages for upto 6 months after



vaccination but drops to 60% at 2 years after vaccination. It has been demonstrated to have a herd effect. The main limitations to wide spread use of the vaccine is the high cost.

The variant WC-rBS vaccine first developed and licensed in Vietnam comprises only of killed whole cell *V. cholerae* O1 (classical and El Tor) and *V. cholerae* O139. There is no recombinant beta subunit toxoid. This inexpensive oral vaccine without buffer and cold chain requirements administered as 2 doses 2 weeks apart has been demonstrated to have 50% efficacy for upto 3 years after vaccination. This vaccine is now manufactured and licensed in India for children above the age of 1 year. A randomized double blind immunogenicity trial with this vaccine in Kolkata demonstrated 4 fold rise in titers in 53% of adults and 80% of children with response to O 139 being lesser than O1. Subsequently a very large cluster randomized double blind placebo controlled trial in Kolkata demonstrated that the average per protocol efficacy of the vaccine to be 67% across all ages for upto 2 years after vaccination. No adverse effects were noted.

Recommendations for use

The ideal method for cholera control is improvement in water supply and sanitation. As recommended by the WHO cholera vaccines should be used preemptively in endemic areas and in crises situations and not as outbreak control measure. The inclusion of new killed whole cell oral cholera vaccine in the national immunization schedule is being considered by the policy makers in those areas where cholera is highly endemic, particularly the states of West Bengal and Orissa. Cost effectiveness analysis studies have demonstrated that vaccination of the 1-14 year old population would be highly cost effective.

For office practice purposes, the cholera vaccine remains a vaccine to be used in special circumstances. These include travel to or residence in a highly endemic area and circumstances where there is risk of an outbreak such as during pilgrimages like Kumbh Mela *etc.* Protection starts 2 weeks after receipt of the 2nd dose.

MENINGOCOCCAL VACCINES

The data available on the background incidence of Meningococcal disease in India (most of which are derived from the tertiary care hospital that served a defined population and may not be representative of the whole country) are suggestive of low incidence of meningococcal disease and are less than that due to Streptococcal Pneumoniae and H influenzae type b. Hence routine childhood vaccination with Meningococcal vaccine is unlikely to be a priority.



As per the review by Sinclair et al, which is a comprehensive study of epidemiology of Meningococcal disease in India, prevalence of meningitis is 1.5 -3.3% of all acute hospital admissions in children. Contribution of Meningococcus to this is just 1.9%. Incidence of pyogenic meningitis is 37/100,000/year. Prevalence of septicemia according to one study is 2.8% of all hospital admissions. Meningococcus was not found in a series of 6000 cases with sepsis. All these facts further confirm that Meningococcal disease is not a problem as a background or endemic disease. There could be many explanations for this. i) The disease is under reported since the culture facilities are not appropriate and the organism is fastidious. ii) Due to overuse of antibiotics in our country, the meningococcal disease is getting aborted largely (since the organism is very sensitive), and iii) The data is published probably from those areas where the disease is not present, since Meningococcal disease follows a typical geographical pattern.

As far as the epidemic disease is concerned, the outbreaks have occurred at a periodicity of 20 years. Each epidemic has lasted for a decade. Large cities of North and coastal areas like Mumbai, Kolkata are being affected sparing the southern and central regions. Major outbreaks of Meningococcal disease are mainly seen in large cities of northern, western and eastern India like New Delhi, Mumbai Kolkata and north eastern states. There is relative sparing of central and southern India. The important contributing factors in major outbreaks may be overcrowding or vulnerability to importation of new strain or a suitable climatic condition.

The epidemic period coincides with dry season of November – March and the cases reduce with onset of monsoon and again increase November onwards. The outbreaks occur when season is dry and temperature is low. The seasonal cycle is similar to that seen in Africa where outbreaks peak in hot dry season and subside during monsoon. The mechanism of this seasonal association is not exactly known. This happens probably because during dry period there is damage to natural mucosal barrier of the nasopharynx increasing the chance of invasion of viral infection. Most of the epidemics in India are reported from the drier northern parts of the country than the more humid south is supportive of the current view of seasonal effect of the disease.

Endemic disease occurs primarily in infants and children with highest attack rates in infants aged 3-12 months. The disease is found more in males than females. During an epidemic condition, the disease is found in children; however, shift is noted from young children to adolescents and young adults later. Overall carriage rates are lower in India than other similar settings. High carriage rates are found in close household contacts which justifies chemoprophylaxis.



Severe Meningococcal disease is associated with high case-fatality rates (5-15%) even where adequate medical facilities are available and permanent disability occurs in about 19% survivors. Chemoprophylactic measures are in general insufficient for the control of epidemics because secondary cases comprise only 1-2% of all meningococcal cases.

There are 13 known serogroups but 90% of the disease causing isolates belong to serogroups A, B, C, Y and W-135. The burden of Meningococcal disease is greatest in the African meningitis belt. In these areas, disease occurs endemically in the dry season and also as epidemics every 7-14 years and is usually due to serogroups A and W-135. Disease outbreaks in Haj Pilgrims have been attributed to A and W-135. Disease in industrialized countries is primarily due to B, C and Y. There is lack of information of serogroup responsible for endemic meningococcal disease in India. In one study from Post graduate Institute of Medical Education and Research in Chandigarh, out of 12 isolates, eight were found to be serogroup A and four were serogroup C. However Group A Meningococci is the cause of all the major investigated Indian epidemics Surat, Gujarat (1985-87), areas adjoining Delhi (1966-1985) and (2004 - 2005) and more recently in Meghalaya and Tripura in (2008 -2009). (The most complete data available for this period is taken from an unpublished National Institute of Communicable Disease Report 2009)

Vaccines

Unconjugated Meningococcal Polysaccharide Vaccine (MPSV)

These are either bivalent (A+C) or quadrivalent (A, C, Y, W135) and contain 50 µg of each of the individual polysaccharides, available in lyophilized form, reconstituted with sterile water and stored at 2 to 8°C. These "T cell independent" vaccines do not induce immunological memory and the response in children younger than two years is poor. Hence these are indicated for adults and children older than 2 years (only under special circumstances in children three months to two years of age). The antibody responses to each of the four polysaccharides in the quadrivalent vaccine are serogroup-specific and independent. Protective antibody levels are usually achieved within 10-14 days of vaccination. The serogroup A polysaccharide induces antibody in some children as young as three months of age, although a response comparable with that occurring in adults is not achieved until age 4-5 years. The serogroup C component is poorly immunogenic in children less than 2 years. The serogroup A and C vaccines have good immunogenicity, with clinical efficacy rates of 85 percent or higher among children five years of age or older and adults. Serogroup Y and W-135 polysaccharides are safe and immunogenic in older children and adults;



although clinical protection has not been documented. In infants and young children aged < 5 years, measurable levels of antibodies against serogroup A and C polysaccharides, as well as clinical efficacy, decrease substantially during the first three years after a single dose of the vaccine administration. Antibody levels also decrease in healthy adults, but antibodies are still detectable up to 10 years after immunization. Multiple doses of serogroup A and C polysaccharides are known to cause immunologic hyporesponsiveness (impact on clinical efficacy has not been demonstrated). Vaccines are safe and most common side effects are local pain and redness at site of injection.

Conjugated Meningococcal Polysaccharide Vaccine (MCV)

These Meningococcal conjugate vaccines induce a T-cell-dependent response; thus resulting in an improved immune response in infants, priming immunologic memory and a booster response to subsequent doses, and herd effect through protection from nasopharyngeal carriage.

A conjugate Meningococcal serogroup C vaccine (conjugated to CRM 197 or TT) has been part of routine immunization in the United Kingdom since November 1999. These vaccines were licensed on the basis of safety and immunogenicity studies without any data on clinical efficacy. The dosing schedule was three doses at interval of 4-8 weeks interval in children below 6 months, 2 doses in age group 6-12 months and a single dose in older children along with the routine childhood immunizations. A dramatic decline in meningococcal disease in both vaccinated and unvaccinated was noted following introduction of the vaccine; effectiveness of the vaccine within the first year of vaccination ranged from 88% to 98% among different age groups; however efficacy dropped by 80% after the first year but the incidence of meningitis did not increase due to herd effect. No serotype replacement has been observed till date.

A quadrivalent A, C, Y and W-135 conjugate vaccine has been licensed for use in individuals aged 11-55 years in USA (2-55 years in Canada). This vaccine contains 4 µg each of A, C, Y and W-135 polysaccharide conjugated to 48 µg of diphtheria toxoid. A single dose of 0.5 ml IM is recommended. This vaccine had comparable immunogenicity to the previously used polysaccharide vaccine. It is associated with minor local side effects such as pain, and swelling. Guillain-Barré Syndrome (GBS) was noted as a possible but unproven risk in some adolescents following immunization with Quadrivalent MCV, occurring in an estimated 1 in 1 million vaccine recipients. A chart review study presented at the ACIP meeting indicated that 99 cases of GBS were confirmed among 12,589,910 adolescents who received the meningococcal vaccine. They concluded that there was no increased risk for GBS associated with the meningococcal vaccine. Another study, conducted from 2005 to 2008, included



data on 889, 684 doses of meningococcal vaccine. Among those, 5 cases of GBS occurred within 6 weeks of vaccination; however, none were considered new-onset GBS. Thus, neither study indicated an increased risk of GBS following Meningococcal vaccination. As a precaution, people who have previously been diagnosed with GBS should not receive this vaccine unless they are at increased risk of Meningococcal disease. This vaccine is not currently available in India but will be available soon after the ongoing safety and immunogenicity study in healthy subjects of India is completed.

First monovalent Meningococcal A conjugate vaccine was launched in Burkina Faso in Africa on 6th Dec 2010. Meningococcal A Conjugate vaccine is a lyophilized vaccine of purified meningococcal A polysaccharide covalently bound to tetanus toxoid (TT). The vaccine consists of purified group-specific bacterial polysaccharide from *Neisseria meningitides* group A. Each dose of 0.5 mL contains: Meningococcal A polysaccharide 10 mcg, TT (carrier protein) 10 to 33 mcg and excipients: mannitol, sucrose and Tris (hydroxymethyl) aminomethane. The vaccine is recommended for children aged 1 year, adolescents and adults up to 29 years of age, for the prevention of invasive disease caused by *Neisseria meningitides* Group A. A single dose. of 0.5 ml should be administered by deep intramuscular injection, The vaccine shows safety and high immunogenicity in India and Africa. This vaccine is not currently available in India

Recommendations for use

The IAPCOI recommends the use of Meningococcal vaccines only in certain high risk situations as enumerated below in children aged 2 years or more (3 months or older if risk of meningococcal disease is high, e.g. outbreaks/ close household contact).

- During disease outbreaks, if caused by serogroups included in the vaccine, mass chemoprophylaxis is generally not recommended for control of mass outbreaks due to cost, implementation problems, drug side effects and drug resistance.
- Children with terminal complement component deficiencies.
- Children with functional/ anatomic asplenia/ hyposplenia (vaccination should ideally be done 2 weeks prior to splenectomy)
- Laboratory personnel and healthcare workers who are exposed routinely to *Neisseria meningitides* in solutions that may be aerosolized should be considered for vaccination.
- Travelers to Saudi Arabia for Haj (mandatory requirement)



- Travelers to the African meningitis belt particularly between December to June and especially if there is an ongoing epidemic.
- As an adjunct to chemoprophylaxis in close contacts of patients with Meningococcal disease (HCW in contact with secretions, household contacts, day care contacts).
- Students going for study abroad (mandatory in most universities in the USA)

The conjugate vaccines are preferred but currently unavailable in India (Will be available soon). At present only the quadrivalent and bivalent polysaccharide vaccines are available. The quadrivalent vaccine is preferred for Haj pilgrims and international travelers and students as it provided added protection against emerging W-135 and Y disease in these areas. A single dose 0.5 ml SC/ IM is recommended. In infants aged 3 months to 2 years 2 doses 3 months apart are recommended. For the quadrivalent A, C, Y and W-135 conjugate vaccine a single dose of 0.5 ml IM is recommended in age group 2-55 years. Monovalent vaccine is to be given as a single dose of 0.5 ml IM from age 1yr to 29 year. Though it is not yet available in India in future this could be useful in India to contain epidemics of group A meningococcal disease provided they are detected early through improved surveillance.

ACIP in October 2010 recommended 1) routine vaccination of adolescents, preferably at age 11 or 12 years, with a booster dose at age 16 years and 2) a 2-dose primary series administered 2 months apart for persons aged 2 through 54 years with persistent complement component deficiency (e.g., C5–C9, properdin, factor H, or factor D) and functional or anatomic asplenia, and for adolescents with human immunodeficiency virus (HIV) infection. CDC guidance for vaccine providers regarding these updated recommendations also is included.

Three characteristics of conjugate vaccines are believed to be important for establishing long-term protection against a bacterial pathogen: memory response, herd immunity, and circulating antibody. Recent data from the United Kingdom indicate that although vaccination primes the immune system, the memory response after exposure might not be rapid enough to protect against meningococcal disease. After initial priming with a serogroup C meningococcal conjugate vaccine, a memory response after a booster dose was not measurable until 5–7 days later. The incubation period for meningococcal disease usually is less than 3 days. In UK, to date no evidence of herd immunity has been observed. Therefore, circulating bactericidal antibody is critical for protection against meningococcal disease. There is sufficient evidence to indicate that approximately 50% of persons vaccinated 5 years earlier had bactericidal antibody levels protective against meningococcal disease. Therefore,



more than 50% of persons immunized at age 11 or 12 years might not be protected when they are at higher risk at ages 16 through 21 years. ACIP recommended revaccination with conjugated meningococcal vaccine in individual previously vaccinated with either conjugated or polysaccharide vaccine who are at increased risk for meningococcal disease. Those who are vaccinated at age greater than 7 years should be vaccinated 5 years after their previous meningococcal vaccine and those vaccinated at ages 2-6 years should be revaccinated 3 years after their previous meningococcal vaccine. Persons who remain in one of these increase risk group indefinitely should continue to be revaccinated at 5 year interval.

JAPANESE ENCEPHALITIS VACCINES

Background

Japanese encephalitis (JE) is one of the most important causes of viral encephalitis in Asia. Japan, South Korea, North Korea, Taiwan, Vietnam, Thailand, and the Peoples Republic of China (PRC) practice routine childhood immunization against JE. In India, JE is believed to be responsible for approximately 2000-3000 clinical cases and 500-600 deaths every year. JE has been reported from all states and union territories in India except Arunachal, Dadra, Daman, Diu, Gujarat, Himachal, Jammu, Kashmir, Lakshadweep, Meghalaya, Nagar Haveli, Orissa, Punjab, Rajasthan, and Sikkim. Highly endemic states include West Bengal, Bihar, Karnataka, Tamil Nadu, Andhra Pradesh, Assam, Uttar Pradesh, Manipur, and Goa. The risk is highest in children aged 1-15 years, in rural areas and in the monsoon/ post monsoon season. Periods of greatest risk are May to October in Goa, October to January in Tamil Nadu, August to December in Karnataka (second peak, April to June in Mandya District), September to December in Andhra Pradesh, and July to December in Northern States. Urban cases have been reported from Lucknow. JE vaccination remains the single most important control measure in JE endemic states of India.

Vaccines

Mouse Brain-Derived Inactivated JE Vaccine

This vaccine is prepared from either the Nakayama/ Beijing strain of JE virus grown in mice brain, purified, inactivated by formalin and preserved with thiomersol. No myelin basic protein is detectable in the finished product. Efficacy trials in Taiwan & Thailand demonstrated 80- 91% efficacy with two doses of the vaccine. The vaccine is given subcutaneously – 0.5 ml in children 1-3 years, and 1 ml in older children. Primary immunization consists of three doses given on 0, 7 and 30 days. In special



circumstances when time is short a 0, 7 and 14 day schedule may be used. Two doses 7 days apart provide only short term immunity in 80% of vaccinees for 6 months and may be used in travelers for logistic reasons. The last dose should be given at least 10 days prior to travel to the endemic area. For long term protection regular boosters every 2-3 years are recommended. Common adverse reactions include fever, malaise, local tenderness and redness in 20% of recipients. Acute neurologic events have been reported in 1-2.3 per million vaccinees. Allergic reactions mainly Type I hypersensitivity reactions, including anaphylactic shock, have been reported at a frequency of 1-100 per 10, 000 traveler vaccinees varying with different batches of the vaccine. The risk of reactions is higher in those with history of hypersensitivity. All vaccinees should be cautiously monitored for possible allergic reactions and asked to remain in the vicinity of medical facility for 10 days after vaccination. Owing to drawbacks (high cost, complicated dosing schedule, requirement of numerous doses and boosters, concerns about side-effects and reliance neurological tissue for production) and availability of better vaccines, production of this vaccine and availability has markedly declined in the current scenario.

Cell culture derived inactivated vaccine

This vaccine made from Primary Hamster Kidney cell line was used in China in millions of doses but has now been given up with the availability of the SA14-14-2 live vaccine. Clinical trials with vero cell derived inactivated vaccines are currently in advanced stages of clinical trials in Japan, Taiwan, South Korea and China and show promising results.

Cell culture derived live SA-14-14-2 vaccine

This vaccine is based on a stable neuro-attenuated strain of JE virus (SA-14-14-2). It was first licensed for use in 1988 in People's Republic of China and current usage is over sixty million doses per year. It is also licensed in India, South Korea and Nepal. This live attenuated vaccine constitutes over 50% of global production of all JE vaccines. Dose is 0.5ml subcutaneously for all ages. Initial studies done with this vaccine demonstrated an efficacy of about 80% with single dose and 98% with 2 doses. However, more recent case control studies from Nepal have shown efficacies of 98.5 % at 12-15 months and 96.2% at 5 years with a single dose of the vaccine. As per recent WHO reports and as recent Cochrane meta analysis, no serious adverse effects have been reported with this vaccine.

In 2005, India witnessed a massive outbreak of JE which resulted in 2000 deaths and even greater disability. In response to this outbreak the Government of India with support of PATH initiated a pilot project in 2006 of immunizing children in



hyperendemic districts against JE. 7 districts in UP, 2 in Assam and one each in West Bengal and Karnataka were targeted. SA-14-14-2 live JE vaccine manufactured by Chengdu institute of Biological Products, Chengdu, China was used. It was given in a campaign mode to children aged 1-15 years as a single subcutaneous dose using AD syringe. Eleven million children were targeted as beneficiaries and 9 million children actually received the vaccine *i.e.* nearly 86% of the target was achieved. UP recorded 96% coverage against all expectations. There were 504 adverse effects following the campaign of which 482 were minor adverse effects. 22 deaths were reported but none were causally related to the vaccine as cleared by an expert committee set up to monitor the adverse effects. This project reached 20 million children in 2007 and aims to reach 20 million more in 2008.

Recommendations for use

JE vaccine should not be used as an "outbreak response vaccine". IAPCOI recommends that the government should implement universal immunization with this vaccine in all children in JE endemic states. The SA-14-14-2 vaccine appears best suited for this purpose. A recent study from Phillipines shows acceptable efficacy and safety of this vaccine when co administered with the measles vaccine at 9 months. Along with all infants, all susceptible children upto the age of 15 years should be administered catch up vaccination.

JE vaccine is also recommended for travelers to JE endemic areas provided they are expected to stay for a minimum of 4 weeks in rural areas in the JE season.

YELLOW FEVER VACCINE

Background

Yellow fever is a mosquito borne illness confined to certain countries in sub Saharan Africa and Central/ South America and varies in severity from influenza like illness to severe hepatitis and hemorrhagic fever. The overall risk of serious illness and death in travelers to yellow fever endemic areas ranges from .05 – 0.5 per 100,000 travelers. Though yellow fever does not exist in India, conditions are conducive for its spread in the country due to the widespread presence of the mosquito vector *Aedes aegypti* and favorable environmental conditions. Therefore, the government of India has strict regulations in place to restrict the entry of susceptible and unvaccinated individuals from yellow fever endemic countries.

Vaccine

It is a live attenuated vaccine derived from 17D strain of the virus grown in chick



embryo cells. The vaccine is available as a freeze dried preparation in single/multidose vials that should be stored at 2 to 8°C (must not be frozen) along with sterile saline as diluent. The reconstituted vaccine is heat labile, must be stored at 2 to 8°C and discarded within 1 hour of reconstitution. The dose is 0.5 ml subcutaneously. It can be safely given along with all other childhood vaccines. Immunogenicity and efficacy are greater than 90%. Immunogenicity is lower in pregnancy and immunocompromised. Protective immunity is attained by 10th day of vaccination and lasts for at least 10 years. Adverse reactions usually minor local and systemic side effects are seen in 25% of the vaccines. Rare and serious adverse events of neurologic disease (YEL-AND, encephalitis, acute disseminated encephalomyelitis, GBS) and yellow fever vaccine-associated viscerotropic disease (YEL-AVD, which mimics wild yellow fever and is often fatal) have been reported at an incidence of 1 per 400, 000 doses distributed. The risk of neurologic and viscerotropic disease is higher and hence the vaccine is contraindicated in infants below the age of 6 months, those with history of thymus disease and the severely immunocompromised including HIV with severe immunosuppression (CD4 count \leq 15% of age related cutoff) and those with history of serious egg allergy. The vaccine is preferably avoided in infants aged 6-9 months, individuals aged \geq 65 years and in pregnant and lactating women.

Recommendations for use

The vaccine is mandatory for all travelers to yellow fever endemic zones as per International Health Regulations. The list of endemic countries can be obtained at <http://www.nc.cdc.gov/travel/yellowBookCh4-YellowFever.aspx>. All vaccinees receive an international certificate for vaccination duly dated, stamped and signed by the centre administering the vaccine. The certificate is valid from the 10th day after vaccination for a period of 10 years. Individuals with medical contraindications for vaccination are advised to avoid or postpone travel. In case travel is unavoidable, an exemption certificate/waiver letter should be taken from the treating physician and vector control measures should be practiced. The waiver letter does not guarantee entry and the person may face refusal of entry, quarantine or onsite vaccination. In the Indian context, a valid certificate is required for all individuals aged more than 6 months entering India after travel to yellow fever endemic zones even if it was mere transit. Individuals lacking this certificate and sometimes even those with medical contraindications for vaccination are placed under quarantine for 5 days on entry to India. This vaccine is currently available only at select government controlled centers in India and is not within the domain of private vaccination clinics. Unfortunately it is often in short supply causing significant problems to travelers.



IMMUNIZATION OF ADOLESCENTS

Adolescence should be considered an appropriate age for catchup immunization as well as for administration of certain vaccines which may not have been available earlier. Preferred age for administration is at 10-12 years but catch up may be done till 18 years. Vaccines to be considered for adolescents if not received earlier include

IAP recommended vaccines for Adolescents (10 Years to 18 Years)

Vaccine	Schedule
Tdap/Td ^{&}	10 years
HPV [^]	10 to 12 years

[&] Tdap preferred to Td, followed by repeat Td every 10 years (Tdap to be used once only)

[^] Only females, three doses at 0, 1 or 2 (depending on the vaccine used) and 6 months

IAP Recommendations for Catch up Immunization in Adolescents

Vaccine	Schedule
MMR	2 doses at 4-8 weeks interval [@]
Hepatitis B	3 doses at 0, 1 and 6 months [#]
Hepatitis A	2 doses at 0, 6 months (prior check for Anti HAV IgG may be cost effective) ^{##}
Typhoid	1 dose every 3 years ^{**}
Varicella	2 doses at 4-8 weeks interval

[@] one dose if previously vaccinated with one dose

^{#,##} Combination of Hep B and Hep A may be used in 0, 1, 6 schedule

^{**} A minimum interval of 3 years should be observed between 2 doses of typhoid vaccine

IAP Recommendations for Adolescent Immunization in Special Circumstances

Vaccine	Age recommended
Influenza Vaccine	One dose every year
Japanese Encephalitis Vaccine	Catch up up to 15 years [@]
PPSV23 (Pneumococcal) Vaccine	2 doses 5 years apart [*]
Rabies Vaccine 0, 3, 7, 14, 28 day	As soon as possible after exposure

[@] Only in endemic area as catch up; ^{*} Maximum number of doses – Two



IAP Recommendations for Adolescents travellers

All age appropriate vaccines should be completed before travel, in addition to those listed below

Vaccine	Place of Travel	Dose recommended
Meningococcal Vaccine	USA / UK /endemic areas Saudi Arabia and Africa #	2 doses 4-8 weeks apart
Yellow fever ^	Yellow fever endemic zones**	10 days before travel
Oral Cholera vaccine	Endemic Area or area with an outbreak	2 doses 1 week apart
Japanese B encephalitis	Endemic Areas for JE	Single dose (upto 15 years)
Rabies Vaccine (Pre exposure Prophylaxis)	For adolescents going on trekking	0, 7, 28

Quadrivalent vaccine for those travelling to the US and Bivalent (A+C) or Quadrivalent for those travelling to the UK

^ Mandatory for all travellers to yellow fever endemic zones as per International Health Regulations.

** The list of endemic countries can be obtained at <http://www.nc.cdc.gov/travel/yellowBookCh4-YellowFever.aspx> currently available only at select government controlled centres in India.

For more information on travellers vaccination, visit <http://www.nc.cdc.gov/travel/default.aspx>



IMMUNIZATION IN SPECIAL SITUATIONS

Immunization in preterm/low birth weight infants

In principle, all vaccines may be administered as per schedule according to the chronological age irrespective of birth weight or period of gestation. BCG and birth dose of OPV can be safely and effectively given to low birth weight / preterm babies after stabilization and preferably at the time of discharge. Studies have shown that the take of BCG is similar in preterm/low birth weight babies whether given at discharge or later. The birth dose of Hepatitis B vaccine can be administered at any time after birth in babies weighing ≥ 2 kg. In babies less than 2 kg, the birth dose of Hepatitis B vaccine should be delayed for 1 month after birth as immunogenicity is lower if given earlier. In babies less than 2 kg born to a Hepatitis B positive mother, Hepatitis B vaccine should be given along with HBIG within 12 hours of birth and 3 more doses at 1, 2 and 6 months are recommended. All other childhood vaccines may be given as per chronologic age and have acceptable safety, immunogenicity and efficacy. Since preterm, low birth weight babies have increased susceptibility to infections, vaccines such as Pneumococcal conjugate vaccines, Rotavirus and Influenza should be offered if resources permit.

Immunization in the immunocompromised

The immunocompromised are in greater need for vaccines as they are more susceptible to infections. But at the same time the immunogenicity/ efficacy is lower and risk of adverse effects with live vaccines is higher. General principles for vaccination of the immunocompromised are

- In severe immunodeficiency, all live vaccines are contraindicated. In mild / moderate immunodeficiency, live vaccines may be given if benefits outweigh the risks. Patients administered live vaccines inadvertently prior to diagnosis of immunodeficiency should be watched for vaccine related adverse effects.
- Household contacts of immunocompromised should not receive transmissible vaccines such as OPV but can safely receive other non transmissible live vaccines such as MMR & Varicella. All household contacts should be fully immunized including Varicella and Influenza to reduce risk of transmission to the immunocompromised.
- All inactivated vaccines can be given but immunogenicity and efficacy may be lower.
- Higher doses, greater number of doses should be given if indicated



(Hepatitis B), antibody titers should be checked post immunization/ regular basis and regular boosters administered if needed. For major/ contaminated wounds tetanus immunoglobulin is required in addition to TT even if 3 or more doses of TT have been received in the past.

- Some vaccines including Pneumococcal, Varicella (depending on degree of immunocompromise and in 2 doses 4-12 weeks apart), Hepatitis A, inactivated Influenza vaccines should be given if resources permit. There is at present insufficient data on the safety and efficacy of the Rotavirus vaccine in the immunocompromised.

Additional information on immunization in various types of immunodeficiency is discussed further.

Children receiving corticosteroids/ other immunosuppressive therapy/chemotherapy/ radiotherapy

Children receiving oral corticosteroids in high doses (prednisolone > 2 mg/kg/day or for those weighing more than 10 kg, 20 mg/day or its equivalent) for ≥ 2 weeks should not receive live virus vaccines until the steroids have been discontinued for at least one month. Killed vaccines are safe but may be less efficacious. Children on lesser dose of steroids or those on inhaled or topical therapy may be safely and effectively given their age appropriate vaccines. Children on immunosuppressive therapy other than corticosteroids should avoid live vaccines during therapy unless benefits outweigh risks. Children on chemotherapy & radiotherapy for malignancy should avoid all live vaccines during therapy and for at least 3 months after stopping treatment.

Children with asplenia/hyposplenia

Children with asplenia/hyposplenia are at high risk of serious infections with encapsulated organisms. Vaccination with Pneumococcal, Hib and Meningococcal vaccines is indicated in addition to all routine live and inactivated vaccines. In patients with planned splenectomy, vaccination should be initiated at least 2 weeks prior to splenectomy.

Children with HIV infection

Children infected by HIV are vulnerable to severe, recurrent, or unusual infections by vaccine preventable pathogens. The efficacy and safety of vaccines depends on the degree of immunodeficiency. In general, in early life most vaccines are safe and efficacious as the immune system is relatively well preserved. The duration of protection may be compromised as there is impairment of memory response with



immune attrition. Efficacy and safety are significantly lower in advanced disease. Consideration should be given to readministering childhood immunizations to such children when their immune status has improved following anti-retroviral therapy. Vaccination of a baby born to an HIV positive mother but with an indeterminate HIV status should be as per the normal schedule. Table 1 summarizes IAP recommendations for vaccination of HIV infected children.

Table 1: IAPCOI recommendations for immunization of HIV infected children

Vaccine	Asymptomatic	Symptomatic
BCG	Yes (at birth)	No
DTwP/DTaP/TT/Td/Tdap	Yes as per routine schedule at 6w, 10w, 14w, 18m & 5years	
Polio vaccines	IPV at 6, 10, 14 weeks, 15-18 months & 5 years If indicated IPV to household contacts If IPV is not affordable, OPV should be given*	
Measles vaccines	Yes, at 9 months	Yes if CD4 count \geq 15%
MMR vaccine	Yes, at 15 m & at 5 y	Yes if CD4 count \geq 15%
Hepatitis B	Yes, at 0, 1 & 6 months	Yes, four doses, double dose, check for seroconversion, regular boosters
Hib	Yes as per routine schedule at 6w, 10w, 14w & 18m	
Pneumococcal vaccines (PCV & PPV 23)	Yes as per routine schedule at 6w, 10w, 14w & 15m	
Inactivated Influenza vaccine	Yes as per routine schedule beginning at 6m, revaccination every year	
Rotavirus vaccine	Insufficient data to recommend	
Hepatitis A vaccine	Yes	Yes, check for seroconversion, boosters if needed
Varicella vaccine	Yes, two doses at 4-12 weeks interval	Yes, if CD4 count \geq 15%, two doses at 4-12 weeks interval
Vi typhoid vaccine	Yes as per routine schedule at 2 y & every 3 years	
HPV vaccine	Yes (females only) as per routine schedule 3 doses at 0, 1-2 & 6m at 10 years	

* OPV has been found to be generally safe in HIV infected especially in early stages

Children with congenital immunodeficiency

In patients with severe B cell immunodeficiency (X linked agammaglobulinemia) live vaccines including OPV, BCG, oral typhoid, live attenuated influenza are contraindicated. Measles and Varicella vaccines may be given but may be ineffective



due to concomitant immunoglobulin therapy. Inactivated vaccines may be given but are ineffective. In less severe B cell deficiencies such as IgA and IgG subclass deficiency only OPV is contraindicated. In patients with severe T cell immunodeficiencies (SCID) all live vaccines are contraindicated and all vaccines are ineffective. Patients who have received live vaccines especially BCG prior to diagnosis face an increased risk of complications including disseminated BCG disease. For patients with combined immunodeficiencies such as Di George syndrome, Wiskott Aldrich and ataxia telangiectasia, inactivated vaccines may be given but live vaccines are contraindicated. In complement deficiencies, all vaccines may be safely given; Pneumococcal, Hib and Meningococcal vaccines are particularly indicated. In patients with phagocyte defects such as chronic granulomatous disease, only live bacterial vaccines are contraindicated, other vaccines may be safely and effectively given.

Transplant recipients

Recipients of hematopoietic stem cell transplants (HSCT) are like the unimmunized as they have lost all memory responses during marrow ablation. It is recommended that 3 doses each of DTwP/ DTaP/Td/Tdap (depending on age), IPV, Hib, Hepatitis B be given at 12, 14 and 24 months post transplant. Two doses of PCV and 1 dose of PPV 23 with 8 weeks interval between doses beginning 12 months post transplant in children below the age of 5 years and 2 doses of PPV23 at 12 and 24 months post transplant in older children are recommended. Influenza vaccination should be given pre transplant, restarted 6 months post transplant and continue life long. MMR and varicella vaccines may be given 24 months post transplant if the recipient is adjudged immunocompetent. All susceptible contacts of HSCT recipients including household and health care worker contacts (HCW) should be immunized against varicella and influenza. Varicella vaccination of contacts should be completed 6 weeks before the transplant date.

Recipients of solid organ transplants should complete all immunizations prior to transplant in accelerated schedules if needed. Vaccination with live vaccines should be completed at least 2 weeks prior to transplant. It is desirable that seroconversion be documented. In the post transplant period, all live vaccines are contraindicated. In patients where immunization has not been completed prior to transplant, vaccination with inactivated vaccines can recommence 6 months post transplant when immunosuppression has been lowered. Boosters for inactivated vaccines should be given as per schedule/ when antibody levels wane (Hepatitis A and B) starting 6 months post transplant. Annual Influenza vaccination is recommended. All household and HCW contacts should be immunized against Influenza and Varicella.



Immunization of children with chronic diseases

Children with chronic neurologic, endocrinologic (diabetes), liver, renal, hematologic, cardiac, pulmonary and gastrointestinal disease are at increased risk of infections and serious infections. Live vaccines may be given safely in these children. These children should be offered Pneumococcal, Hepatitis A, Varicella, Influenza and Rotavirus vaccines. The immunogenicity, efficacy and duration of protection of vaccines is lower than healthy children and hence if indicated higher antigen content/ more doses (Hep B), assessment for antibody response and frequent boosters (Hep A and B) are recommended. It is important to stress the role of hepatitis A vaccine in patients with liver disease, Pertussis boosting in those with stable neurologic disease and Influenza in those with cardiac/ pulmonary disease.

Immunization in children with history of allergy

First time immunization with any vaccine is contraindicated in children with history of serious hypersensitivity/ anaphylaxis to any of vaccine components. The package label should always be checked for vaccine constituents which in addition to antigen include stabilizers/ buffers, preservatives, antibiotics and residue from the manufacturing process. Children with history of serious egg allergy should not receive Influenza and Yellow fever vaccines but can safely receive other vaccines including Measles and MMR vaccines. Children with history of any hypersensitivity are at increased risk for allergic reactions with inactivated Japanese Encephalitis vaccines and thus should be monitored carefully. Children who have had a serious hypersensitivity reaction/ anaphylaxis to a particular vaccine must never receive it again. A mild reaction is not a contraindication to vaccination. In any case all children should be watched for at least 15 minutes after vaccination for allergy and resuscitation equipment should be kept standby.

Immunization in relation to antibody containing products (whole blood, packed red cells, plasma, immunoglobulin)

Inactivated vaccines can be safely administered simultaneously though at different sites or at any time in relation to antibody containing products with no loss of immunogenicity and efficacy (exception administration of RIG 7 days after rabies vaccine). Live vaccines including MMR and Varicella should be avoided for at least 3 months after antibody containing products and antibody containing products should be avoided for 2 weeks after receipt of these vaccines. If immunization outside this prescribed period has occurred, serologic response should be checked and revaccination done if indicated. Oral Typhoid vaccine, LAIV, OPV and Yellow fever may be given at any time in relation to antibody containing products. Rotavirus vaccine



should be avoided for 6 weeks after giving antibody containing products but if this deferral results in 1st dose of Rotavirus being postponed beyond 15 weeks, the vaccine may be given.

Immunization during illness

All immunizations need to be postponed only during serious illness. Vaccination should be encouraged during minor illness such as upper respiratory tract infections and mild diarrhea so that immunization opportunities of contact with health care provider are not missed. Immunization schedules of hospitalized patients should be completed at the time of discharge.

Lapsed immunization/ postponed immunization/ unknown immunization status

There is no need to restart a vaccine series regardless of the time that has elapsed between individual doses due to immune memory. Immunizations should be given at the next visit as if the usual interval had elapsed and the immunization scheduled should be completed at the next available opportunity. Doses should not be given 4 or less days from the minimum interval. If inadvertently given 5 or more days from the minimum interval, the dose should not be counted. In case of unknown immunization status, the child should be considered unimmunized and vaccinated accordingly. Self reported doses should not be accepted in the absence of documentation with the exception of Influenza and PPV vaccines. Serologic testing is also an option in patients with uncertain status but is usually not cost effective, may reduce compliance and may result in missed opportunities for vaccination.

Interchangeability of brands

There is sufficient data that brands of Hib, Hep B and Hep A may be safely interchanged with no compromise on immunogenicity and efficacy. However robust data for immunogenicity of vaccination with different brands of DTaP is lacking. Hence vaccination with DTaP should be completed with the same brand. However, if previous brand is not known or no longer available any brand may be used and vaccination should not be delayed/cancelled.

Catch up Immunization

Vaccination catch up regimens should preferably be individualized. The basic principles are discussed. Any number of vaccines live/ inactivated may be given on the same day either singly or as combination vaccines maintaining a gap of 5 cm between different vaccines (exception BCG and Measles/ MMR should not be given



on the same day). Inactivated vaccines can be given at any time in relation to any other live/ inactivated vaccines. If not given on the same day a gap of 4 weeks should be maintained between two live injectable vaccines especially MMR & Varicella but also Yellow fever and live attenuated Influenza vaccines. However OPV, Rotavirus and oral Typhoid vaccines may be given at any time in relation to any live/ inactivated vaccine. For catch up immunization, doses should preferably be given at the minimum possible interval to entail early protection.

The following table depicts the suggested catch up schedule. Other vaccines may be given after one to one discussion with parents.

Table 2: Suggested vaccination schedule for an unimmunized child

Visit	Suggested vaccines
First	Measles (MMR if more than 12 months) DTwP1/DTaP1 (Td if 7 years or more) OPV1/IPV1 (only if less than 5 years) Hib 1 (Only if less than 5 years) Hep B 1
Second visit (after 1 month of first visit)	BCG (only in less than 5 years) DTwP2/ DTaP2 (Td if 7 years or more) OPV 2 (if OPV given earlier) Hep B 2 Hib 2 (if less than 15 mths)
Third visit (after 1 month of second visit)	OPV3/IPV2 MMR (if more than 12 months) Typhoid (if more than 2 years)
Fourth visit (6 months after first visit)	DTwP3/DTaP3 (Td if 7 years or more) OPV4/IPVB1 HepB3

Immunization for travelers

The risk of travelers contracting infectious disease depends on the region/country to be visited, duration of trip and nature and conditions of travel. Uniform recommendations are not possible because the epidemiology of disease differs in various geographical areas. The physician should update routine immunization and also provide destination specific immunizations. For instance, vaccines commonly recommended for Indian travelers include Yellow fever vaccine for those intending to go to destinations in South America and Subsaharan Africa, Polio and Meningococcal vaccine for those intending to go on a Haj pilgrimage in Saudi Arabia and the quadrivalent Meningococcal vaccine for those visiting the African meningitis



belt. Similarly, visitors coming to India from abroad are usually advised vaccination against Typhoid, Hepatitis A, Hepatitis B, Rabies and Japanese Encephalitis (if visiting rural JE endemic areas in JE season).

Immunization of children with bleeding disorders or those receiving anticoagulants

Unless contraindicated, the subcutaneous route should be used. For aluminium adjuvanted vaccines that can only be given intramuscularly, vaccination should be scheduled after factor replacement therapy, Needles <23G should be used for injection and the parents should be asked to apply firm and sustained pressure, without rubbing, for at least 5 minutes.

Immunization in pregnancy/ lactation

All live vaccines including MMR, Varicella, LAIV and Yellow fever vaccine should be avoided in pregnancy due to possible risk to the fetus. However, if inadvertently vaccinated, medical termination of pregnancy is not advised as surveillance data does not reveal an increased risk of congenital malformations in accidentally vaccinated women. Inactivated vaccines are safe in pregnancy but should be given only if indicated. All live vaccines with the exception of Yellow fever vaccine may be safely given to lactating women.

Immunization of the elderly

Annual Influenza and a single dose of PPV23 vaccines are indicated in individuals aged 65 years or older.



LICENSING PROCEDURE AND INCLUSION OF A VACCINE IN THE NATIONAL IMMUNIZATION PROGRAM (NIP) OF A COUNTRY

National Regulatory Authority (NRA) & licensing procedure

The National Regulatory Authority (NRA) of a country is a statutory body that performs the task of not only providing license to a particular vaccine to be used in that country, but also acts as a watchdog on all other issues related to performance of that vaccine in the country where it is licensed. NRA supervises the vaccine lot release and performs laboratory inspections along with supervision of post-marketing surveillance for AEFI. NRA also sanctions the vaccine trials, determines the adequacy of the trials by the vaccine companies, supervises the proper conduct of vaccine trials including ethical and humanitarian aspects and has the power to discontinue even an ongoing trial if some irregularities are noted. It is also the duty of NRA to redress all the issues pertaining to safety, efficacy, and effectiveness of a vaccine after licensing.

The vaccines licensing authority in India, *i.e.* the NRA is Drugs Controller General of India (DCGI) which is approved by WHO also. The FDA (Food and Drug Administration) is the government agency responsible for regulating food, dietary supplements, drugs, cosmetics, medical devices, biologics and blood products in the United States. The NRA /DCGI is the equivalent agency in India that performs almost all these tasks.

For licensing of a new vaccine, the vaccine manufacturer should conduct the phase I, II, and III trials and must submit their results to NRA for its approval.

There are both central and state licensing authorities. Good Clinical Practice (GCP) and ethical guidelines (by ICMR) for approval exist. Licensing of products in India is by the Central Licensing Approval Authority (CLAA). The Drug Technology Advisory Board (DATB) approves introduction of vaccines into the immunization services, while all vaccine approval and clinical trials is by the CLAA. The state licensing authority inspects and grants licensing for retail.

Imported products are considered on a case-by-case basis; if trials meet the requirements of the NRA there is no insistence on clinical trials in the country for registration. The advisory committees that review the information follow published guidelines, directed by a responsible person. External clinical experts may be asked for advice on a case-by-case basis.

After licensing, the vaccine manufacturer should undertake a large post-marketing



surveillance (Phase IV) to further ensure the safety of their products. Any complaint regarding the safety, efficacy, *etc* of the licensed vaccine should be directed to NRA. Once the vaccine is licensed in the country, it can be used both by the private as well as the public sector.

Introduction of a new vaccine in the NIP

The issue of introduction of a new vaccine in the National Immunization Program (NIP) is bit complex. There are several factors that determine introduction of a new vaccine in NIP for mass/public use that include burden of disease, cost-effectiveness of a vaccination program, suitability of vaccine product available in the world market, safety and efficacy of the vaccine, programmatic issues, *etc*. Although inclusion of a new vaccine in national schedule adds the cost of vaccine and logistics to the health budget of a country, it also results in savings by reduction of the disease burden. Still, the decision to include a new vaccine in national schedule is not straight-forward as there are numerous issues in prioritizing investments of a NIP. These issues need to be tackled systematically, providing best possible immunization schedule as per the needs and resources of the country.

The Ministry of Health & Family Welfare (MOHFW)/ Government of India (GOI) has an advisory committee to give recommendations to it on inclusion of any new vaccine in the NIP, *i.e.* National Technical Advisory Group on immunization (NTAGI) where IAP has also got its representation through its national president who is an important member of this committee.

Issues in decision making

Issues involved in decision are not only policy issues (whether introduction of the new vaccine is in sync with immunization policy of the country), but also technical or programmatic (whether implementation of the decision is technically feasible). Table-1 lists various issues involved in the decision making.



Table-1: Issues involved in introduction of a new vaccine in National Immunization Program

<p>Policy issues</p> <ul style="list-style-type: none"> • Assessment of public health priority <ul style="list-style-type: none"> - Assessment of disease burden in the country - Other preventive measures available (including other vaccine, if any) • Assessment of candidate vaccine <ul style="list-style-type: none"> - Efficacy, quality and safety - Economic / financial issues
<p>Technical / programmatic issues</p> <ul style="list-style-type: none"> • Vaccine presentation • Programmatic strength (logistic issues) • Supply availability

Assessment of public health priority

Prioritization of various public health measures within limited resources is the most challenging task for any country. Public health importance of a disease varies from country to country. Hence, assessment of disease burden of the disease in question vis-à-vis other diseases is the first important step in decision making. Introduction of vaccine against the disease with highest disease burden will naturally have greatest impact on infant/childhood mortality and morbidity on national basis. This is one of the most important evidence to convince the policy makers to introduce the candidate vaccine.

The disease burden is assessed not only in terms of incidence and prevalence, but also in terms of annual hospitalizations, disability rate and mortality rate of the disease in question. Ideally, either data from surveillance systems of the country or well designed, multi centric studies or metaanalyses of studies from the country should form the basis of such assessment. However, in the absence of local studies, data from countries with similar social and demographic characteristics can be used. If the data available is incomplete, then mathematical models can be used (with due caution) in assessment of disease burden.

For assessment of disease burden, data on causative organism rather than clinical syndrome is needed. For example, in India, diarrhea and pneumonia remain the leading causes of non-neonatal mortality accounting for 15% and 18% of all under 5 deaths respectively. However, only a proportion of these are preventable by vaccines (Rota virus, *Haemophilus influenza* type b and pneumococcus).

Since policy decision for introduction of a vaccine in national immunization schedule



involves political establishment, the perception of the public about the disease and the vaccine is very important in a democratic country. The more important and visible the disease is, and safer and more effective is the vaccine perceived to be, the better is the acceptance and uptake of the new vaccine is. Any misconception or opposition to the vaccine should be cleared using various channels of communication. This helps in taking the decision faster.

When deciding about the priority of a particular vaccine, it is also important to consider other vaccines which are likely to be available in near future. Similarly, vaccine introduction could be postponed if it is likely that another vaccine would become available in near future against another disease that presents a greater burden.

Assessment of other interventions available

The proposed vaccine should be compared with other preventive measures (including any existing vaccine) available in terms of effectiveness, safety and feasibility before making a decision on introduction of the vaccine in national immunization schedule.

Assessment of efficacy, quality and safety of the vaccine

The vaccine needs to be efficacious in preventing the disease in immunized individuals. However, it must be noted that the data on efficacy should also be preferably taken from countries with similar disease epidemiology to one considering the vaccine. This is because the efficacy of a vaccine can vary with nutritional status, genetic 'makeup' of the vaccinee, co-infections and other factors.

The vaccine being considered for introduction should meet international standards of quality and safety. The data on safety should be obtained not only from clinical trials but also from post marketing surveillance from other countries with similar profile. Such data, if available, is very useful as it can throw light on rarer adverse events associated with the vaccine. The effect of introduction of vaccine on efficacy and safety of other vaccines given at the same time also needs to be explored. It is also important to note that the risk: benefit ratio of a vaccine can vary from country to country depending upon disease burden.

Economic/ financial issues

The vaccines other than *EPI vaccines* are "expensive", when cost is compared on dose-to-dose basis. Hence, cost-effectiveness analysis is essential before any decision on the vaccine introduction is taken by a developing country. The total cost (cost of vaccine and logistics) is compared to the potential savings as a result of reduced treatment of the disease. The cost-effectiveness is also compared with that



of another vaccine or another public health program under consideration. Various methods and tools adopted by the WHO for cost-effectiveness analysis can be used for this purpose.

Due care is taken to assess financial sustainability (over medium to long term) of the immunization program after introduction of the new vaccine. If any financial shortfall is expected, then appropriate sources of funding also need to be explored before finalizing introduction of the vaccine. If a donor agency is supporting introduction of a new vaccine in to NIP of a country, then it is imperative for the national government of that country to look in to the log term sustainability of the vaccine program once the collaboration with the funding agency terminates.

Vaccine presentation

The proposed vaccine may be available as monovalent/combination, single dose/multi dose and liquid/lyophilized. A number of issues need to be considered while choosing the presentation/formulation. These include current and proposed immunization schedule, number of injections per visit, cold storage space, vaccine wastage, injection safety equipment, staff training and supervision, recording and reporting mechanisms, and program costs.

If the preferred presentation is unavailable, the country can either postpone introduction or start with another option and switch to preferred option later.

Vaccine supply, availability and quality

This is a crucial issue for developing countries with large populations. The newer vaccines are often manufactured by a limited number of manufacturers and it takes some time to augment production following introduction of vaccine in national immunization program. In addition to current supply situation, future trends need to be assessed carefully before decision-making. A country may decide on phased introduction depending on supply availability. The introduction of conjugated pneumococcal vaccine has been delayed in most countries because of logistic and procurement issues.

Assessment of required doses would obviously depend on target population, estimated coverage and wastage. For vaccine doses requirement in next few years, we need to estimate increase in target population as well as vaccine coverage.

Not only quantity, but the quality of vaccine to be procured also needs to be assessed. Many developing countries prefer to use vaccines procured through UNICEF. These vaccines are already prequalified by the WHO through a standardized procedure



and packaging and transporting conditions are identified for proper cold chain maintenance. In case the country decides to procure its own vaccines, then a number of issues are to be looked into. A technical committee should review the technical issues including efficacy and data of the brand concerned as well as the packaging and transportation conditions required.

Further, post-marketing surveillance is critical to ensure vaccine quality after licensing. An elaborate protocol must be formulated for strict compliance later on.

Programmatic strength

The NIP of the country must be functioning well with existing vaccines before finalizing introduction of the new vaccine. Otherwise, vaccine addition would further worsen the failing system and will have long-term repercussions. Careful assessment of requirement of additional cold chain capacity, safe injection supplies and disposal, adequate staff, staff training and supervision, advocacy and awareness programs (IEC activities) is essential before finalizing introduction of the new vaccine. Any shortfall in this regard (financial or otherwise) must be addressed beforehand for smooth introduction of the vaccine.

Bibliography:

World Health Organization. Vaccine introduction guidelines – adding a vaccine to a national immunization program: decision and implementation, 2005; Available at : http://whqlibdoc.who.int/hq/2005/WHO_IVB_05.18.pdf.



INTERNET RESOURCES ON IMMUNIZATION INFORMATION

Table 1: Internet resources on immunization information

SN	Organization	Web address	Salient Contents
1	National Library of Medicine	www.pubmed.com	Abstracts and full texts of vaccine related articles published in indexed journals
2	IAPCOI	www.iapcoi.com	Electronic copy of guidebook, Q & A facility
3	WHO	www.who.int/immunization/en/index.html	WHO position papers
4	Centers for Disease Control (CDC)	www.cdc.gov/vaccines/	ACIP vaccine recommendations, travel immunization
5	Immunization Action Coalition	www.immunize.org/	Educational material for parents
6	National Network for Immunization Information	www.immunizationinfo.org	Separate sections for parents, listserv that gives updated information
7	Children's Hospital Philadelphia	www.vaccine.chop.edu/	Info for parents, vaccine safety
8	GAVI	www.gavialliance.org	Info on GAVI policy and funding
9	PATH	www.path.org/vaccineresources/index.php	Vaccine resource library
10	Vaccine Manufacturers (In Alphabetical Order)	www.bharatbiotech.com www.biomed.co.in www.biologicale.com www.gskvaccines.com www.indimmune.com www.merckvaccines.com www.novartisvaccines.com www.panacea-biotec.com www.sanofipasteur.com www.shanthabiotech.com www.seruminstitute.com www.pfizer.com	Prescribing information for various vaccines



READY RECKONER FOR VACCINES CURRENTLY AVAILABLE IN INDIA

Vaccine	Content/dose	Nature and diluent	Storage	Dose, Route, Site	Schedule	Protective efficacy	Major adverse effects	Contraindications
BCG (LAV)	0.1 to 0.4 million viable bovine mycobacteria	Lyophilized, normal saline	Freezer/ 2 to 8°C, Protect from light	0.1 ml ID, left deltoid	Single dose at birth or first contact below 5 yrs	0-80%	Axillary lymphadenitis	Cellular immunodeficiency Should not be given with measles/MMR
OPV (LAV)	Sabin strain Type 1- 10 ⁵ CCID ₅₀ Type 2- 10 ⁵ CCID ₅₀ Type 3- 10 ⁵ CCID ₅₀	Liquid vaccine	Freezer/ 2 to 8°C	2 drops oral	Birth, 6,10,14 weeks, 15-18 mths, 5 yrs, NID's, SNID's	10-15% per dose (India), 30% per dose (world)	Rarely VAPP	Immunodeficient patients and household contacts
IPV (Inactivated)	Salk strain Type 1- 40 units Type 2- 8 units Type 3- 32 units	Liquid vaccine	2 to 8°C	0.5 ml IM or SC, thigh/ deltoid	6,10,14 weeks, booster at 15-18 mths	95-100%	None	Serious hypersensitivity
DTwP/DTaP	Diphtheria toxoid 20-30 Lf, tetanus toxoid 5-25 Lf, wP 4 IU/ aP 3 µg to 25 µg of 2 to 5 purified pertussis antigens	Liquid vaccine	2 to 8°C Protect DTwP from light	0.5 ml IM thigh/ deltoid	6,10,14 weeks, booster at 15-18 mths, 5 years Not recommended above 7 yrs	95-100% for diphtheria/ tetanus and 70-90% for pertussis	Rare. More with DTwP High fever, excessive crying, seizures, HHE, encephalopathy	Serious hypersensitivity, encephalopathy following previous dose
DT	Same as above with no pertussis	Liquid vaccine	2 to 8°C	0.5 ml IM thigh/ deltoid	Replacement for DTwP/DTaP in those with contraindications for pertussis vaccination, not recommended above 7 yrs			
TT	Tetanus toxoid 5 Lf	Liquid vaccine	2 to 8°C	0.5 ml IM thigh/ deltoid	As routine at 10 years and every 10 years thereafter, pregnancy, wound management (Td/ Tdap preferred to TT)			
Td	Tetanus toxoid 5 Lf, Diphtheria 2 Lf	Liquid vaccine	2 to 8°C	0.5 ml IM thigh/ deltoid	As replacement for DTwP/DTaP/DT for catch up vaccination in those aged above 7 yrs (along with Tdap), and as replacement for TT at all ages			



Vaccine	Content /dose	Nature and diluent	Storage	Dose, Route, Site	Schedule	Protective efficacy	Major adverse effects	Contraindications
Tdap	Tetanus toxoid 5Lf, Diphtheria toxoid 2Lf, 2.5 to 8 µg of three pertussis antigens	Liquid vaccine	2 to 8°C	0.5 ml IM thigh/ deltoid	Single dose at 10-12 yrs	90%	None	As for DTWp/ DTaP
Measles (LAV)	1000 CCID ₅₀ of Edmonston Zagreb strain of measles virus	Lyophilized, diluent sterile water	Freezer/ 2 to 8°C Protect from light	0.5 ml SC thigh/ deltoid	Single dose at 9 months	80%	Mild measles like illness in < 5%, Rarely thrombocytopenic purpura	Severely immuno- compromised, pregnancy
Rubella (LAV)	5000 CCID ₅₀ of RA 27/3 strain of rubella virus	Lyophilized, diluent sterile water	Freezer/ 2 to 8°C	0.5 ml SC thigh/ deltoid	As for MMR, MMR preferred	95%	Mild rubella like illness in <5%, rarely arthritis, ITP	Severely immuno- compromised, pregnancy
MMR (LAV)	Measles & rubella as above Mumps 5000 CCID ₅₀ of Jeryl Lynn/ Urabe strain	Lyophilized, diluent sterile water	Freezer/ 2 to 8°C Protect from light	0.5 ml SC thigh/ deltoid	Two doses at 15-18 mths and 5 years	95%	Same as measles & rubella, high fever, Rarely parotid swelling, aseptic meningitis	Severely immuno- compromised, pregnancy
Hep B	20 µg/ml of HBsAg antigen	Liquid vaccine	2 to 8°C	<18 yrs 0.5 ml, >18 yrs 1 ml IM deltoid/ thigh	Birth, 6, 14 weeks OR 6,10,14 weeks OR 0,1, 6 mths	>90%	None	Serious hypersensitivity
Hib	10 µg of PRP- T or HbOC	Liquid or lyophilized (diluent sterile water)	2 to 8°C	0.5 ml IM deltoid/thigh	6,10,14 weeks, booster at 15-18 months	>90%	None	Serious hypersensitivity



Vaccine	Content /dose	Nature and diluent	Storage	Dose, Route, Site	Schedule	Protective efficacy	Major adverseeffects	Contraindications
DTwP+ Hib	As for DTwP and Hib	Liquid vaccine OR lyophilized Hib reconstituted with liquid DTwP	2 to 8°C	0.5 ml IM deltoid/ thigh	6,10,14 weeks, booster at 15-18 months	As for DTwP and Hib		
DTwP+ HepB	As for DTwP and 10µg of Hep B	Liquid vaccine	2 to 8°C	0.5 ml IM deltoid/ thigh	6, 10, 14 weeks	As for DTwP and Hep B		
DTwP+ Hib+ HepB	As for DTwP, Hib, 10µg of Hep B	Liquid vaccine or lyophilized Hib reconstituted with liquid DTwP+HepB	2 to 8°C	0.5 ml IM deltoid/thigh	6 +10,14 weeks	As for DTwP, Hib and Hep B		
DTaP+ Hib	As for DTaP and Hib	Lyophilized Hib reconstituted with liquid DTaP	2 to 8°C	0.5 ml IM thigh/deltoid	6,10,14 weeks and booster at 15-18 months	As for DTaP and Hib		
DTaP+ Hib+IPV	DTaP (two component), IPV and Hib	Liquid vaccine	2 to 8°C	0.5 ml IM thigh/deltoid	6,10,14 weeks and booster at 15-18 mths	As for DTaP, IPV and Hib		
Vit typhoid	25-30µg of Vi polysaccharide	Liquid vaccine	2 to 8°C	0.5 ml IM deltoid/ thigh	Above 2 yrs, single dose, revaccination every 3 years	60%	None	Serious hypersensitivity



Vaccine	Content/dose	Nature and diluent	Storage	Dose, Route, Site	Schedule	Protective efficacy	Major adverse effects	Contraindications
HPV quadrivalent	L1 protein of serotypes 6, 11, 16, 18	Liquid vaccine	2 to 8°C Protect from light	0.5 ml IM deltoid	10-12 yrs, 0.2, 6 mths 10-12 yrs 0.1, 6 mths	>95% against serotype specific cervical cancer	None	Serious hypersensitivity Pregnancy
HPV bivalent	L1 protein of serotypes 16, 18	Liquid vaccine	2 to 8°C	0.5 ml IM thigh/deltoid	6, 10, 14 weeks, booster at 15-18 mths	95% against serotype specific invasive disease	None	Serious hypersensitivity
PCV	Capsular polysaccharide of serotypes 4, 6B, 9V, 14, 18C, 19F, 23, 1, 5, 6A, 19A, 7F, 3 linked to CRM 197	Liquid vaccine	2 to 8°C	0.5 ml SC/IM thigh/deltoid	Single dose at ≥2 yrs Revaccination only once after 3-5 yrs	70% against invasive disease in high risk children	None	Serious hypersensitivity
PPV23	Capsular polysaccharides of 23 serotypes	Liquid vaccine	2 to 8°C	0.5 ml SC/IM thigh/deltoid	Two doses 6 months apart, 18 months onwards	>95%	None	Serious hypersensitivity
Inactivated Hep A	HM 175 strain Composition varies with brands/ age	Liquid vaccine	2 to 8°C	Below 15/18 yrs (as per brand) 0.5 ml IM deltoid/ thigh	0, 1 and 6 months, 18 months onwards	>95%	None	Serious hypersensitivity
Hep A & Hep B	Composition varies with age	Liquid vaccine	2 to 8°C	Below 18 yrs 0.5 ml	Two doses 6 months apart 18 months onwards	>95%	None	Serious hypersensitivity
Live attenuated Hep A	6.5 log particles of H2 strain	Lyophilized, sterile water	2 to 8°C	1 ml SC deltoid/ thigh	Two doses 6 months apart 18 months onwards till 15 yrs	>95%	None	Immunodeficient patients



Vaccine	Content /dose	Nature and diluent	Storage	Dose, Route, Site	Schedule	Protective efficacy	Major adverseeffects	Contraindications
Varicella	> 1000 PFU of Oka strain	Lyophilized, sterile water	2 to 8°C Protect from light	0.5 ml SC deltoid/ thigh	< 13 yrs 2 doses, at 16 months & 5years ≥ 13 yrs two doses 4-8 wks apart	70-90% with one dose, >95% with 2 doses	Varicella like rash in 5%	Pregnancy, severely immuno-compromised
Rotavirus (monovalent) LAV	Human rotavirus strain 89-12 (G1P8)	Lyophilized, sterile water based specific liquid diluent	2 to 8°C Protect from light	1 ml orally	2 doses, first dose at 6-15 weeks, second at least 4 weeks later Schedule to be completed by 32 weeks and not to be initiated after 15 weeks	85-98% against severe rotavirus diarrhea	None	Acute gastroenteritis, beyond 6 mths
Human Bovine Penta-valent vaccine	5 rotavirus reassortant strains G1,G2,G3,G4 and P1A[8]	Liquid vaccine	2 to 8°	2ml orally	3 doses, 1st dose at 6-15weeks and then at 4w interval schedule to be completed by 32 weeks	85-98% against severe rotavirus diarrhea	None	Beyond 32 weeks AGE
Inactivated influenza	Split virus vaccine having 7.5- 15µg of three chosen strains	Liquid vaccine	2 to 8°C	0.25 ml for 6 mths to 3 yrs and 0.5ml for older children IM deltoid/ thigh	First time: < 9 yrs two doses 1 month apart, ≥ 9 yrs single dose Revaccination: annually	50-90% against lab confirmed disease	None	Severe egg allergy History of GBS



Vaccine	Content/dose	Nature and diluent	Storage	Dose, Route, Site	Schedule	Protective efficacy	Major adverse effects	Contraindications
Rabies	Inactivated rabies virus grown on human diploid/ chick embryo or vero cells	Lyophilized, diluent sterile water	2 to 8°C	1ml (0.5 ml for vero cell vaccine) IM deltoid/ thigh	Any age 0, 3, 7, 14 and 28 days for post exposure and 0, 7 and 28 days for pre exposure	90-100% (along with RIG if indicated)	None	None
Inactivated JE vaccine	Nakayama/ Beijing strain of JE virus	Lyophilized, diluent sterile water	2 to 8°C	0.5 ml for 1-3 yrs and 1ml for ≥ 3 yrs SC deltoid	Three doses at 0, 7 and 30 days, boosters every 2-3 years	80-90%	Rarely allergic reactions/ acute neurologic events	Serious hypersensitivity
Live JE vaccine	5.4 log PFU of SA 14-14-2 strain of JE virus	Liquid vaccine	2 to 8°C	0.5 ml SC thigh/ deltoid	Single dose at ≥ 9 months	>90%	None	Immunodeficient patients and their household contacts
MPSV	Bivalent (A + C) Quadrivalent (A + C + Y + W135)	Lyophilized, diluent sterile water	2 to 8°C	0.5 ml SC or IM thigh/ deltoid	If indicated, Single dose above 2 yrs, revaccination once after 3-5 years	90%	None	Serious hypersensitivity
Yellow fever (LAV)	17 D strain of yellow fever virus	Lyophilized/ saline diluent	2 to 8°C	0.5 ml SC thigh/ deltoid	Single dose, revaccination every 10 yrs if needed	>90%	Rarely neurologic/ viscerotropic disease	Below 6 months, serious egg allergy, severe immunodeficiency, thymus disease
Cholera	-	Liquid vaccine	2 to 8°C	1.5 ml po	Two doses above 1 year & 6 weeks apart	60%	None	None

* thigh refers to anterolateral thigh throughout the table



ANNEXURE 1

IAP Immunization Time Table 2011

Age (completed weeks/ months/years)	Vaccines
Birth	BCG OPV0 HepB 1
6 weeks	DTwP1/DTaP1 OPV1*/ OPV1 + IPV1 Hib1 HepB2 Rotavirus 1 [#] PCV 1
10 weeks	DTwP2/ DTaP2 OPV2*/ OPV2 + IPV2 Hib 2 Rotavirus 2 PCV 2
14 weeks	DTwP3/ DTaP3 OPV3*/ OPV3 + IPV3 Hib3 Rotavirus 3 HepB3** PCV 3
9 month	Measles
12 months	Hepatitis A 1
15 months	MMR1 Varicella PCV Booster
16 to 18 months	DTwP B1/ DTaP B1 OPV4*/ OPV4 + IPV4 Hib B1
18 months	Hepatitis A 2
2 years	Typhoid 1 [#]
5 years	DTwP B ₂ / DTaP B ₂ OPV5 MMR2 [§] Typhoid 2 Varicella 2 ^{§§}
10 to 12 years	Tdap/Td ^{&} HPV [^]

* OPV alone if IPV cannot be given

[#] Rotavirus vaccine (2/3 doses (depending on the brand) at 4-8 weeks interval)

** The third dose of Hepatitis B can be given at 6 months

[§] The second dose of MMR vaccine can be given at any time 4-8 weeks after the first dose

^{§§} Varicella (2nd dose may be given any time 3 months after the 1st dose)

[#] Typhoid revaccination every 3 years

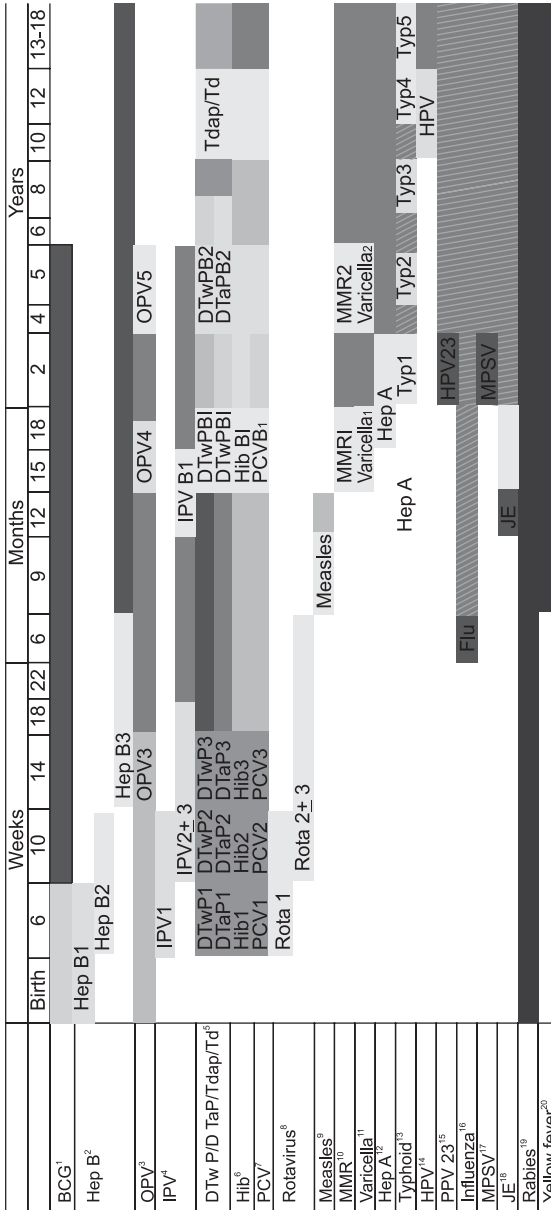
[&] Tdap preferred to Td, followed by repeat Td every 10 years

[^] Only females, three doses at 0, 1-2 and 6 months



ANNEXURE 2

IAP Immunization Schedule 2011



■ Solid fill : Recommended vaccination age ■ Diagonal fill : Catch up vaccination (For color version see palate)



- 1 BCG: birth or at first contact, catch up may be given up to 5 years.
- 2 Hep B: Acceptable schedules 0, 6, 14 weeks/ 0, 1, 6 months/ 6, 10, 14 weeks.
- 3 OPV: Additionally OPV on all NID's and SNIDS.
- 4 IPV: Primary schedule: 3 doses at 6, 10, 14 weeks or 2 doses at 8/10 and 16/18 weeks; Catch up: 2 dose 2 months apart
- 5 DTwP/DTaP/Tdap/Td: Catch up below 7 years: DTwP/DTaP at 0, 1 and 6 months; Catch up above 7 years: Tdap, Td, Td at 0, 1 and 6 months.
- 6 Hib: Catch up in 6-12 months; 2 doses 1 month apart and 1 booster; 12-15 months: 1 primary and 1 booster; above 15 months single dose.
- 7 PCV: Catch up in 6-12 months: 2 doses 1 month apart and 1 booster; 12-23 months: 2 doses 2 months apart.
- 8 Rotavirus: Two or three doses at 4-8 weeks interval depending on brand; vaccination should be completed before 8 months; initiation of catch up vaccination not permitted beyond 15 weeks.
- 9 Measles: At completed months/270 completed days; Catch up vaccination beyond 12 months should be MMR
- 10 MMR: MMR2 may be given at any time 4-8 weeks after 1st dose.
- 11 Varicella: 2 doses 16 months and 5 years in those below 13 years.
- 12 Hep A: Two doses 6 months apart.
- 13 Typhoid: Revaccination every 3 years.
- 14 HPV: Only females, three doses at 0, 1/2 (depending on brand) and 6 months.
- 15 PPV23: Revaccination only once after 3-5 years only in certain high risk patients.
- 16 Influenza: First time vaccination: 6 months to below 9 years to doses 1 month apart; 9 years and above single dose; Annual revaccination with single dose.
- 17 MPSV: Revaccination only once after 3 years in those at continued high risk.
- 18 JE: Live JE vaccine single life time dose; Inactivated vaccine three doses at 0, 7 and 30 days, boosters every 2-3 years.
- 19 Rabies: Pre-exposure prophylaxis: 0, 7 and 28 days; Post exposure prophylaxis: 0, 3, 7, 14 and 28 days.
- 20 Yellow fever: Single dose; revaccination every 10 years if indicated.
- 21 Cholera Vaccine: 2 doses 2 weeks apart for ≥ 1 year



ANNEXURE 3

List of Vaccine brands available in India

VACCINE	BRAND	Marketed by
BCG	Tubervac	Serum Institute of In India
OPV	Biopolio Primopol	Biomed GSK Biologicals Bharat Biotech Chiron Panacea
IPV	Imovax Polprotec	Sanofi Pasteur Chiron Panacea
DTwP	Triple	Serum Institute of India
DTaP	Infanrix Tripacel	GSK Biologicals Sanofi Pasteur
DT	Dual	Serum Institute of India
TT	Tetanus Toxoid Abhaytox BETT	Serum Institute of India Biological Evans
Td	Tdvac	Serum Institute of India
Tdap	Boostrix Adacel	GSK Biologicals Sanofi Pasteur
Measles	M Vac AbhayM	Serum Institute of India
Rubella	R vac	Serum Institute of India
MMR	Tressivac Priorix	Serum Institute of India GSK Biologicals
Hepatitis B	Genevac B Engerix B Revac B	Serum Institute of India GSK Biologicals Bharat Biotech
Hib	Hibpro Hibrix ActHib	Serum Institute of India GSK Biologicals Sanofi Pasteur
DTwP + Hib	Qudrovax Tetra ActHib Easy four	Serum Institute of India Sanofi Pasteur Chiron Panacea
DTwP + HepB		
DTwP + HepB + Hib	Pentavac SD Easy five Comvac 5	Serum Institute of India Chiron Panacea Bharat Biotech



VACCINE	BRAND	Marketed by
DTaP + Hib		
DTaP +Hib+ IPV	Pentaxim	Sanofi Pasteur
Vi typhoid	Typhbar Typhim Vi Typhrix Biotyph	Bharat Biotech Sanofi Pasteur GSK Biologicals Biomed
HPV quadrivalent	Gardasil	MSD
HPV bivalent	Cervarix	GSK Biologicals
PCV13	Prevenar 13	Pfizer-Wyeth
PPV23	Pneumo 23 Pneumovax 23	Sanofi Pasteur MSD
Inactivated Hepatitis A	Havrix Avaxim	GSK Biologicals Sanofi Pasteur
Hep A and Hep B	Twinrix	GSK Biologicals
Live attenuated Hep A	Biovac A	Wockhardt
Varicella	Varilrix Okavax	GSK Biologicals Sanofi Pasteur
Human Monovalent Rotavirus	Rotarix	GSK Biologicals
Bovine Human Pentavalent Rotavirus	Rotateq	MSD
Trivalent Inactivated Influenza	Vaxigrip Agripal Influvac	Sanofi Pasteur Chiron Panacea Solvey
Rabies	Rabivac (HDCV) Rabipur (PCEC) Abhayrab (PVRV) Verorab Vaxirab (PDEV)	Serum Institute of India Novartis Abhay Sanofi Pasteur
MPSV- A +C+ Y + W135	Quadrimeningo Mencivax	Biomed GSK Biologicals
A + C	Biomeningo	Biomed
Yellow Fever	Stamaril	Sanofi Pasteur
Cholera	Shanchol	Shanta Biotech

The Table provides commonly available licensed brands of the vaccine and the list is not exhaustive



INDEX

A

- Adverse Events following Immunization 43
 - Adverse vaccine reactions 44
 - Controversies in vaccine safety 45
 - Introduction 43
 - Vaccine associated adverse event reporting system (VAERS) 46

Annexures

- IAP Immunization Time Table 2011 168
- IAP Immunization Schedule 2011 169
- List of Vaccine brands available in India 171

B

- Basic Immunology and Elementary Epidemiology 15
 - Basics of epidemiology 23
 - Determinants of intensity & duration of immune responses 19
 - Epidemiologic shift 26
 - First steps after immunization 17
 - Force of transmission and Basic Reproductive Number (R_0) 24
 - Herd immunity and Herd effect 26
 - How do vaccines work? 16
 - Humoral Vs Cell mediated immunity: 15
 - Immune Memory and need for boosters 21
 - Immune responses during early life immunization 21
 - Immune responses to vaccines 17
 - Immunology of Vaccination 15
 - Impact of vaccinology on disease epidemiology 23
 - Incidence and Prevalence of diseases 24
 - Phases in vaccine development 26

Primary Vs Secondary Immune responses 18

Section 1: Basic Immunology of Vaccination 15

Section 2: Elementary

Epidemiology of Vaccination 23

Type of Vaccines 16

Vaccine characteristics and development 25

C

- Cold Chain 32
 - Cold box / Vaccine carriers 39
 - Cold chain equipment 35
 - Domestic refrigerator 36
 - Introduction 32
 - Storage of Vaccines 40
 - Temperature and light sensitivity of vaccines 32
 - Thermometers 34
 - Vaccine Monitoring Tools 33
 - Vaccine Vial Monitors 33

I

- Immunization in Special Situations 147
 - Catch up immunization 152
 - Immunization during illness 152
 - Immunization for travelers 153
 - Immunization in children with history of allergy 151
 - Immunization in pregnancy/ lactation 154
 - Immunization in preterm/low birth weight infants 147
 - Immunization in relation to antibody containing products 151
 - Immunization in the immunocompromised 147
 - Immunization of children with bleeding disorders or those receiving anticoagulants 154
 - Immunization of children with chronic diseases 151



- Immunization of the elderly 154
- Interchangeability of brands 152
- Lapsed immunization/ preponed immunization/ unknown immunization status 152
- Immunization of Adolescents 145
 - IAP Recommendations for Adolescent immunization in special circumstances 145
 - IAP Recommendations for Adolescents travellers 146
 - IAP Recommendations for Catch up Immunization in Adolescents 145
 - IAP Recommended vaccines for Adolescents 145
- Immunization Schedule 47
 - Expanded Program of Immunization (EPI) and Universal Immunization Program (UIP) 47
 - IAP Immunization Schedule 48
 - National Immunization Schedule 47
- Individual Vaccines 51
 - Bacillus Calmette Guerin (BCG) Vaccine 51
 - Cholera Vaccines 134
 - Combination Vaccines 83
 - DT Vaccine 65
 - DTaP VACCINE 62
 - DTwP VACCINE 60
 - Hemophilus Influenzae Type B (Hib) Conjugate Vaccines 74
 - Hepatitis A Vaccines 108
 - Hepatitis B (Hep B) Vaccine 78
 - Human Papilloma Virus (HPV) Vaccines 88
 - Influenza Vaccines 127
 - Japanese Encephalitis Vaccines 141
 - Measles Vaccine 69
 - Meningococcal Vaccines 135
 - MMR Vaccine 73
 - Pneumococcal Vaccines 94
 - Polio Vaccines 53
 - Rabies Vaccines 123
 - Rota Virus Vaccines 116
 - Rubella Vaccine 71
 - Td VACCINE 66
 - Tdap VACCINE 66
 - Tetanus Toxoid (TT) 64
 - Typhoid Vaccines 85
 - Varicella Vaccine 111
 - Yellow Fever Vaccine 143
- Internet Resources for Immunization Information 161
- Introduction 10
 - Immunization in India - Past, Present and Future 10
- L**
 - Licensing procedure and inclusion of a vaccine in the NIP in India 155
 - Assessment of efficacy, quality and safety of the vaccine 158
 - Assessment of other interventions available 158
 - Assessment of public health priority 157
 - Economic/ financial issues 158
 - Introduction of a new vaccine in the NIP 156
 - Issues in decision making 156
 - National Regulatory Authority (NRA) & licensing procedure 155
 - Programmatic strength 160
 - Vaccine presentation 159
 - Vaccine supply, availability and quality 159
- P**
 - Practical Aspects of Immunization 27
 - Communicating with parents/care givers 27
 - Injection procedure 28
 - Medicolegal aspects 31
 - Record keeping 30
- R**
 - Ready Reckoner for Vaccines currently available in India 162



OFFICE BEARERS OF IAP - 2011

Dr. T.U. Sukumaran, President	Dr. Piyush Gupta, Editor - In - Chief, IP
Dr. Rohit C. Agrawal, President - Elect	Dr. K. Nedunchelian, Editor - In - Chief, IJPP
Dr. Deepak Ugra, Imm. Past President	Dr. Mahaveer Prasad Jain, Joint Secretary
Dr. Rajeshwar Dayal, Vice President	
Dr. Tanmay Amladi, Secretary General	
Dr. Sailesh G. Gupta, Treasurer	

MEMBERS OF THE EXECUTIVE BOARD OF IAP-2011

Andhra Pradesh	Karnataka	Rajasthan
Dr. M. Arif Ahmed	Dr. Karunakara B.P.	Dr. Alok Gupta
Dr. Paleti Durga Prasad	Dr. Devaraj V. Raichur	Dr. Munish Kumar Kakkar
Dr. M. Indra Shekhar Rao	Dr. Dinesh R. Shivara	
Assam	Kerala	Tamil Nadu
Dr. Helina Rahman	Dr. S.S. Kamath	Dr. S. Balasubramanian
	Dr. T.M. Ananda	Maj. K. Nagaraju
Bihar	Kesavan	Dr. Somu Sivabalan
Dr. Nigam Prakash Narain	Dr. Remesh Kumar R.	
Chhattisgarh	Madhya Pradesh	Uttar Pradesh
Dr. Pradeep Sihare	Dr. C.P. Bansal	Dr. Atul Kumar Agarwal
	Dr. Sharad Thora	Dr. Arun Kumar Agrawal
Delhi	Maharashtra	Dr. Rajeshwar Dayal
Dr. Anju Aggarwal	Dr. Sanjay K. Ghorpade	Uttarakhand
Dr. Sunil K. Mehendiratta	Dr. Rajendra V. Kulkarni	Dr. Sudhir Kumar
Gujarat	Dr. Bakul Jayant Parekh	West Bengal
Dr. Satish V. Pandya	Dr. Yashwant Patil	Dr. Manjori Bose (Mitra)
Dr. Baldev S. Prajapati	Dr. Rhishikesh P. Thakre	Dr. Arup Roy
Haryana	Manipur	Services
Dr. Joginder Singh	Dr. Ksh. Chourjit Singh	Brig. Sunil Kumar Jatana
Himachal Pradesh	Orissa	Executive Director
Dr. Ashwani K. Sood	Dr. Gopabandhu Nanda	Dr. A. S. Vasudev
Jharkhand	Punjab	A.A.A.
Dr. Phalguni Chatterjee	Dr. Harinder Singh	Dr. Pravin J. Mehta



OFFICE BEARERS OF IAP - 2010

Dr. Deepak Ugra, President	Dr. Sailesh G. Gupta, Treasurer
Dr. T.U. Sukumaran, President - Elect	Dr. Piyush Gupta, Editor – In – Chief, IP
Dr. Panna Choudhury, Imm. Past President	Dr. K. Nedunchelian,
Dr. Santosh T. Soans, Vice President	Editor - In - Chief, IJPP
Dr. Tanmay Amladi, Secretary General	Dr. Tarun Patni, Joint Secretary

MEMBERS OF THE EXECUTIVE BOARD OF IAP-2010

Andhra Pradesh	Haryana	Maharashtra	Tripura
Dr. A. Arumugam	Dr. H.S. Sabharwal	Dr. Vasant M. Khalatkar	Dr. C.M. Chhajer
Dr. Ajoy Kumar	Jharkhand	Dr. Bakul Jayant Parekh	Uttar Pradesh
Dr. C. Suresh Kumar	Dr. Brij Bhushan Sahn	Dr. Manoj T. Rathi	Dr. Arun Kumar Agrawal
Assam	Jammu & Kashmir	Dr. Anand K. Shandilya	Dr. Girish C. Agrawal
Dr. Garima Saikia	Dr. Rekha Harish	Dr. Rhishikesh P. Thakre	Dr. B.D. Bhatia
Bihar	Karnataka	Orissa	Uttarakhand
Dr. Shashi BP Singh	Dr. L.H. Bidari	Dr. Arabinda Mohanty	Dr. Geeta D. Khanna
Chhattisgarh	Dr. Prahalad Kumar A.	Punjab	West Bengal
Dr. Ashwani K Agrawal	Kerala	Dr. Rajinder Gulati	Dr. Arup Roy
Delhi	Dr. Shaji Thomas John	Rajasthan	Dr. Amaresh De
Dr. Anju Aggarwal	Dr. T.M. Ananda Kesavan	Dr. Ashok Gupta	Services
Dr. A.S. Vasudev	Dr. George F Moolayil	Dr. Raj Kumar Gupta	Brig Prem Lochan Prasad
Gujarat	Madhya Pradesh	Tamil Nadu	Executive Director
Dr. Satish V. Pandya	Dr. Suhas B Dhonde	Dr. S Balasubramanian	Dr. Shyam Kukreja
Dr. Digant D. Shastri	Dr. J.S. Tuteja	Dr. Maj K. Nagaraju	A.A.A.
		Dr. S. Thangavelu	Dr. Pravin J. Mehta

OFFICE BEARERS OF IAP - 2009

Dr. Panna Choudhury, President	Dr. Tanmay Amladi, Treasurer
Dr. Deepak Ugra, President - Elect	Dr. Piyush Gupta, Editor - In - Chief, IP
Dr. R.K. Agarwal, Imm. Past President	Dr. K. Nedunchelian,
Dr. Atul Kumar Agarwal, Vice President	Editor - In - Chief, IJPP
Dr. Rohit C. Agrawal, Secretary General	Dr. S. Sanjay, Joint Secretary

MEMBERS OF THE EXECUTIVE BOARD OF IAP-2009

Andhra Pradesh	Haryana	Maharashtra	Tripura
Dr. M. Arif Ahmed	Dr. Mahaveer P. Jain	Dr. Hemant A. Joshi	Dr. C. M. Chhajer
Dr. Neeli Ramchander	Jammu & Kashmir	Dr. U.S. Kinjawadekar	Uttar Pradesh
Dr. P. Sudershan Reddy	Dr. Ashok Kumar Gupta	Dr. Vasant M. Khalatkar	Dr. Ashok Kumar Rai
Assam	Jharkhand	Dr. Pravin J. Mehta	Dr. Vineet K. Saxena
Dr. Shyama Saikia	Dr. Arun Kumar Sharma	Dr. Manoj T. Rathi	Uttarakhand
Bihar	Karnataka	Orissa	Dr. Sandhya Bhatnagar
Dr. Arun Kumar Thakur	Dr. Kishore Kumar R.	Dr. Niranjan Mohanty	West Bengal
Chhattisgarh	Dr. D. Narayanappa	Punjab	Dr. Nabendu Chaudhuri
Dr. Arvind P. Savant	Dr. R. Nisarga	Dr. Harmesh Singh	Dr. Arup Roy
Delhi	Kerala	Rajasthan	Services
Dr. A.S. Vasudev	Dr. Achamma Joseph	Dr. Rajiv Kumar Bansal	Air Cmde. Dr. Uma
Dr. Sangeeta Yadav	Dr. George F. Moolayil	Dr. Tarun Patni	Raju
Gujarat	Dr. T.U. Sukumaran	Tamil Nadu	IAP's Representative
Dr. Yagnesh O. Popat	Madhya Pradesh	Dr. D. Gunasingh	Dr. A.P. Dubey
Dr. Abhay Kantilal Shah	Dr. V.P. Goswami	Dr. S. Venkateshwaran	A.A.A
	Dr. P.G. Walvekar		Dr. Vijay N. Yewale



IAP COMMITTEE ON IMMUNIZATION (IAPCOI) 2009-2011

Chairperson

Dr. Panna Choudhury

Co-Chairperson

Dr. Naveen Thacker

Convener

Dr. Vijay Yewale

Immediate Past Convener

Dr. Tanu Singhal

Members

Dr. Vipin M. Vashishtha
Dr. Sangeeta Yadav
Dr. Baldev Prajapati
Dr. S. Balasubramaniam
Dr. Nupur Ganguly

Ex-Officio Members

Dr. Y.K. Amdekar
(IAPCOI Chairperson, 2007-08)
Dr. Deepak Ugra
Dr. T.U. Sukumaran
Dr. Rohit Agrawal
Dr. Tanmay Amladi
Dr. Indrashekhar Rao
Dr. Ritabrata Kundu
Dr. Digant Shastri
Dr. Pravin Mehta

Address for correspondence:

Indian Academy of Pediatrics

Kailas Darshan, Kennedy Bridge, Near Nana Chowk, Mumbai, India 400 007